Application and Effectiveness of Online Interventions for Depression in Adults with Multiple Sclerosis

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DECLARATION

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Literature Review

Online Interventions for Depression in Adults with Multiple Sclerosis: A Literature Review

Abstract

Depression is common in the clinical presentation of multiple sclerosis (MS) and can lead to a range of adverse health outcomes. Online interventions provide a cost-effective, accessible treatment option for those who often have difficulty accessing face-to-face psychotherapy due to MS-related complications. There is preliminary evidence for the efficacy of online service delivery. However, this literature is characterised by small studies with passive control groups; methodological features which may overestimate intervention effects. This review examines the efficacy of online interventions targeted to the MS cohort, highlighting a need for high-quality randomised trials to establish a stronger evidence base.

Depressive symptoms and disorders are highly prevalent in people with multiple sclerosis (MS); a patient group that faces an unpredictable and debilitating disease course. Depression is not only a main predictor of quality of life in this cohort but is associated with decreased cognitive functioning, increased suicidal intent and completion, relationship difficulties, and reduced compliance with disease-related treatments (Feinstein, 2011). There is strong evidence for pharmacological (Price et al., 2011) and psychotherapeutic (Fernie, Kollman, & Brown, 2015) management of depression in MS. However, these interventions can be costly and, moreover, require high clinician input (Hind et al., 2014). Online interventions provide an accessible, cost-effective alternative to conventional medical or psychological treatments. This review critically examines the application and effectiveness of online interventions in the management of MS-related depression. Online interventions will be presented as a viable treatment option, with preliminary research demonstrating promising effects. However, these conclusions are limited by methodological issues and a scarcity of studies measuring longer-term outcomes.

Multiple Sclerosis

Symptoms, Diagnosis and Aetiology

MS is a chronic neurodegenerative disease affecting 2.5 million people globally (MS Trust, 2018). The disease is characterised by demyelination and damage to axons in the central nervous system (Morrow, Brown, Smith, & Thrower, 2003). MS most commonly takes a relapsing-remitting course but can be progressive, whereby symptoms generally do not remit. Disease progression varies greatly between individuals, with unpredictable symptom severity and frequency. Onset and diagnosis generally occur in early adulthood, between the ages of 20 and 40 (Kidd et al., 2017; Thompson, Baranzini, Geurts, Hemmer, & Ciccarelli, 2018), although

cases of pediatric MS have been documented (Jancic et al., 2016). Symptoms typically experienced include visual and other sensory impairment, deficits in cognitive and motor functioning, fatigue, depression and neuropathic pain (Cooper et al., 2011; Kidd et al., 2017; Ziemssen, 2011).

The diagnosis of MS is challenging in the absence of a single, clinical test (Rae-Grant & Fox, 2013). Magnetic Resonance Imaging is used in conjunction with detailed history-taking, symptom examination and pattern recognition (Stone, 2013). MS-specific symptoms, such as unilateral loss of vision, are also considered in this process. Symptoms non-specific to MS, such as fatigue, depression and memory impairment, whilst important in the management of disease burden, are not critical to diagnosis (Stone, 2013).

The cause of MS is unclear although a genetic component has been suggested (Morrow et al., 2003). Environmental and lifestyle factors such as vitamin D deficiency, obesity and cigarette smoking, have also been implicated (Thompson et al., 2018; Morrow et al., 2003). Despite advances in treatments to slow the disease course, there is no known cure for MS. Consequently, medical treatment is aimed at slowing disease progression and reducing symptom burden (Ziemssen, 2011).

Depression Prevalence, Incidence and Risk Factors

Psychological symptoms and comorbidities are common in people with MS. An estimated 50% of this patient group will experience depressive symptoms in their lifetime compared to 17% of the general population (Proctor, Moghaddam, Vogt, & das Nair, 2018). The functional burden of depression is particularly high for people with MS given the demands of coping with a highly debilitating, incurable disease (Berzins et al., 2017). Indeed, depression is associated with poorer quality of life and, concerningly, heightened suicide risk in persons with

MS (Kidd et al., 2017; Ziemssen, 2011). Untreated or poorly managed symptoms can lead to severe complications and limitations in daily living including reduced working hours, disruption to social support and decreased treatment adherence (Boeschoten et al., 2012).

The aetiology of depression in people with MS is unknown, as psychological distress may arise through various pathways (Proctor et al., 2018). In their 6-month prospective cohort study, Berzins et al. (2017) found that gender and income were significantly associated with depression incidence: the 2-week incidence of depression was doubled in males (incidence rate = 0.044 vs. females 0.019) while higher income acted as a protective factor. However, there is also evidence to suggest a higher prevalence of depression in women with MS (Marrie et al., 2017). Additional illness-related risk factors for depression include chronic fatigue and severe physical disability (Berzins et al., 2017; Jones et al., 2014). Psychosocial correlates of depression for people with MS include uncertainty, helplessness, lack of leisure time and recreational activities, poor quality relationships, high stress, maladaptive coping styles, low self-esteem and low self-efficacy (Berzins et al., 2017; Feinstein, 2011). Berzins et al. (2017) demonstrated that longer time from diagnosis was also associated with depression, highlighting the need for early, targeted intervention and ongoing availability of mental health services to people with MS.

Interventions for Depression

The National Institute for Clinical Excellence (NICE, 2009) recommend a stepped-care approach to the treatment of depression for chronic physical health problems. This approach consists of increasingly intensive levels of cognitive behavioural therapy (CBT) informed interventions prior to the introduction of antidepressants (NICE, 2009), with both of these interventions demonstrating strong efficacy (Feinstein, 2011).

However, traditional anti-depressants are not always recommended. Findings from randomised controlled trials (RCT's) suggest that side effects from antidepressants, including hypotension, dry mouth, constipation, head-ache and nausea, are particularly prominent for those diagnosed with MS (Feinstein, 2011). Furthermore, antidepressant medications may pose risks for interaction effects with disease-modifying medications typically prescribed to manage illness-related symptoms (Fernie et al., 2015). Similarly, whilst research suggests that 'talking therapies' are moderately effective in reducing depression following MS diagnosis, the high costs of staffing such services have led to conclusions that clinician-led psychotherapy may not be a cost-effective treatment option (Fernie et al., 2015; Hind et al., 2014). Even low intensity treatment, such as telephone-based CBT, requires further large-scale studies to prove superior effectiveness, including cost-effectiveness, compared to routine care (Hind et al., 2014, Proctor et al., 2018). Moreover, gains associated with CBT-based therapies are not sustained in the longer term (Proctor et al., 2018). For these reasons, online interventions framed by evidence-based treatment principles (i.e. CBT) have been piloted as a cost-effective alternative that can be widely distributed while requiring fewer resources. Indeed, online psychological-based interventions have been the focus of increasing interest in MS research.

Online Interventions for Depression

The internet has drastically influenced the way information is stored and accessed, how services are delivered and consumed, and the way we communicate. Although a "digital divide" still exists between developed and developing countries, advances in technology have embedded the internet into nearly every aspect of modern life, with an estimated 4 billion internet users worldwide (Andersson, 2016; Evans, 2019). Meanwhile, health systems globally are struggling to meet the increasing demand for mental healthcare – particularly for those living with a chronic

condition, such as MS (Porter and Thompson, 2012). With the now widespread accessibility of online materials, it is no surprise that health providers have turned to the internet as a mode of service delivery, and that researchers predict the use of online interventions will only continue to grow.

According to Barak and colleagues (2009, p. 5), online psychological interventions are primarily self-guided programs accessed via the internet, with the primary aim to create positive change and to enhance knowledge, awareness and understanding related to health and mental health, through evidence-based materials and interactive web-based components. Despite considerable advances in technology since this definition was put-forward, the essence of Barak's definition remains relevant and accurate in describing the general role and application of current online interventions (Andersson, 2016; Boeschoten et al., 2017; Cooper et al., 2011; Twomey, O'Reilly, & Meyer, 2017).

The content and format of online psychological interventions are typically designed to be brief, with a variety of multimedia used to boost learning. A recent literature review found that modules are usually accessed weekly over five to 15 weeks, and are composed of text, images and even audio-visual content (Andersson, 2016). Other features may include homework tasks, monitored discussion forums, automated e-mail support, and interactive components, such as online quizzes (Andersson, 2016). Most online psychological interventions are informed by CBT, although other theoretical frameworks including psychodynamic theory (Johansson, Ekbladh, et al., 2012), social cognitive theory (Motl et al., 2017; Pilutti, Dlugonski, Sandroff, Klaren, & Motl, 2014), interpersonal psychotherapy (Dagöö et al., 2014), and mindfulness (Boettcher, Rozental, Andersson, & Carlbring, 2014), have been used. Therapist involvement also varies, ranging from self-guided interventions to interventions monitored and delivered

online by a trained therapist (Dear et al., 2016; Mehta, Peynenburg, & Hadjistavropoulos, 2019). The distinction between self- and therapist-guided intervention is, however, blurred. Indeed, both formats incorporate similar features, such as automated reminders and the provision of technical support (Andersson, 2016). Moreover, while therapist-guided treatment might involve weekly contact via online messaging or by telephone, the nature of this input is poorly understood and can range from technical advice to the provision of targeted psychological support (Marks, Cavanagh, & Gega, 2017; Mehta et al., 2019).

A key advantage of online interventions is their accessibility to a high number of people at low cost. Online platforms allow for remote treatment access, helping to reduce the burden for consumers of mental health care who continue to face extensive waitlists as well as health care providers who struggle to manage ever-increasing caseloads (Porter and Thompson, 2012). Communication with therapists is often minimal and may occur either in real time (e.g. via chat) or asynchronously (e.g. via email), the latter reducing the need for scheduled appointments and enabling clinicians to consult with colleagues as needed (Andersson, 2016). A fall-back of online communication is the increased likelihood of misunderstandings through written communication and reduced ability to immediately detect and repair such misunderstandings (Andersson, 2016). Furthermore, the information conveyed through verbal and non-verbal communication is missed, meaning clinicians are less able to judge a client's affect and reactions. Concerns have also been expressed about data security, necessitating the need for secure communication systems (Andersson, 2016).

