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REVIEW ARTICLE

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Online psychological interventions to improve symptoms in multiple sclerosis: A systematic review

Brenda Montañés-Masias[1] | Judit Bort-Roig[2] | Juan Carlos Pascual[3,4,5] | Joaquim Soler[3,4,5] | Laia Briones-Buixassa[1]

[1]Research group in Mental Health and Social Innovation (SaMIS), Centre for Health and Social Care Research, Universitat de Vic – Universitat Central de Catalunya, Vic, Catalonia, Spain

[2]Sport and Physical Activity Research Group, Centre for Health and Social Care Research, Universitat de Vic – Universitat Central de Catalunya, Vic, Catalonia, Spain

[3]Department of Psychiatry, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[4]Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Institut de Recerca Biomèdica Sant Pau (IIB-Sant Pau), Barcelona, Spain

[5]Department of Psychiatry and Forensic Medicine & Institute of Neurosciences, Universitat Autònoma de Barcelona, Bellaterra, Spain

Correspondence
Judit Bort-Roig, Sport and Physical Activity Research Group, Centre for Health and Social Care Research, Universitat de Vic – Universitat Central de Catalunya Vic, Catalonia, Spain.
Email: judit.bort@uvic.cat

The aim of this systematic review was to assess the effectiveness of Internet-based psychological interventions in the treatment of physical, socio-affective and cognitive symptoms and quality of life (QoL) in people with multiple sclerosis (pwMS) to provide currently available evidence.

Systematic searches for eligible studies were carried out in four databases (August 2021) using key words. Studies were screened, data extracted, quality appraised and analysed by three independent reviewers, using predefined criteria and following the PRISMA rules. Study quality was assessed using Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields QUALSYST tool. Physical, socio-affective and cognitive symptoms and QoL were the primary outcomes.

Thirteen studies were included. Two principal approaches were reported: Cognitive behavioural therapy (CBT) and mindfulness-based interventions (MBI). Interventions varied from tailored versions to videoconference by a clinician, duration mean 8 weeks, delivered via individually and groups, all online. The review found that iCBT interventions were effective for improve depression, anxiety, fatigue and QoL, and slightly in cognitive functioning in pwMS, whereas MBI interventions reported benefits in depression, anxiety, stress and QoL, and less evidence in fatigue. Generally, study quality was acceptable in most studies; eleven of the studies scored a low risk of bias on all items in the Qualsyst Tool, whereas only two studies were considered unacceptable.

Psychological online interventions may improve physical, socio-affective and cognitive symptoms as well as QoL in pwMS, overcoming the face-to-face barriers (i.e. disability). Contact with the therapist and groups sessions have been identified as enablers of the online interventions. Nevertheless, the limited number of studies and the heterogeneity of health outcomes reported made difficult to afford robust conclusions on psychological intervention effects in pwMS.

KEYWORDS
multiple sclerosis, online intervention, psychological therapy, quality of life, symptoms

1 | INTRODUCTION

Multiple sclerosis (MS) is a chronic and progressive inflammatory autoimmune disorder of the central nervous system.[1] MS is a relatively common neurological disease that affects approximately 1–2 per 1000 individuals. It usually begins between the ages of 20 and 40 and affects mostly women with a 3:1 ratio.[2,3] The clinical course of the disease is highly variable, although it is common to manifest as outbreaks associated with clinical signs of neurological dysfunction with full or partial recovery. This type of MS is called relapsing–remitting (RRMS) and affects 85%–90% of people with MS (pwMS).[4] After an average of 10–20 years, most people transition to another type of MS called secondary progressive (SPMS), which is characterized by a gradual worsening between relapses.[4] There are also two more types that represent around 15% of patients: primary progressive MS (PPMS), which is characterized by experiencing disability progression without relapses, and progressive relapsing MS (PRMS), which combines relapses and disability progression from the beginning.[4]