Support for the effectiveness of online interventions for the general population is promising. In their meta-analytic review of eight studies, Twomey and O'Reilly (2017) found a positive medium effect size for depression symptoms - although this result became non-

significant when correcting for the effects of publication bias (via 'trim and fill method' which excludes small, outlier studies and imputes data from omitted studies based on the bias-corrected estimate; Duval & Tweedie, 2000; Shi & Lin, 2019). Participants did, however, report significant improvement in a related psychological outcome, anxiety. The study pointed to several important factors in online intervention efficacy, noting larger effects among studies that utilised a no-treatment control than those with an active treatment control, but also larger effects associated with face-to-face therapist guidance compared to remote (i.e. e-mail or telephone) guidance (Twomey & O'Reilly, 2017). Favourable results have also been reported by online CBT programs targeting comorbid depression and anxiety: medium to large and significant effect sizes have been noted for both of these constructs, alongside improvements in perceived quality of life more broadly (Newby, Twomey, Yuan Li, & Andrews, 2016).

Despite offering a feasible solution for accessibility problems, and potentially an effective option, the acceptability of online interventions in primary health care requires further evaluation. The suggestion is that online interventions can enhance and complement best practice rather than replace it. Specifically, online interventions can help to increase the capacity for clients to self-manage their symptoms (Porter & Thompson, 2012). There is also argument for online treatments to be integrated with face-to-face treatment. This notion of integrated care is particularly pertinent for chronic illness populations which do not fit the pre-screening criteria for typical RCT's (e.g. those with severe symptoms or complex comorbidities; Gun, Titov, & Andrews, 2011). Nevertheless, the benefits of online interventions are promising and, accordingly, an increase in the use of blended online and face-to-face interventions in the future is expected (Mansson, Ruiz, Gervind, Dahlin, & Andersson, 2013).

Online Interventions for Depression in MS

Online interventions provide a practical solution for those with MS who are hindered by disease-specific cognitive, sensory, and physical disabilities in addition to financial access to services (Porter & Thompson, 2012; Proctor et al., 2018). Comorbid depression may also reduce adherence to traditional face-to-face psychotherapy in this patient group (Bruce et al., 2010). Treatment adherence is especially an issue for those who may not consider their depressive symptoms severe enough to seek help or may not perceive themselves as having depression because a depression diagnosis compounds, rather than validates, their emotional difficulties (Bruce, Hancock, Arnett, & Lynch, 2010; Hind et al., 2010).

The scope of this research, however, varies considerably in content and format making it difficult to ascertain the effectiveness of online psychological interventions for MS. For example, Cooper et al. (2011) conducted a pilot feasibility trial to examine the efficacy of the CBT-based online program "Beating the Blues", compared to a treatment as usual (TAU) control group. The program was self-guided, with therapist input restricted to screening for study eligibility and monitoring of depression outcomes. Greater reductions in depression symptom severity were observed in their online group at both 8- and 21-week follow-up, compared to controls. However, concerns over baseline imbalances in gender and MS type may have influenced outcomes. Indeed, there is evidence that men and women with MS may benefit from different treatment strategies and coping styles for managing depressive symptoms (Berzins et al., 2017). Boeschoten et al. (2017) conducted a more recent RCT on the efficacy of a guided self-help intervention, "Minder Zorgen" or "Worry Less", with content adapted for patients with MS. However, their program involved weekly e-mail support from psychologists and supervised postgraduate psychology students. Although depression severity among intervention participants

was largely reduced following completion of the online program, with gains maintained at four-month follow-up, between-group differences did not reach statistical significance. Indeed, large and unexpected gains were also noted in the control group. This result may reflect a sample bias, with the sample primarily comprising of participants who self-referred in response to advertisements in newsletters and internet sites and were, quite likely, highly motivated and receptive to mental health help-seeking.

Other RCT's have reviewed the efficacy of online interventions targeting depression in MS as a secondary outcome. This includes programs which have focused on MS-related fatigue. For example, Moss-Morris et al. (2012) found a significant difference in depression outcomes between their intervention ('MS Invigor8') and control groups in favour of the online intervention. Notably, their online intervention was supplemented with three telephone support sessions from a psychologist. These findings were not replicated by van Kessel et al. (2016) who reviewed the same online intervention ('MS Invigor8') but compared the specific benefits of e-mail support to no e-mail support. However, van Kessel et al. (2016) noted that both intervention and control groups reported low depression scores at baseline. Consequently significant changes in depressive symptoms, with corresponding large effects, would not be expected in this sub-clinical group. A similar pattern was noted in Pöttgen et al.'s (2018) controlled trial of a 12-week online program targeting MS-related fatigue; no significant between-group differences in depression were found although low depression severity scores were reported by their intervention and control groups at baseline. MS-based online interventions have also targeted physical activity-related improvements in depression as a key outcome. Motl et al. (2017) evaluated an intervention which involved video support from a behavioural coach. Non-significant but medium effects were noted for depression. Interestingly,

these authors did report moderate improvements in favour of the online intervention in an earlier 6-month pilot trial (Pilutti et al., 2014).

These heterogeneous findings are reflected in the meta-analysis conducted by Charova et al. (2015), which examined online interventions for comorbid depression and chronic illness more broadly. Results from 11 independent studies, two involving an MS population, were pooled. The overall effect size for improvement in depression severity was moderate (d = 0.36, CI = 0.20 – 0.52). Importantly, immediate improvements in depression and problem-solving style were reported by participants with MS (d range = 0.44 to 0.92). However, longer-term treatment effects could not be established due to limited data ($N_{studies}$ = 2).

Barriers to Accessing Online Intervention

The role of therapist assistance alongside online interventions represents a key confound in available studies. Without clinician guidance, many participants may struggle with the core therapy concepts, such as goal setting and distinguishing between external stimuli and their responding thoughts in CBT (Hind et al., 2010). The value of targeted and clinician-supported interventions cannot be underestimated (Johansson, Sjoberg, et al., 2012). Meta-analytic data suggest that therapist-guided online programs for chronic illness groups, in general, have a greater effect on depression symptoms compared to a self-guided approach (Mehta et al., 2019). However, there is also evidence that self-guided online interventions may contribute to positive psychosocial outcomes provided that key elements are incorporated to promote treatment adherence. These elements include pre-screening of participants for suitability, provision of engaging materials and automated email messages or telephone reminders (Dear et al., 2016; Mehta et al., 2019). Nonetheless, consumers with MS have identified a preference towards clinician-supported interventions, having reported that the lack of human contact associated with

online interventions exacerbated their social isolation (Hind et al., 2010). The aforementioned research is, however, based on small-scale qualitative studies which may not represent the broader experiences of the MS population at large.

These findings are also in contrast with research conducted with non-clinical populations. In their RCT comparing an online intervention for depression to the same program with weekly e-mail support, Berger, Hämmerli, Gubser, Andersson, and Caspar (2011) reported that both groups achieved greater gains than wait-list control, with no significant differences in effect size when their guided and unguided groups were compared. Notably, the therapist-guided group in this study received weekly e-mail feedback and the therapist input was reported as "low-intensity". Perhaps more intensive therapist support may contribute to larger treatment gains. Vernmark et al. (2010) compared a therapist-guided online intervention, consisting of positive reinforcement, e-mail reminders and the capacity to ask questions, to weekly individualised e-mail therapy. A small reduction in depression severity was found in favour of e-mail therapy. Notably, this difference was not economically viable given the required therapist time: e-mail therapy participants received almost 10 times more therapist contact than that of the self-help group.

Additional problematic factors identified in the usage of online interventions for those with MS include the time commitments required. Participants have typically reported that hour-long modules can be difficult to complete due to MS-related fatigue, poor concentration and memory, and physical discomfort. This is consistent with research involving other chronic illness groups (e.g. cancer survivors); physical and cognitive difficulties can lead to study withdrawal and/or low treatment adherence (Alberts, Hadjistavropoulos, Titov, & Dear, 2018). Although online interventions may allow participants to work at their own pace and repeat

modules (Andersson, 2016), some participants report a reluctance to take breaks due to a lack of confidence that the internet servers will save their progress (e.g. Hind et al., 2010). In addition, participants have commented that some of the psychoeducational material (e.g. CBT-based programs) fail to acknowledge the role that MS, an incurable condition, played in their depression. In their qualitative evaluation of online treatment acceptability among the MS population, Hind et al. (2010) found that participants expressed difficulty challenging thoughts that reflected the reality of their condition, whilst others found the online content did not account for loss of usual activity due to physical restrictions.

Limitations of Current Research

The current literature on online interventions for depression for people with MS is limited by a number of methodological weaknesses. The majority of RCT's have incorporated a wait-list or TAU control. However, as identified by Cooper et al. (2011), TAU in the MS population may often reflect no treatment given the low help-seeking nature of this group. Direct comparisons between online and face-to-face interventions are lacking, despite evidence to suggest that larger effect sizes are observed when psychological treatments for depression in this population are compared to inactive control groups than when active comparators are used (Fernie et al., 2015). Indeed, Mehta et al.'s (2019) systematic review demonstrated that CBT-based online interventions for disability groups, in general, may not produce gains beyond that of information-only programs. Similarly, online interventions with therapist-guidance are believed to result in stronger treatment adherence and subsequent therapeutic gains than unguided interventions, yet studies directly comparing the two are lacking (Mehta et al., 2019). Furthermore, researchers often do not clearly describe the extent of clinician support in their

study protocol in order to distinguish between guided and unguided online treatments to confirm these findings.

In addition, external validity is often compromised in a RCT due to controlled conditions and specific sample groups. Studies on MS and depression often restrict eligibility to participants with reduced MS symptom burden (e.g. relapse free for 30 days; Motl et al., 2017) or disability (Cooper et al., 2011), and low to moderate depressive symptoms. Furthermore, high heterogeneity in exclusion criteria and outcome measures exists, making comparisons of results across studies difficult. Many trials, to date, have been pilot studies characterised by small sample sizes which are often underpowered to detect significant intervention effects or may even inflate noted effects (Button et al., 2013). Due to the nature of psychological therapies and self-report measures, participants are also unable to be blinded to group assignment and outcome data are prone to self-report biases. These methodological features increase the risk that outcomes are influenced by awareness of allocation to the treatment or control group, and therefore detection bias is poorly mitigated.

A final consideration when evaluating the current research are the statistical methods used to analyse intervention effects. The gold standard approach for evaluating the efficacy of psychological therapies is an intention-to-treat (ITT) analysis (Schnurr, 2007). An ITT approach analyses outcome data according to participants' initial group assignment. Thus, data from all participants are included regardless of their treatment adherence, and missing data is accounted for using a last observation carried forward model (Schulz, Altman, & Moher, 2010). This is considered to provide a conservative outcome estimate whilst still maintaining the benefits of the initial random allocation (Gordis, 2014). Alternative methods, such as per-protocol analysis and complete case analysis, which only include data from participants who complete the study, may

overestimate treatment effects. Indeed, adherent patients generally perform better than non-adherents who are no longer represented in the sample (Ten Have et al., 2008). While most on-topic RCT's have adhered to the ITT approach, some studies have used less rigorous per-protocol or complete case methods.

Summary

There is preliminary data to suggest that online interventions may provide an effective treatment option for depression in people with MS. However, results are mixed, and available trials lack methodological rigor and longer-term effect measurements (Charova et al., 2015). Heterogeneity in the duration and content of available online treatments also needs to be considered when interpreting the available data. In order to improve current understandings of the key components, benefits and limitations of online interventions, a quantitative, critical review of the research for online treatments of depression for people with MS may be an important first-step.

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Online Interventions for Depression in Adults with Multiple Sclerosis: A Systematic Review

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Abstract

Objective: To evaluate the existing evidence for the efficacy of online interventions in managing depression in community-dwelling adults living with multiple sclerosis (MS). ***Methods:*** A systematic search of the Embase, PubMed and PsycINFO databases was undertaken to identify randomised controlled trials (RCTs), with wait-list, usual care or other control conditions, in adult MS populations with reported depression-related outcomes. Study reporting quality was assessed using the Cochrane Risk of Bias tool (RoB 2.0). Hedges' *g* effect sizes, with associated confidence intervals and *p* values, were calculated to estimate short- and longer-term treatment effectiveness. ***Results:*** Nine unique RCTs, comprising a pooled sample of 815 adults with MS, were identified. All studies were evaluated as having 'some concerns' in one or more RoB domains. Intervention effects were mixed: four studies reported significant, medium to very large improvements in depression symptoms immediately post-intervention (*g* range: 0.50 to 1.77). Large secondary gains in anxiety, health distress and self-efficacy (g range: .87 to 1.57) were also noted by these studies, although these findings were susceptible to publication bias. Longer-term effects could not be confirmed: the three studies that provided these data reported non-significant results with the exception of one, which reported larger improvements in self-efficacy among wait-list controls. ***Conclusions:*** Preliminary data suggests that online interventions may provide an efficacious treatment option for managing depression symptoms in people with MS, however more studies with larger sample sizes, rigorous methodologies and longitudinal data are needed to confirm these findings.

Keywords: depression, multiple sclerosis, online, internet, technology

Impact and Implications

- This exploratory review examines the evidence for the efficacy of online interventions in managing depression symptoms for adults living with chronic multiple sclerosis (MS).

- The present findings suggest that online interventions may help to promote short-term improvements in MS-related depression, with secondary benefits to perceived anxiety, distress and symptom self-efficacy.

- Online interventions present a promising treatment option in MS care. However, in the absence of high-level evidence, an integrated approach - whereby online interventions are used to enhance and complement best practice - is recommended.

Online Interventions for Depression in Adults with Multiple Sclerosis: A Systematic Review

Multiple Sclerosis (MS) is an autoimmune disease characterised by demyelination and damage to axons in the central nervous system (Morrow, Brown, Smith, & Thrower, 2003). Disease progression varies greatly between individuals depending on the extent and location of CNS damage, with unpredictable trajectory of remission and relapse periods (Kidd et al., 2017). The effects and symptoms of MS vary from person to person but typically include visual and other sensory impairment, deficits in motor and cognitive functioning, fatigue, and neuropathic pain (Cooper et al., 2011; Kidd et al., 2017; Ziemssen, 2011). This symptom complex significantly and adversely affects mental health: an estimated 50% of people with MS will experience depressive symptoms in their lifetime compared to 17% of the general population (Proctor, Moghaddam, Vogt, & das Nair, 2018). The functional burden of depression is heightened given the demands of coping with MS as a highly debilitating, incurable disease (Berzins et al., 2017). Indeed, depression in people with MS is typically associated with poorer quality of life and increased suicide risk, as well as disruptions to employment, social support and treatment adherence (Boeschoten et al., 2012). In combination, these issues highlight the need for early, targeted intervention (Berzins et al., 2017).

There is some evidence that pharmaceuticals can be effective in the treatment of depression in people with MS (Price et al., 2011). However tricyclic antidepressants can pose risks for excessive adverse effects, including hypotension, headache and nausea, in addition to interaction effects with CNS-active drugs that are typically prescribed to persons with MS (Fernie, Kollmann, & Brown, 2015). Depressed patients respond well to psychotherapeutic interventions, particularly those with an emphasis on coping skills (Fernie et al., 2015). Psychological services are, however, often difficult to access for this patient group due to

condition-related fatigue, reduced mobility and other physical, cognitive and sensory impairments (Porter & Thompson, 2012). Moreover, noted intervention effects for both face-to-face and telephone administered psychotherapy typically require high clinician input, leading to concerns that traditional psychotherapy may not be a cost-effective treatment option (Fernie et al., 2015).

Online interventions provide an accessible, cost-effective alternative to conventional medical or psychological treatments. Programs delivered via the internet typically consist of text-, image- and sometimes audio-visual-based modules, designed to be accessed weekly over a time-limited period (Andersson, 2016). Interventions differ in their delivery, with some being primarily self-guided whilst others may be facilitated by a trained therapist (e.g. psychologist). Program content is typically based on established theoretical frameworks, including cognitive behaviour therapy (CBT; Twomey, O'Reilly, & Meyer, 2017), social cognitive theory (Motl et al., 2017; Pilutti, Dlugonski, Sandroff, Klaren, & Motl, 2014) and mindfulness (Boettcher, Rozental, Andersson, & Carlbring, 2014).

Consumers with MS have reported high acceptance and satisfaction with online interventions (Tallner, Pfeifer, & Mäurer, 2016). However, issues with fatigue, poor concentration and memory, physical discomfort and exacerbated feelings of isolation have been cited as potential barriers to accessing online mental health services (Hind et al., 2010). Indeed, there are concerns that online service delivery may decrease treatment compliance (Tallner et al., 2016). Nevertheless, online interventions tailored for users with chronic health conditions have the flexibility to instigate procedural changes from face-to-face therapies, such as providing more frequent breaks, and may even provide a pathway to accessing healthcare for those who generally exhibit low help-seeking behaviours (Bruce, Hancock, Arnett, & Lynch, 2010; Fernie

et al., 2015). Importantly, preliminary findings from systematic reviews and meta-analyses have demonstrated the potential effectiveness of online interventions for targeting mental health symptoms, including depression, anxiety and quality of life in general, in people with chronic health issues (Charova, Dorstyn, Tully, & Mittag, 2015; Mehta, Peynenburg, & Hadjistavropoulos, 2019). However, these findings are tempered by low methodological rigour in addition to quasi-experimental (i.e. single group) designs; features which may over-estimate or inflate noted treatment effects (Peinemann, Labeit, Thielscher, & Pinkawa, 2014).

Thus, online psychological interventions appear suited for use with persons who have been diagnosed with MS. To date, no review has systematically examined whether this form of service delivery can be effectively integrated into MS care. The current review examines the evidence-base for online interventions in multiple sclerosis, namely: 1) how such interventions have been used (e.g. session frequency, duration, content), and 2) whether online interventions lead to better mental health outcomes, relative to those receiving standard care or another intervention, or those on a wait-list.

Method

Literature Search

Three electronic databases, Embase, PsycINFO and PubMed, were searched for eligible studies using search terms developed in consultation with a specialist research librarian. Logic grids were tailored to each database using a combination of keywords for '*multiple sclerosis'*, '*depression*' and '*telecounselling*' (see Appendix A for example search strategy). A secondary search of two international peer-reviewed journals dedicated to online or remote care, *Journal of Telemedicine and Telecare* and *Journal of Telemedicine and e-Health*, was also conducted to locate other potentially relevant research. Finally, the reference lists of retrieved studies and of

topic-related systematic reviews and meta-analyses (Charova et al., 2015; Dorstyn, Mathias, & Denson, 2011; Proctor et al., 2018) were searched and Scopus citation searching of identified studies undertaken. Three additional studies were identified during this final process.

Eligibility Criteria

This review was informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix B; Moher, Liberati, Tetzlaff, & Altman, 2009). To be eligible for inclusion, studies needed to be published in journals written in the English language, or with English translation. Studies also had to meet the following PICO (Population, Intervention, Comparator, Outcomes) components (da Costa Santos, de Mattos Pimenta, & Nobre, 2007).