MS patients suffer from a variety of physical, socio-affective and cognitive symptoms. The main physical symptoms are fatigue, poor balance, impaired speech, bladder and bowel dysfunction, chronic pain and spasms,[5] while the main socio-affective symptoms are depression, stress, anxiety and sleep disturbance, which are associated with lower quality of life (QoL).[6,7] Cognitive alterations are also common, mainly in attention, memory, processing speed, executive function and visuospatial processing.[8]

To date, there is no cure for MS, but there are a number of treatments available. A recent review[9] defended a multifaceted approach for an effective management and recommend the use of drugs as first-line treatment for many patients with early MS. In general, the goals of the treatment are intended to accelerate recovery after an outbreak, slow disease progression down, manage symptoms and improve the QoL.[9,10] In the same line, another review[11] also defended medication are more effective in the early stages of disease, and the most used medication is disease-modifying therapies (DMTs), which can reduce the number and severity of relapses, and slow down the damage caused by relapsing MS that builds up over time.[11]

Although MS drugs have shown reliable good results, they are not suitable for all the patients. A proper monitoring has to be provided, and they have multiple side effects including chest pain, chills, cough, fever, flu-like symptoms, headache, nausea, pain, trouble breathing and unusual fatigue weakness, among others.[12] Moreover, the literature suggests that pwMS are not adequately treated for their mood disorders (i.e. anxiety and depression) and for other symptoms, such as fatigue and pain.[13] In this regard, psychological interventions may improve the psychological and physical well-being of pwMS by treating mood disorders, improving self-management and adherence, reducing stress, and improving coping skills to cope with emotions and thoughts, and QoL.[13] In addition, psychological group therapy may contribute to improving acceptance, facilitating the expression of emotions related to the disease and providing peer support.

Cognitive behavioural therapy (CBT) is the most commonly used approach and has shown effectiveness in reducing depression, anxiety and stress, and improving cognitive functioning and the management of symptoms such as pain and fatigue.[12,13]

Another psychological intervention that has shown encouraging results and is in increasingly used healthcare is mindfulness-based interventions (MBIs),[14] which are complex interventions based on paying attention to the present moment with a non-judgmental attitude.[15] Several studies have reported that MBIs can help people adjust to chronic illness and to relate to their symptoms more positively.[16,17] MBI have considerable evidence as a potential treatment for anxiety and depression, as well as fatigue, pain and improving QoL in pwMS.[16,17] However, despite these promising results, many pwMS are unable to access these interventions due to limited mobility, fatigue and related issues, costs associated with travel and limited access to services.[10] In addition, the ongoing global pandemic makes it even more difficult to access psychological services and receive support. In such circumstances, online intervention is good option to overcome many of these barriers.[18] Several studies have evaluated Internet-based interventions and suggest that they were feasible and effective in various neurological disorders.[19]

Some studies demonstrated that online psychological interventions had potential benefits on physical, socio-affective and cognitive symptoms in pwMS.[7,20,21] However, less is known in pwMS with respect to (a) their efficacy compared to face-to-face intervention; (b) which psychological interventions (CBT, MBI) are more effective in Internet-based format; (c) which symptoms improve; and (d) which is the most efficient format (web-based, video conferencing, app) to carry out the intervention. Therefore, the primary aim of this systematic review was to examine the impact of online psychological interventions to improve physical, socio-affective, cognitive symptoms and QoL in pwMS. As a secondary aim, we analyse the mode of delivery of those interventions to explore the most efficient format to design online interventions in a future.

2 | METHODS

2.1 | Design

A systematic review was developed considering the PRISMA statements.[22] The protocol has been registered in the National Institute for Health Research (NHS) on PROSPERO (International Prospective Register of Systematic Reviews) database: CRD42021266181.

2.2 | Search strategy and selection criteria

The search strategy was carried out in August 2021 (Pubmed, Web of Knowledge, Psycinfo and Scopus). Research for eligible studies was conducted from the earliest available ones to the most recent. We performed a keyword search using the terms ("Multiple Sclerosis" OR "Disseminated Sclerosis" OR "MS" OR "Sclerosis,

Multiple" OR "Disseminated, Sclerosis") AND ("therapy" OR "intervention" OR "program" OR "treatment") AND ("Mindfulness" OR "CBT" OR "psychology" OR "Cognitive behavioural therapy" OR "mental health") AND ("internet" OR "online" OR "website" OR "virtual").