Population. Eligible studies targeted adult participants (18 years or older) with a diagnosis (medical or self-reported) of any subtype of MS (i.e. relapse-remitting or progressive forms).

Intervention. Studies needed to evaluate an intervention that was delivered remotely via the internet, with the primary aim to create positive change and to enhance knowledge, awareness and understanding related to MS symptom management (Barak, Klein, & Proudfoot, 2009). Included interventions needed to be grounded in an evidence-based psychological framework (e.g. CBT) and include one or more online modules. The provision and combination of different components within the online intervention, including the discipline and extent of therapist involvement (i.e. program content, multimedia use, interactive activities and guidance and supportive feedback; Barak et al., 2009) was not specified. Studies in which the evaluated intervention primarily involved face-to-face or telephone contact, with only supplementary materials delivered online, were excluded.

Study design. Only randomised controlled trial (RCT) designs, whereby the online intervention was compared to a wait-list or usual care group or to another comparison treatment, were eligible. Controlled designs are considered the 'gold standard' for evaluating efficacy in clinical research (American Psychological Association, 2006). Studies also had to provide parametric data (e.g. means, standard deviations, one way ANOVA, *p* values) that could be converted into standardised mean group differences, or Hedges' *g*.

Outcomes. Studies were required to include a measure of depression symptom severity validated for the MS population (see Appendix C for a list of eligible measures). Depression measurement had to be administered both prior to and following the completion of the online intervention. Self-report and clinician-administered measures of depression were eligible. Secondary psychological outcomes included anxiety, distress, quality of life and coping ability – constructs which are highly correlated with depressive symptoms in the MS population (Dorstyn, Black, Mpofu, & Kneebone, 2017).

Data Collection and Organisation

In accordance with the PRISMA guidelines (Moher et al., 2009), key information was extracted from each study and summarised in a purposely designed Excel spreadsheet. These data included: sample characteristics (e.g. sample size, MS subtype), study characteristics (e.g. outcome measures, control condition), intervention characteristics (e.g. attrition rate, therapy framework, target symptom) and effect size data (e.g. means, standard deviations for each repeated measure, for both intervention and control groups extracted at baseline, immediately post-intervention, and follow-up). Effect size data were grouped under six broad psychological domains: depression, anxiety, quality of life, distress, self-efficacy and problem solving.

Risk of Bias Assessment

The reporting quality of included studies was evaluated using the revised Cochrane Risk of Bias tool (RoB 2.0) which is widely used for the assessment of RCT's (Munder & Barth, 2018; Savovic et al., 2017). Risk of bias refers to methodological deficits encountered during design and data collection for an intervention study that are likely, but not necessarily certain, to lead to systematic error in the estimation of an observed effect (Munder & Barth, 2018). Studies were rated on five domains: (1) the randomisation process (selection bias); (2) deviations from intended interventions, as determined by participant adherence to the assigned intervention and whether co-interventions are balanced across intervention and control groups (performance bias); (3) missing outcome data (attrition bias); (4) measurement of the outcome of interest (detection bias); and (5) selection of the reported results (reporting bias). For each domain, studies were assigned a rating of 'low', 'high' or expressing 'some concerns', based on a series of signaling questions outlined in the RoB tool. The author (J.H) completed this process in consultation with a senior researcher (D.D).

Statistical Analysis

Effect size data were entered into, and analysed with, Meta Essentials software (Suurmond, van Rhee, & Hak, 2017). Both short-term intervention effects (i.e. from baseline to immediately post-intervention) and longer-term effects (i.e. gains maintained post-intervention to follow-up) were calculated, based on the formula provided by Morris (2008) for studies with a repeated measures, independent-groups (treatment and control) design. Hedges' g, which utilises a standard deviation weighted by sample size, was the most suitable estimate and was calculated using Morris's (2008) pooled standard deviation formula. The interpretation of Hedges' g was based on Cohen's (1988) guidelines, with values of 0.2, 0.5 and $\geq$ 0.8 reflecting small, medium

and large to very large intervention effects. For ease of data interpretation, the direction of each *g* was standardised such that a positive value reflected symptom improvement among individuals who received the online intervention, whereas a negative value reflected deterioration of symptoms among intervention participants, or greater improvement by those in the control group.

Ninety-five percent confidence intervals (CIs) were calculated to determine the precision, or accuracy, of each effect estimate, whilst *p* values determined the statistical significance of each *g* (Altman, Machin, Bryant, & M., 1989; Ferrin et al., 2007). Given the pervasive file drawer problem, whereby significant and strong results are more likely to be published, some publication bias may be possible. To account for this, Orwin's (1983) fail-safe N (N_{fs}) was calculated for each effect estimate. The N_{fs} gives an indication of the number of hypothetical studies required to invalidate the individual *g*'s reported by included studies to a small, statistically unimportant effect size (i.e. $g < 0.2$) (Orwin, 1983). The larger the N_{fs} value, the more robust the effect estimate is likely to be.

For the purposes of interpretation, an online intervention was considered to have important personal and clinical implications for persons with MS on a given psychological outcome if it was: (a) found to have at least a medium effect ($g \geq .50$), that was (b) statistically significant (i.e. $p < 0.05$; 95% CI $\neq 0$), and was (c) robust to publication bias (i.e. $N_{fs} > N_{studies}$ included in review). Given the variation in intervention focus (depression examined as a primary or secondary outcome), data analysis (intent-to-treat vs. data based on intervention completers only), and theoretical framework (Cognitive Behaviour Therapy vs. Social Cognitive Theory), effect sizes were calculated and examined for each individual study. Although effect sizes from individual studies are considered to be less reliable, it was important to report all available data using an

equivalent metric (i.e., Hedges' g) given that current research on the topic of online interventions for persons with MS is limited.

Results

Initial database and topic-specific journal searches retrieved 284 records for screening, following the removal of duplicates (see Figure 1). Titles and abstracts were then screened, identifying 32 articles for full-text screening. From this, a final sample of nine independent studies that met all eligibility criteria were identified. A second reviewer, a postgraduate psychology student, screened the titles and abstracts of 29 (10%) randomly selected articles. Inter-rater agreement was moderate ($\kappa = .63$) (McHugh, 2012). Disagreements were resolved through consensus discussion.

Study Characteristics

All studies originated from Western countries (e.g. United States, United Kingdom, New Zealand; $N_{studies} = 7$) and relied on self-reported data, usually administered online, to evaluate intervention effectiveness (see Table 1). The Hospital Anxiety and Depression Scales (HADS; $N_{studies} = 6$) was the most commonly used measure, followed by the Beck Depression Inventory (BDI; $N_{studies} = 3$), and the Multiple Sclerosis Impact Scale (MSIS); a disease-specific measure of quality of life ($N_{studies} = 3$; Hobart, Lamping, Fitzpatrick, Riazi, & Thompson, 2001). Eight of the included RCTs were primary studies. Tietjen, Wilson, Amiri, and Dietz (2018) undertook a secondary analysis of data from a subgroup of adults with MS who had participated in a larger randomised controlled pilot study targeted to a broader chronic illness group.

Sample Characteristics

The pooled sample included 815 participants (398 intervention, 417 control) who were primarily female (80%) with an average age of 46 years (see Table 2). Participants had been

living with their MS for at least 10 years, although this data was not consistently reported by studies. Relapsing-remitting MS was the most common disease subtype, consistent with the MS profile in the general population (Morrow et al., 2003). Three studies recruited participants with at least mild depression symptomology as measured by the BDI (Boeschoten et al., 2017; Cooper et al., 2011) or the Patient Health Questionnaire-8 (Tietjen et al., 2018). Half (53%) of the participants in the Fischer et al. (2015) study had mild or greater scores on the BDI at baseline, while participants of the remaining studies generally reported low and non-clinical levels of depression at baseline, as measured by the HADS. Both the intervention and control groups were comparable on key sample parameters.

Risk of Bias Assessment

Selection and performance biases were minimised by using computer software programs to generate the random allocation sequence and by concealing the group allocation process from research personnel (see Figure 2 and Appendix D for individual study ratings). Attrition bias was also addressed, with studies typically reporting low (<10%) attrition rates and/or appropriate statistical analyses to account for missing data (i.e. intention-to-treat analyses, linear mixed model analyses). A single study (Moss-Morris et al., 2012) removed data for five control participants who erroneously accessed the online intervention, and thus adhered to a per protocol analysis. Tietjen et al. (2018) also used a per protocol analysis, while Pilutti et al. (2014) and Motl et al. (2017) followed a complete case analysis in which only participants who completed follow-up testing were included in the primary analysis (Joseph, Sim, Ogollah, & Lewis, 2015). Detection bias was a risk for all studies: participants were aware of their group allocation and they provided self-reported outcome data. Finally, reporting bias was minimised by adhering to pre-designed study protocols and registering trials prior to participant enrolment. In summary,

all nine studies were identified as having 'some concerns' in one or more RoB domains, however no studies were excluded due to reporting quality.

Intervention Characteristics

The online interventions were typically brief, ranging from four to 12 modules which were accessed over five weeks to six months (median length = 8 weeks). Three studies measured follow-up effects at 4 months (Boeschoten et al., 2017), 21 weeks (Cooper et al., 2011) and 24 weeks (Pöttgen et al., 2018) post-randomisation. Individual modules were estimated to take up to 60 minutes to complete. Although studies recommended that participants complete one module per week, extra time (if required) was allowed. Treatment adherence was assessed by usage time or the number of modules completed; data tracked through the intervention website. Few participants completed all modules, although the majority completed over half the program content and were considered treatment 'completers'. The mean attrition rate was a low 15% (SD = 9.39), although this varied considerably across studies (range: 7%-39%).