The eligibility of the studies was formulated according to the following criteria: that (i) they were focused on the adult population (over 18 years); (ii) the participants were diagnosed with MS by a neurologist; (iii) they were psychological intervention studies; (iv) the programme was mainly online (more than 50%); (v) they reported effectiveness on physical (e.g. pain), socio-affective (e.g. depression and anxiety) and/or cognitive symptoms (e.g. attention) and/or QoL; and (vi) the language of the study was French, English or Spanish. The exclusion criteria were studies (i) where participants had another physical or neurological disorder; (ii) in which interventions were fully provided via telephone; (iii) that evaluated only acceptance or satisfaction of the intervention; and (iv) grey literature (e.g. these editorials). Studies that involved participants with other diagnoses or neurological conditions where data were specifically provided for pwMS were included. To attain additional eligible articles, reference lists of located studies and previous systematic reviews were checked.

To identify potentially eligible studies, two reviewers independently performed the selection of articles. Any disagreements were resolved through discussion among the reviewers. First, B.M-M identified records from the databases, and once duplicates and incomplete records were eliminated using management software (Mendeley), a list of articles that satisfied the eligibility criteria was compiled. Second, B.M-M and L.B-B performed the selection of articles by examining abstracts and subsequently screening full-text articles. Finally, a third author (J.B-R) was available to resolve any disagreement and revised full-text records that were in doubt.

2.3 | Data extraction

Extracted data included study characteristics (e.g. authors, age and country), diagnosis (e.g. type of MS and time since diagnosis), study design (e.g. RCT and pre–post measures), sample (e.g. *N*, mean age and gender), intervention (e.g. type, time and follow-up), main outcomes and measurement tools, and findings.

If relevant data were not included in the article, the authors of the study were contacted for further details.[23]

2.4 | Quality assessment

Study quality was reported using the Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields QUALSYST tool.[24] Studies were scored on 14 items (e.g. eligibility criteria, random allocation). Criteria can be answered as 'yes' (2), 'partial' (1), 'no' (0) and 'NA'. Three reviewers (B.M-M, J.B-R and L.B-B) independently assessed the included studies by pairs. In case of disagreement, consensus was reached via discussion and a more conservative (the lowest score) approach was applied. A summary score was calculated for each paper by summing the total score obtained across relevant items and dividing by the total possible score. Items not applicable to a particular study were excluded from the calculation of the summary score.

3 | RESULTS

3.1 | Study selection

The literature review retrieved 2211 articles. From these, 13 duplicate articles and 10 incomplete records were eliminated. Three more studies were added from checking reference lists from systematics reviews. Subsequently, records were examined by title, a total of 258 full-text articles were selected, and 43 full-text articles were critically appraised for final eligibility. Twenty-seven of these articles did not meet the inclusion criteria, the main reasons being: (a) the intervention was not focused on psychological therapy (e.g. behavioural change and physical activity); (b) they were not interventional studies (e.g. observational and protocol study); (c) the results were not specific on pwMS; and (d) they were systematic reviews. Finally, thirteen studies were included for the qualitative synthesis.

The flow diagram in Figure 1 shows the study selection process, and details from all studies were summarized in Table 1.

3.2 | Characteristics of included studies

Table 1 shows the main characteristics of the included studies. The first article was published in 2011 and the most recent in 2021. A wide variety of countries were represented (e.g. the Netherlands, Germany, the UK, New Zealand, the United States and Australia). Diagnosis was mainly performed by a specialized neurologist. The average time since diagnosis was 11.10 years (±4.82), although two studies did not provide this detail.[25,26] All studies were focused on the pwMS, although one study included participants with other neurological disorders reporting specific data for pwMS.[27] Six studies[20,21,25,28,29,30] included all types of MS, while three studies[31,32,33] recruited only participants with diagnosis of RRMS and SPMS, and four studies did not report information about MS diagnosis/type. Most participants had RRMS, and in only one study was SPMS the predominant type of MS.