The online programs varied in their intervention targets, which included symptoms of depression ($N_{studies}$ = 4) and MS-related fatigue ($N_{studies}$ = 3) but also activity goals (i.e. increased physical exercise; $N_{studies}$ = 2). Six studies evaluated interventions that were either modified for users with MS ($N_{programs}$ = 2) or specifically designed for this cohort ($N_{programs}$ = 2). For example, Boeschoten et al. (2017) tailored an existing online intervention ("Worry Less") by providing information about MS and its psychosocial consequences, and ensuring text and examples were disease-specific (Boeschoten et al., 2012). Motl et al. (2017) and Pilutti et al. (2014) modified their online interventions for physical activity behaviour based on the research team's experience with this patient group, in addition to focus group feedback and formative evaluation from pilot testing. Their modified content included written material about the benefits of activity for people

with MS, and supplementary videos of persons with MS discussing their experiences with exercise and increased activity (Motl et al., 2017; Pilutti et al., 2014). In a series of studies by Moss-Morris et al. (2012) and colleagues (van Kessel, Wouldes, and Moss-Morris, 2016) on the effectiveness of "MSInvigor8", a program targeting MS-related fatigue, tailored content on MS fatigue was designed in consultation with consumers. Similarly, the ELEVIDA program for MS-related fatigue used in the study by Pöttgen et al. (2018) was designed via focus groups with patients, physicians and psychologists in addition to interview feedback from prototype users. Five studies (Cooper et al., 2011; Fischer et al., 2015; Moss-Morris et al., 2012; Pöttgen et al., 2018; van Kessel et al., 2016) even customised their content to the individual participant, either through participant self-selection or by tailoring content based on participants' responses as they worked through the online modules. The evaluated interventions were informed by evidence-based theoretical frameworks, namely cognitive behavioural strategies (e.g. behavioural activation, cognitive modification, mindfulness, relaxation and problem solving; $N_{studies} = 7$). Two studies (Motl et al., 2017; Pilutti et al., 2014) were informed by Bandura's (2004) Social Cognitive Theory (SCT), the aim being to promote behavior change through incremental, achievable goals which are self-monitored and reinforced.

Module format varied, with written educational material ($N_{studies} = 9$) usually supplemented with video-audio material ($N_{studies} = 5$), homework activities ($N_{studies} = 5$), case examples ($N_{studies} = 3$), and simulated dialogue - or the imitation of real conversation through scripts based on multiple-choice options ($N_{studies} = 2$). Other interactive features included activity trackers ($N_{studies} = 2$), discussion forums ($N_{studies} = 2$), and automated emails ($N_{studies} = 2$). The online interventions evaluated by Motl et al. (2017) and Pilutti et al. (2014) included a

behavioural component which required participants to monitor physical activity via pedometers and an online tracker feature which facilitated weekly reporting over six months.

Therapist support was integrated in five studies. This included support from a psychologist or supervised postgraduate psychology student ranging from brief weekly emails (Boeschoten et al., 2017; van Kessel et al., 2016), to three 30-60-minute telephone sessions (Moss-Morris et al., 2012), or up to 15 one-on-one video chats (Motl et al., 2017; Pilutti et al., 2014). Cooper et al. (2011) reported that technical advice was provided but no therapeutic support was offered. Tietjen et al. (2018) provided weekly email or phone prompts, although their function was solely around facilitating treatment adherence and addressing questions or concerns. Four studies also specified that clinicians could be contacted for additional support (Boeschoten et al., 2017; Motl et al., 2014; Tietjen et al., 2018) or monitored self-reported depression outcome scores (Cooper et al., 2011), although the extent of requested support provided was not detailed.

Five studies evaluated participants' satisfaction with the intervention using questionnaires (Boeschoten et al., 2017; Fischer et al., 2015; Motl et al., 2017; Tietjen et al., 2018) or qualitative feedback (Cooper et al., 2011; Moss-Morris et al., 2012). Participants generally reported strong satisfaction with the online programs and indicated they would recommend this type of treatment to others with MS and depression. Some participants reported technical difficulties, and some thought further modifications were necessary to meet the needs of people with MS.

Control Conditions

Control conditions consisted of wait list or medical treatment and care as usual. The exception was the study by van Kessel et al. (2016), which compared an online program, MSInvigor8, with and without email support.

Intervention Effectiveness

Depression. All nine studies examined the effectiveness of online CBT or SCT on depression symptoms, as per the requirements of this review (see Table 3). Of these, four demonstrated significant and medium to very large and positive effects (Cooper et al., 2011; Fischer et al., 2015; Moss-Morris et al., 2012; Tietjen et al., 2018). Notably, these effect estimates were associated with wide confidence intervals, likely due to large within-study variability in individual responses. The remaining five studies (Boeschoten et al., 2017; Motl et al., 2017; Pilutti et al., 2014; Pöttgen et al., 2018; van Kessel et al., 2016) reported a non-significant trend for intervention participants to perform better than controls. The associated N_{fs} values suggest that these collective findings may, however, be characterized by publication bias.

As seen in Table 4, continued effects, ranging from 16 to 24 weeks post-randomisation, were measured by three studies (Boeschoten et al., 2017; Cooper et al., 2011; Pöttgen et al., 2018). No significant group differences were noted. These findings were also associated with low N_{fs} values ($N_{fs} \leq 3$), suggesting that the findings need to be interpreted cautiously.

Anxiety. Six studies assessed anxiety, either with the HADS or the Beck Anxiety Inventory (BAI; Table 3). A single study reported a sizeable and significant effect in favour of online CBT (Moss-Morris et al., 2012), although the N_{fs} was not robust. The associated wide confidence interval may likely reflect the small sample size (N = 40).

Only two studies (Boeschoten et al., 2017; Pöttgen et al., 2018) examined the longer-term effects of online CBT (Table 4). Changes that had initially been reported by participants immediately after completing the online intervention were not sustained at 4 to 6 months follow-up, although the Nfs values were very low.

Quality of Life. Five studies, using six generic or disease-specific quality of life measures, reported non-significant short-term effects (Table 3). The large effect noted by Cooper (2011) did not reach significance due to their underpowered sample (N = 8). Of these studies, three provided follow-up data at 4 to 6 months, with all reporting non-significant results. The low Nfs values indicate that further research is needed to confirm these findings.

Distress. A single study measured disease related emotional distress using the Health Distress Scale (Table 3). Tietjen et al. (2018) reported a large effect in favour of their online intervention, Think Clearly About Depression, although this estimate may not be precise given the wide confidence interval, which ranged from small (g = 0.26) to very large (g = 3.18).

Self-efficacy. Two studies measured disease-specific and general self-efficacy outcomes, with markedly different results (Table 3). Tietjen et al. (2018) provided outcome data for eight subscales of the Chronic Disease Self-Efficacy Scale. Large and significant group differences were noted for the "social/recreational" subscale: intervention participants reported greater confidence in undertaking these activities. However, Boeschoten et al. (2017) reported comparable effects for their intervention and wait-list control groups on the Pearlin Mastery Scale. Follow-up data were provided by Boeschoten et al. (2017; Table 4). A moderate significant effect size was found in favour of the wait-list control at 4-month follow-up; an improvement that had not been noted earlier on (immediately post-intervention).

Problem-solving. Boeschoten et al. (2017) was the only study to provide short- and longer-term data for three subscales of the Social Problem-Solving Inventory (see Tables 3 and 4), all of which were non-significant.

Discussion

The current findings provide some evidence that online interventions may be more effective than standard care or being on a wait list in promoting mental health outcomes, including improved affect (depression, anxiety, distress) and a stronger belief that lifestyle changes are possible (greater self-efficacy) in persons with MS. However, the extent to which these interventions lead to sustained improvements (i.e. 4 months) could not be confirmed; with few studies providing these data and only one reporting significant results (Boeschoten et al., 2017). Included studies were also limited by small sample sizes and the use of passive control groups.

These heterogeneous findings are consistent with earlier systematic reviews, which offer tentative short-term evidence in favour of online interventions for comorbid depression in chronic illness populations (Charova et al., 2015; Mehta et al., 2019). The noted changes to self-efficacy are also consistent with suggestions that consumers who access internet-based interventions, particularly interventions that are focused on self-management, are likely to attribute treatment gains to themselves, compared to peers who engage in face-to-face or pharmaceutical treatment (Andersson, 2016). Indeed, the majority of the studies that reported significant between-group differences across the examined psychological outcomes were self-guided in nature (Cooper et al., 2011; Fischer et al., 2015; Tietjen et al., 2018). The single study which directly compared a therapist- versus self-guided intervention reported no significant group differences, over time, in depression ratings (van Kessel et al., 2016). However, depression was not the primary symptom target in this study; rather the primary target was fatigue (van Kessel et al., 2016). Furthermore, attrition rates were higher in the self-guided group (55%) compared to the therapist-guided group (21%), suggesting that therapist guidance

alongside online interventions can improve treatment adherence (Cooper et al., 2011; Fischer et al., 2015; Tietjen et al., 2018). Further comparative research is therefore needed to examine the potential critical differences in the delivery of online interventions, including the degree to which therapist input moderates symptom change.

The contribution of targeted versus generic online interventions also requires further evaluation. It is argued that disease-specific modifications to psychological interventions are pertinent for people with MS given the role that their incurable condition plays in their depression (Hind et al., 2010; Johansson et al., 2012). However, the studies which produced the largest group differences in depression involved interventions that were not specifically tailored for users with MS (Cooper et al., 2011; Fischer et al., 2015; Tietjen et al., 2018). Notably these same three studies did target depression as the primary symptom, suggesting that depression-specific content may play a more vital role in program success than MS-specific content.

Interestingly, the current findings failed to support the efficacy of online interventions for quality of life and problem-solving skills, as secondary outcomes. More in depth and individualised treatment may be required before changes in multidimensional constructs are demonstrated. Certainly, Pöttgen et al. (2018) reported sustained improvements on some subscales of the Hamburg Quality of Life Questionnaire for Multiple Sclerosis (fatigue, thinking) but not others (mobility, mood, communication), highlighting the intricacies of such constructs. MS is also a complex condition, involving transitions along a continuum of care. Consequently, those living with this disease may require ‘booster’ sessions to reinforce behavior-change as their disease evolves or progresses (Haselkorn et al., 2015).

Limitations

The current findings need to be considered in the context of several methodological limitations encountered during data extraction and analysis for this review. The majority of included studies incorporated a wait-list or treatment-as-usual control. Notably, the latter often reflects no treatment given the low help-seeking nature of the MS population (Cooper et al., 2011). Wait-list controls often result in the largest trial effect sizes; however, they do not provide insight into confounding factors that may influence outcomes, such as increase in activity or symptom attention (Boeschoten et al., 2017; Mehta et al., 2019). Active comparator groups, such as in the study by van Kessel et al. (2016) which examined the unique effects of email-based support for their 8-module 'MS Invigor8' program, are necessary for demonstrating the features of online interventions that are essential to their effectiveness.

While the inclusion of RCTs, the most robust research protocol for evaluating intervention efficacy, is a strength of the current review, external validity remained compromised (Spring, 2007). As an emerging area of research, available studies are limited to pilot and feasibility studies which are typically characterised by small sample sizes. These studies are often underpowered to detect significant intervention effects and may even inflate noted effects (Button et al., 2013). Furthermore, many of the included studies restricted eligibility to participants with reduced MS symptom burden (e.g. relapse free for 30 days; Motl et al., 2017) or disability (Cooper et al., 2011). Several studies also cited low depression at baseline as possible explanations for their non-significant results (Pöttgen et al., 2018; van Kessel et al., 2016). Consequently, the current findings cannot be generalised to those with poor mental health, a profile that is characteristic of at least 50% of patients with MS (Proctor et al., 2018).

Lastly, few studies adhered to intention-to-treat (ITT) analysis; the recommended approach for evaluating the efficacy of psychological therapies (Schnurr, 2007). An ITT approach analyses outcome data according to participants' initial group assignment, thus maintaining the benefits of the initial random allocation (Gordis, 2014). Alternative methods, such as the per-protocol and complete case analyses, only include data from participants who complete the study. This may lead to an overestimation of treatment effects, as adherent patients generally perform better than non-adherents who are no longer represented in the sample (Ten Have et al., 2008).

Conclusion

Overall, the preliminary findings are promising: online psychological-based interventions appear to promote short-term improvements in self-reported depression and anxiety symptoms for persons with MS. Secondary benefits to perceived distress and self-efficacy were also noted. However, follow up assessments of at least one year are needed to establish whether the observed positive effects are sustained in the longer-term. Controlled trials with larger sample sizes and more detailed monitoring of adherence to, and satisfaction with, online interventions are an important next-step.

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Declaration of conflicting interests

None declared.

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Tables

Table 1

Study Characteristics

Lead author (date)	Sample				Psychological Measures	Online Intervention				Control condition
	Total [a]	I	C	Country		Attrition (%) [b]	Framework	Target symptom/behaviour (Program name)	Contact time	
Boeschoten (2017)	171	85	86	Netherlands	BDI, HADS, BAI, MSIS, SPSI-R, EuroQol, PMS	11.00	CBT	Depression (Worry Less)	5 modules + weekly email support over 5-10 weeks	Wait list
Cooper (2011)	24	12	12	UK	BDI, MSIS	12.50	CBT	Depression (Beating the Blues)	8 modules x 50 mins over 8 weeks	Treatment as usual
Fischer (2015)	90	45	45	Germany	BDI, WHO-QoL, HAQUAMS	21.11	CBT	Depression (Deprexis)	10 modules x 60 mins over 9 weeks	Wait list
Moss-Morris (2012)	40	23	17	UK	HADS	7.50	CBT	Fatigue (MS Invigor8)	8 modules x 25-50 mins + 3 x 30-60 mins telephone sessions over 8-10 weeks	Treatment as usual
Motl (2017)	47	23	24	US	HADS	8.51	SCT	Physical activity	4 modules + 13 video chats over 6 months	Wait list
Pilutti (2014)	82	41	41	US	HADS, MFIS, MSIS	7.32	SCT	Physical activity	4 modules + 15 video chats over 6 months	Wait list
Pöttgen (2018)	275	139	136	Germany	HADS, HAQUAMS	18.55	CBT, mindfulness	Fatigue (ELEVIDA)	1-2 modules per week over 12 weeks	Wait list
Tietjen (2018) Wilson (2018) [c]	47	11	36	US	PHQ-8, Health Distress Scale, CDSES	11.32 [d]	CBT	Depression (Think Clearly About Depression)	4 modules over 8 weeks	Treatment as usual
van Kessel (2016)	39	19	20	New Zealand	HADS	38.46	CBT	Fatigue (MS Invigor8)	8 modules x 25-50 mins + weekly email correspondence	MS Invigor8 (no email support)

[a] number of participants allocated to groups at baseline; I = Online Intervention; C = control or comparison group; [b] percentage who did not complete post-treatment (Time 1) measurements; [c] primary study; [d] attrition rate of primary study; CBT= Cognitive Behaviour Therapy; SCT= Social Cognitive Theory; TAU= treatment as usual. Measure abbreviations: BDI= Beck Depression Inventory (includes 2nd edition), HADS = Hospital Anxiety and Depression Scales, BAI= Beck Anxiety Inventory, MSIS=Multiple Sclerosis Impact Scale, SPSI-R= Social Problem Solving Inventory-Revised, EuroQol= EuroQol Quality of Life measure, PMS= Pearlin Mastery Scale, WHO-QoL= World Health Organization Quality of Life Scale- Psychological Wellbeing subscale, HAQUAMS= Hamburg Quality of Life Questionnaire in Multiple Sclerosis- mood subscale, MFIS= Modified Fatigue Impact Scale- psychosocial subscale, PHQ-8= Patient Health Questionnaire-8, CDSES= Chronic Disease Self-Efficacy Scales.

Table 2

Sample Characteristics

			Online Intervention					Control		
Variable	$N_{studies}$	$N_{participants}$	Mean (SD)	Median	Range	$N_{studies}$	$N_{participants}$	Mean (SD)	Median	Range
Sample size	9	398	44.22 (39.91)	23	11-139	9	417	46.33 (37.98)	36	12-136
Age (in years)	9	398	45.71 (10.88)	45.36	40.14-52.30	9	417	46.01 (9.65)	45.70	41.81-51.40
Disease duration (in years)	6	352	10.77 (7.27)	9.76	4.78-21.00	6	345	10.50 (7.35)	10.25	5.12-16.00
			N (%)					N (%)		
Gender										
Female	9	398	318 (79.90)			9	417	332 (79.62)		
Male	9	398	80 (20.10)			9	417	85 (20.38)		
MS subtype										
Relapsing-remitting	7	364	228 (62.64)			7	357	238 (66.67)		
Progressive	7	364	105 (28.85)			7	357	87 (24.37)		
Not specified	7	364	25 (6.87)			7	357	28 (7.84)		
Benign	7	364	3 (0.82)			7	357	1 (0.28)		
Clinically isolated syndrome	7	364	3 (0.82)			7	357	3 (0.84)		

Note: $N_{studies}$ = number of studies; $N_{participants}$ = number of participants providing this data; SD = standard deviation.

Table 3

Short-Term Effects Associated With Online Interventions

Construct	Measure	$N_{studies}$	$N_{participants}$	Time	Framework	Analyses	*g*	95% CI		SE	*p*	N_{fs}	Lead author (date)
								L	U				
Depression	Patient Health Questionnaire-8	1	11	8	CBT	PP	**1.77**	**0.42**	**3.46**	**0.67**	**0.027***	8	Tietjen (2018)
	Hospital Anxiety Depression Scale	1	40	10	CBT	PP	**1.42**	**0.74**	**2.16**	**0.35**	**0.000***	6	Moss-Morris (2012)
		1	39	10	CBT	ITT	0.43	-0.20	1.08	0.32	0.182	1	van Kessel (2016)
		1	47	24	SCT	CC	0.39	-0.18	0.98	0.29	0.181	1	Motl (2017)
		1	82	24	SCT	CC	0.39	-0.04	0.83	0.22	0.080	1	Pilutti (2014)
		1	275	12	CBT, mindfulness	ITT	0.09	-0.15	0.32	0.12	0.475	1	Pöttgen (2018)
	Beck Depression Inventory	1	24	8	CBT	ITT	**1.04**	**0.20**	**1.95**	**0.42**	**0.022***	4	Cooper (2011)
		1	90	9	CBT	ITT	**0.50**	**0.08**	**0.92**	**0.21**	**0.022***	2	Fischer (2015)
		1	171	5-10	CBT	ITT	0.26	-0.04	0.57	0.15	0.088	0	Boeschoten (2017)
Anxiety	Hospital Anxiety Depression Scale	1	40	10	CBT	PP	**0.87**	**0.23**	**1.56**	**0.33**	**0.011***	3	Moss-Morris (2012)
		1	82	24	SCT	CC	0.39	-0.04	0.84	0.22	0.079	1	Pilutti (2014)
		1	47	24	SCT	CC	0.37	-0.21	0.96	0.29	0.208	1	Motl (2017)
		1	275	12	CBT, mindfulness	ITT	0.16	-0.08	0.40	0.12	0.189	0	Pöttgen (2018)
		1	171	5-10	CBT	ITT	0.09	-0.21	0.39	0.15	0.541	1	Boeschoten (2017)
		1	39	10	CBT	ITT	0.09	-0.55	0.73	0.31	0.781	1	van Kessel (2016)
	Beck Anxiety Inventory	1	171	5-10	CBT	ITT	0.26	-0.05	0.56	0.15	0.097	0	Boeschoten (2017)
Quality of life	Multiple Sclerosis Impact Scale												
	- Psychological	1	23	8	CBT	ITT	0.65	-0.18	1.54	0.41	0.129	2	Cooper (2011)
	- Total	1	171	5-10	CBT	ITT	0.09	-0.21	0.39	0.15	0.573	1	Boeschoten (2017)
	- Psychological	1	82	24	SCT	CC	-0.04	-0.48	0.39	0.22	0.841	1	Pilutti (2014)
	World Health Organisation-Quality of Life												
	- Psychological	1	90	9	CBT	ITT	0.32	-0.10	0.74	0.21	0.132	1	Fischer (2015)