Most included studies were randomized controlled trials (RCT). Six of these studies[20,23,25,28,29,30] employed a wait-list control group; one study[21] used usual care; two studies used comparison group interventions such as CBT without therapeutic contact[31] and online psychoeducation[33]; in one study[26] the control group were participants without MS; and one[34] used a mixed-methods design embedded within a three-arm RCT of two different interventions against a wait-list control group. The remaining two studies[27,33] used single group pre–post designs.

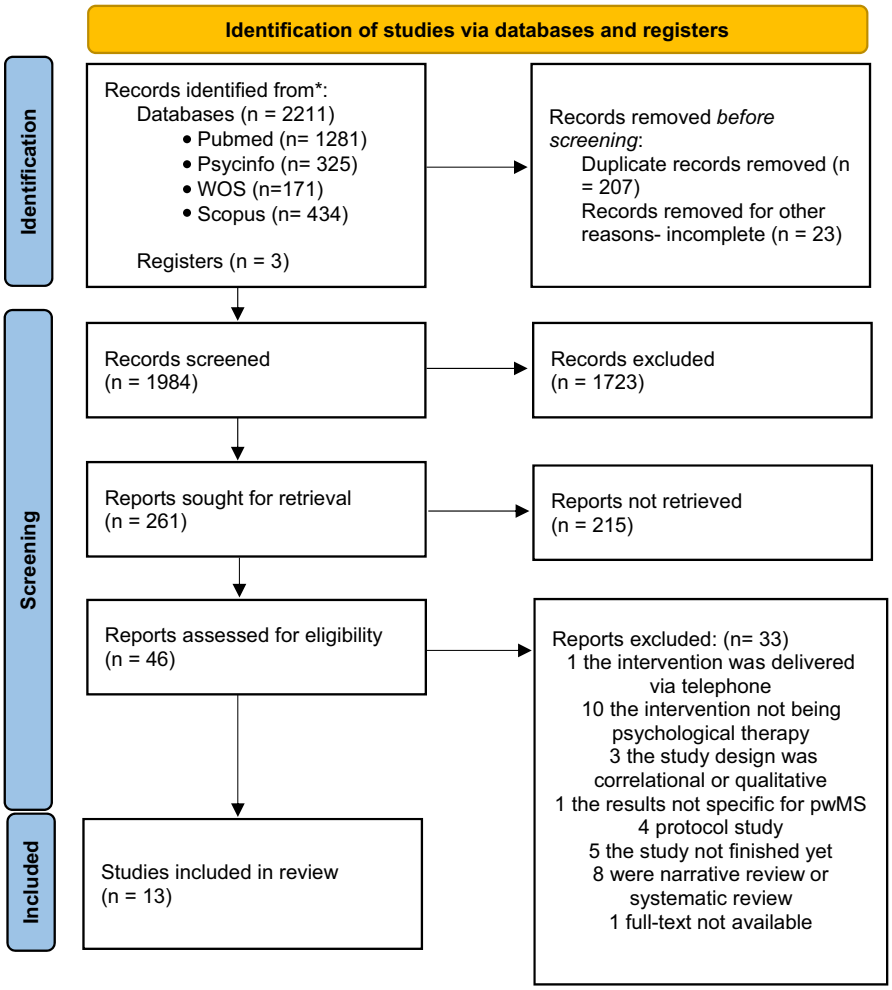

FIGURE 1 Search and exclusion process flow diagram *From*: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Bmj*. 2021;372:71. Doi: 10.1136/bmj.n71

3.3 | Quality assessment

The mean quality score was 87.77% (±9.81) with 15.38% of articles scoring below 75% (a 'relatively' conservative cut-off for acceptable articles).[24] The main reasons for lower scores were inappropriate study design, robust measurement of outcome and estimate for variance reported in insufficient detail, and lack of control for confounding variables.