Table 3 *(cont.)*

Construct	Measure	$N_{studies}$	$N_{participants}$	Time	Framework	Analyses	*g*	95% CI		SE	*p*	N_{fs}	Lead author (date)
								L	U				
Quality of life	Hamburg Quality of Life Inventory												
	- Mood	1	275	12	CBT, mindfulness	ITT	0.12	-0.12	0.36	0.12	0.318	0	Pöttgen (2018)
	- Mood	1	90	9	CBT	ITT	-0.04	-0.46	0.37	0.21	0.848	1	Fischer (2015)
	EuroQol-5D	1	171	5-10	CBT	ITT	-0.07	-0.37	0.23	0.15	0.664	1	Boeschoten (2017)
	Modified Fatigue Impact Scale												
	- Psychosocial	1	82	24	SCT		-0.04	-0.48	0.39	0.22	0.845	1	Pilutti (2014)
	EuroQol-Visual Analogue Scale	1	171	5-10	CBT	ITT	-0.02	-0.32	0.28	0.15	0.883	1	Boeschoten (2017)
Distress	Health Distress Scale	1	11	8	CBT	PP	**1.56**	**0.24**	**3.16**	**0.65**	**0.039***	7	Tietjen (2018)
Self-efficacy	Chronic Disease Self-Efficacy Scales												
	- Social/recreational activities	1	11	8	CBT	PP	**1.57**	**0.26**	**3.18**	**0.65**	**0.038***	7	Tietjen (2018)
	- Do chores	1	11	8	CBT	PP	1.25	-0.02	2.76	0.61	0.072	5	Tietjen (2018)
	- Exercise regularly	1	11	8	CBT	PP	0.70	-0.53	2.07	0.57	0.251	3	Tietjen (2018)
	- Manage disease	1	11	8	CBT	PP	0.63	-0.60	1.97	0.57	0.299	2	Tietjen (2018)
	- Help from community/family/friends	1	11	8	CBT	PP	0.42	-0.80	1.73	0.56	0.469	1	Tietjen (2018)
	- Communicate with physician	1	11	8	CBT	PP	0.18	-1.06	1.45	0.55	0.755	0	Tietjen (2018)
	- Manage symptoms	1	11	8	CBT	PP	0.31	-0.92	1.60	0.56	0.591	1	Tietjen (2018)
	- Manage shortness of breath	1	11	8	CBT	PP	-0.66	-2.01	0.57	0.57	0.280	2	Tietjen (2018)
	Pearlin Mastery Scale	1	171	5-10	CBT	ITT	0.06	-0.25	0.36	0.15	0.717	1	Boeschoten (2017)
Problem solving	Social Problem Solving Inventory												
	- Avoidance	1	171	5-10	CBT	ITT	0.18	-0.13	0.48	0.15	0.254	0	Boeschoten (2017)
	- Positive problem	1	171	5-10	CBT	ITT	0.14	-0.16	0.44	0.15	0.352	0	Boeschoten (2017)
	- Negative problem	1	171	5-10	CBT	ITT	0.12	-0.18	0.42	0.15	0.440	0	Boeschoten (2017)

$N_{studies}$ = number of studies providing this data; $N_{participants}$ = number of participants providing this data; Time = assessment interval (in weeks from baseline); *g* = effect size Hedges' *g*; SE = standard error of *g*; CI = confidence interval; L = lower limit; U = upper limit; N_{fs} = fail-safe N; CBT= Cognitive Behaviour Therapy; SCT= Social Cognitive Theory; ITT = intention-to-treat; PP = per-protocol; CC = complete case.

Table 4

Longer-Term Effects Associated With Online Interventions

Construct	Measure	$N_{studies}$	$N_{participants}$	Time	Framework	Analyses	*g*	95% CI		SE	*p*	N_{fs}	Lead author (date)
								L	U				
Depression	Beck Depression Inventory	1	24	21	CBT	ITT	0.79	-0.03	1.67	0.41	0.067	3	Cooper (2011)
		1	171	16	CBT	ITT	0.05	-0.25	0.35	0.15	0.762	1	Boeschoten (2017)
	Hospital Anxiety Depression Scale	1	275	24	CBT, mindfulness	ITT	0.13	-0.11	0.37	0.12	0.280	0	Pöttgen (2018)
Anxiety	Hospital Anxiety Depression Scale	1	275	24	CBT, mindfulness	ITT	0.18	-0.06	0.41	0.12	0.145	0	Pöttgen (2018)
		1	171	16	CBT	ITT	0.03	-0.27	0.33	0.15	0.838	1	Boeschoten (2017)
	Beck Anxiety Inventory	1	171	16	CBT	ITT	0.11	-0.19	0.41	0.15	0.464	0	Boeschoten (2017)
Quality of life	Multiple Sclerosis Impact Scale												
	- Psychological	1	23	21	CBT	ITT	0.37	-0.46	1.23	0.41	0.368	1	Cooper (2011)
	- Total	1	171	16	CBT	ITT	0.01	-0.29	0.31	0.15	0.953	1	Boeschoten (2017)
	EuroQol-5D	1	171	16	CBT	ITT	-0.23	-0.53	0.07	0.15	0.130	0	Boeschoten (2017)
	Hamburg Quality of Life Inventory												
	- Mood	1	275	24	CBT, mindfulness	ITT	0.12	-0.12	0.36	0.12	0.318	0	Pöttgen (2018)
	EuroQol-Visual Analogue Scale	1	171	16	CBT	ITT	-0.11	-0.41	0.19	0.15	0.464	0	Boeschoten (2017)
Self-efficacy	Pearlin Mastery Scale	1	171	16	CBT	ITT	**-0.41**	**-0.72**	**-0.11**	**0.15**	**0.008***	1	Boeschoten (2017)
Problem solving	Social Problem Solving Inventory												
	- Positive problem	1	171	16	CBT	ITT	-0.23	-0.53	0.07	0.15	0.138	0	Boeschoten (2017)
	- Avoidance	1	171	16	CBT	ITT	-0.11	-0.41	0.20	0.15	0.493	0	Boeschoten (2017)
	- Negative problem	1	171	16	CBT	ITT	-0.08	-0.38	0.22	0.15	0.607	1	Boeschoten (2017)

$N_{studies}$ = number of studies; $N_{participants}$ = number of participants providing this data; Time = assessment interval (in weeks from baseline); *g* = effect size Hedges' *g*; SE = standard error of *g*; CI = confidence interval; L = lower limit; U = upper limit; N_{fs} = fail-safe N; CBT= Cognitive Behaviour Therapy; ITT = intention-to-treat.

Figures

Figure 1

PRISMA Flow Diagram of Study Selection Process (Moher et al., 2009)

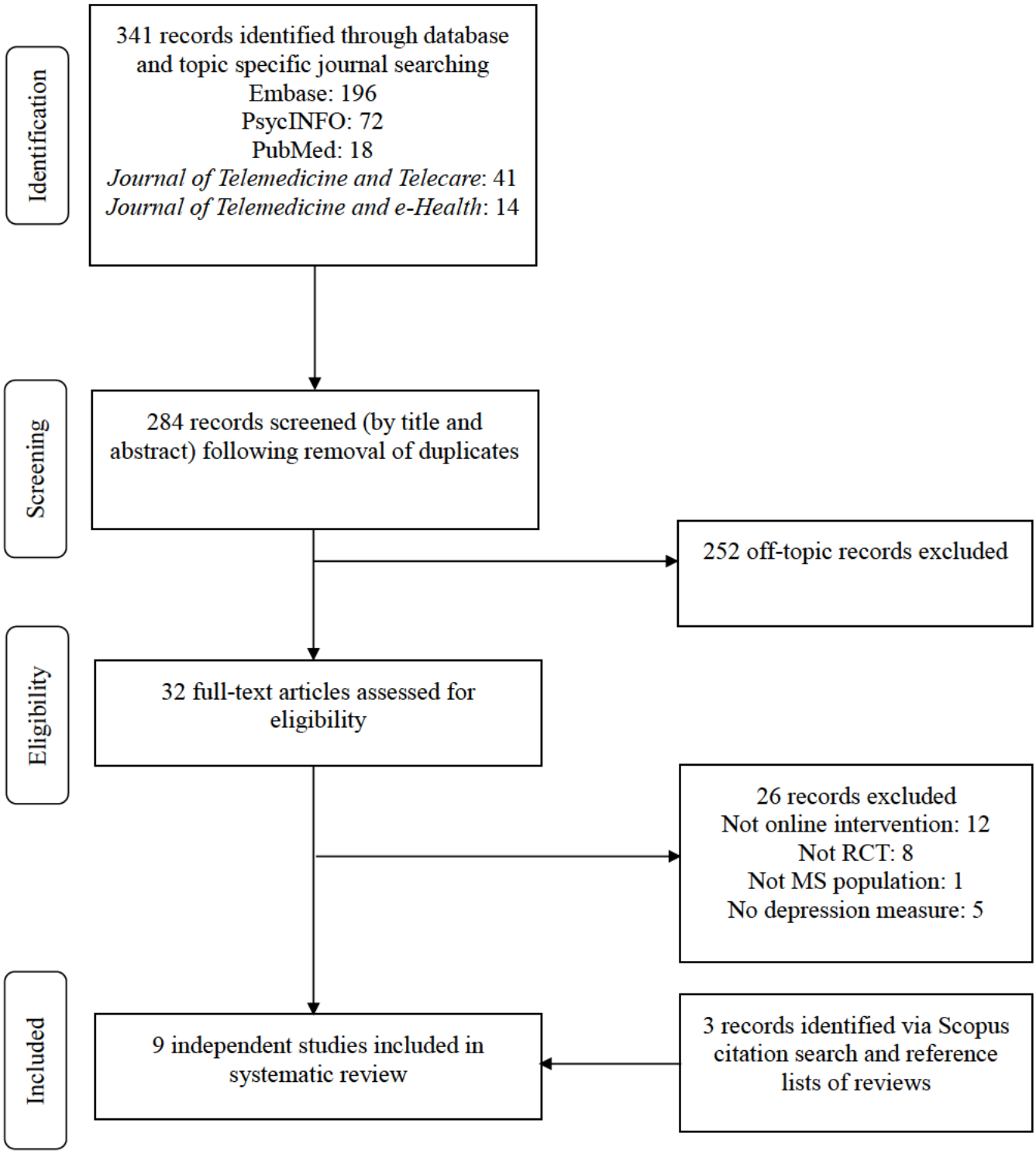
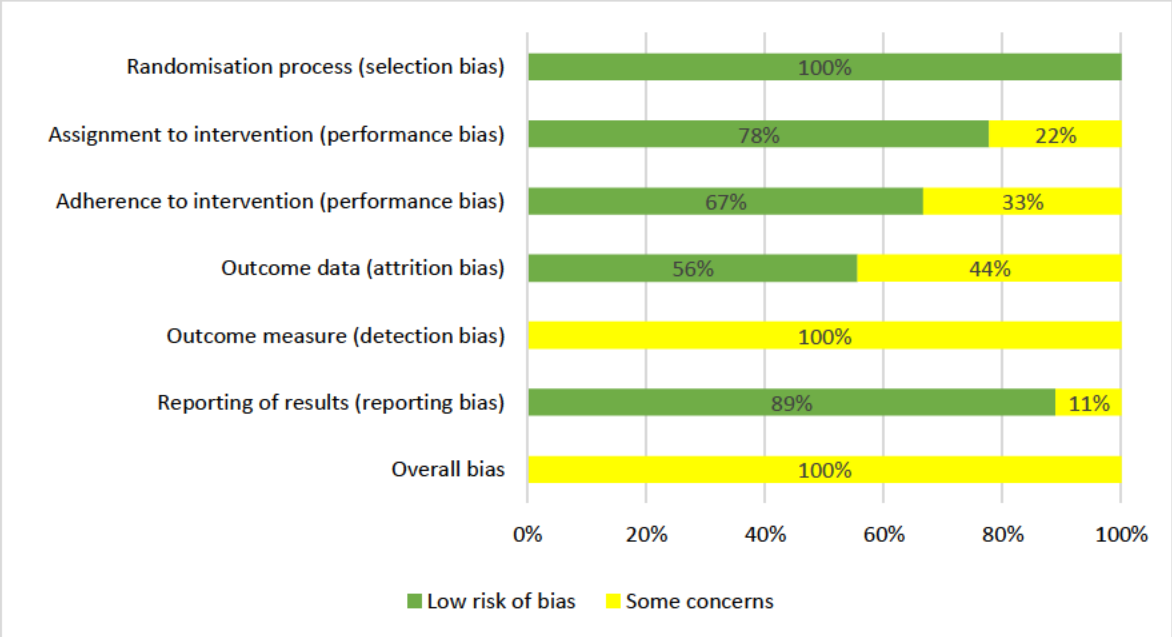


Figure 2

Cochrane Risk of Bias Evaluation across Included Studies



Appendix A

Example of keywords and Boolean (logical) operators used in database search of PsycINFO

Depression	MS	Telecounselling
major depression.sh OR depression.tw OR depressed.tw OR depressive.tw OR dysthymic disorder.sh OR dysthym*.tw OR sadness.sh OR melanchol*.tw	multiple sclerosis.sh OR multiple sclerosis.tw OR disseminated sclerosis.tw	internet.sh OR internet.tw OR web-based.tw OR websites.sh OR website*.tw OR telemedicine.sh OR tele-med*.tw OR telemed*.tw OR telepsych*.tw OR tele-psych*.tw OR telecare.tw OR tele-care.tw OR remote consult*.tw OR emental.tw OR e-mental.tw OR exp electronic communication OR informatic*.tw OR computer-assisted therapy.sh OR computer assisted therap*.tw OR computer mediated.tw OR online therapy.sh OR online.tw OR e-health.tw OR ehealth.tw OR mhealth.tw OR m-health.tw OR world wide web.tw OR telecounsel*.tw OR tele-counsel*.tw OR telehealth.tw OR tele-health.tw OR telerehabilitat*.tw OR tele-rehabilitat*.tw OR cyber-counsel*.tw OR cybercounsel*.tw OR e-therap*.tw OR etherap*.tw OR tele-therap*.tw OR teletherap*.tw OR telecommunications media.sh OR tele-communicat*.tw OR telecommunicat*.tw OR teleconferencing.sh OR teleconferenc*.tw OR tele-conferenc*.tw OR tele-consult*.tw OR teleconsult*.tw OR technology.tw OR text-based.tw OR text-messag*.tw OR mobile phone*.tw OR smartphone*.tw OR exp mobile devices OR mobile device*.tw OR

		handheld device*.tw OR cell phone*.tw OR cellular phone*.tw OR app.tw OR apps.tw OR patient portal*.tw OR computer assisted instruction.sh OR computer assisted instruct*.tw OR distance counsel*.tw OR blog*.tw OR distance education.sh OR distance educat*.tw OR distance learn*.tw OR social media.tw OR webcast*.tw OR web cast*.tw OR videotape record*.tw OR video record*.tw OR videorecord*.tw OR skype.tw OR e-learn*.tw OR elearn*.tw OR e-mail*.tw OR videoconferenc*.tw OR video-conferenc*.tw

Appendix B

PRISMA checklist for current systematic review (Moher et al., 2009)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	25
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	26
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	30
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	30
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	31-32
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	30-31
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	62-63
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	30-32
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	32-33
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	31-32
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	33
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	33-35
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	33
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	35, 60
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	35
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	36-37, 61, 68
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	40-41, 57-59
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	36-37, 61, 68
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	42-43
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	44-45
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	45
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	46

Appendix C

Validated Depression Measures for MS

- Beck Depression Inventory (BDI; includes 2nd edition; Beck, Steer, Ball, & Ranieri, 1996; Moran & Mohr, 2005)
- Hospital Anxiety and Depression Scales (HADS; Marrie et al., 2018; Zigmond & Snaith, 1983)
- Patient Health Questionnaire (PHQ-8; Kroenke, Spitzer, Williams, & Lowe, 2010; Patrick & Connick, 2019)
- Kessler Distress Scale (Marrie et al., 2018)
- Patient-Reported Outcomes Measurement Information System Emotional Distress Depression Short-Form 8a (PROMIS Depression; Marrie et al., 2018; Pilkonis et al., 2011)

References

Beck, A. T., Steer, R. A., Ball, R., & Ranieri, W. F. (1996). Comparison of Beck Depression Inventories-IA and-II in Psychiatric Outpatients. *Journal of Personality Assessment, 67*, 588-597.

Kroenke, K., Spitzer, R. L., Williams, J. B., & Lowe, B. (2010). The patient health questionnaire somatic, anxiety, and depressive symptom scales: a systematic review. *Gen Hosp Psychiatry, 32*(4), 345-359. doi:10.1016/j.genhosppsych.2010.03.006

Marrie, R. A., Zhang, L., Lix, L. M., Graff, L. A., Walker, J. R., Fisk, J. D., . . . Bernstein, C. N. (2018). The validity and reliability of screening measures for depression and anxiety

disorders in multiple sclerosis. *Mult Scler Relat Disord, 20*, 9-15. doi:10.1016/j.msard.2017.12.007

Moran, P. J., & Mohr, D. C. (2005). The validity of Beck depression inventory and Hamilton rating scale for depression items in the assessment of depression among patients with multiple sclerosis. *J Behav Med, 28*, 35-41.

Patrick, S., & Connick, P. (2019). Psychometric properties of the PHQ-9 depression scale in people with multiple sclerosis: A systematic review. *PLoS One, 14*(2), e0197943. doi:10.1371/journal.pone.0197943

Pilkonis, P. A., Choi, S. W., Reise, S. P., Stover, A. M., Riley, W. T., & Cella, D. (2011). Item banks for measuring emotional distress from the patient-reported outcomes measurement information system (PROMIS(R)): depression, anxiety, and anger. *Assessment, 18*(3), 263-283.

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica, 67*, 361-370.

Appendix D

Evaluation of individual studies using Cochrane Risk of Bias Tool (Savovic et al., 2017)

Lead author (date)	Randomisation process (selection bias)	Intended intervention (performance bias)		Outcome data (attrition bias)	Outcome measure (detection bias)	Reporting of results (reporting bias)	Overall bias
		Assignment	Adherence				
Boeschoten (2017)							
Cooper (2011)							
Fischer (2015)							
Moss-Morris (2012)							
Motl (2017)							
Pilutti (2014)							
Pöttgen (2018)							
Tietjen (2018)							
van Kessel (2016)							

Low risk of bias	
Some concerns	

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- a statement that the paper has been seen and approved by all authors

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After the abstract, please supply up to five keywords.

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