3.4 | Sample characteristics

Samples sizes ranged from 24 to 275 participants. The age of the participants ranged from 18 to 65 years old (mean = 47.80, ±5.65). Most participants were females (75.42%). Almost half of the studies based participant recruitment on clinical cut-off scores indicative of problematic fatigue, distress or depression from baseline self-report, clinical-interview or both (7/13).[21,25,28,29,30,31,34]

Eight studies[20,25,26,27,28,29,33,34] provided information about psychotropic medication, while five studies did not report this.[21,23,31,32,34] Most studies differentiated between disease-modifying medication and medication for symptom relief (e.g. antidepressant and fatigue medication).

Nine studies[21,23,25,2733] reported physical functioning and disability. Five of these studies[21,29,31,32,33] assessed disability using the Expanded Disability Status Scale (EDSS: scores 0–6.5); three studies[23,25,30] reported similar information using the Patient Determined Disease Steps (PDDS) scale; and one study[27] used the World Health Organisation Disability Assessment Schedule (WHODAS 2.0).

3.5 | Intervention characteristics and delivery

In general, the included studies used Internet-based psychological interventions that were based on contents of CBT and educational components: (a) Boeschoten et al. (2012)[28] used problem-solving therapy (PST) based on an online cognitive–behavioural self-help intervention that was modified and included additional information about MS and its psychosocial consequences; (b) Fischer et al. (2015)[20] used an online programme based on principles of CBT (Deprexis); (c) Moss-Morris et al. (2012)[21] and Van Kessel et al. (2015)[31] examined a programme based on CBT principles including psychoeducation and self-monitoring (Ms Invigor8: Breaking the Cycle of fatigue); (d) Pöttgen et al. (2018)[25] explored a self-guided, interactive, online fatigue management programme (ELEVIDA) also based on principles of CBT; (e) Boeschoten et al. (2017)[29] evaluated an Internet-based

TABLE 1 Summary of included studies

Authors, year, and country	Criteria (type, time since MS diagnosis)	Study design	Sample	Intervention (type, frequency, time and mode of deliverable)	Main outcomes, measurement tools and periods	Main findings	Quality assessment (%)
Finlayson et al., 2011 (USA)[30]	Self-reported diagnosis of MS 15 years since diagnosis RRMS- 95 SPMS- 39 PPMS – 16 PRMS- 11 Unknown 17 Missing 3	RCT, two-group time series design with a wait-list control group	*n* = 181 (*n* = 89 intervention and 92 control group) Mean age = 56 143 women, 38 males FSS score of 4 or greater (i.e. moderate to severe fatigue); and score 12 or more on a short blessed test. Mean PDSS = 4	6/w fatigue management program (CBT contents), weekly 70-min teleconference calls via group Homework activities	FIS FSS SF-36 Secondary outcome: Self-Efficacy for Energy Conservation Questionnaire Baseline, post, 3- and 6-month follow-up	Intervention group compared to wait list showed a significant reduction (mean difference) in all three FIS subscales: Cognitive (− 3.12, $p = .001$); Physical (− 2.53, $p = .014$); Social (− 6.01, $p = .002$); and a significant improvement in the SF-36 Role Physical subscale (18.06, $p = .002$). Intervention group compared to baseline scores, after interventions showed (Cohen's D effect) a large effect size in all FIS subscales at 3 months: Cognitive 0.58; Physical 0.68; Social 0.65 and 6 months: Cognition 0.55; Physical: 0.61 and Social: 0.67; a significant reduction in the FSS scores: at 3-month: (−0.38) and 6-month (− 0.33). Significant improvement in the SF-36 subscales except the physical functioning and body pain subscales: Mental Health 5.78; Social Functioning 7.95; General Health 3.61; Role Physical 11.12. Significant improvement in Self-Efficacy for Managing Fatigue Scale 0.51.	92% Selection strategies were not ideal but did not likely seriously distort the results (telephone survey sampled from listed phone numbers only) and comparability within groups at baseline insufficient detailed
Boeschoten, et al., 2012 (Netherlands)[28]	Diagnosis of MS confirmed by a neurologist (>3 months ago) Years since diagnosis, median = 5 (2 to 40) RRMS (48%) SPMS (23%) PPMS (18%) Not reported (11%)	Single group pre-test/post-test design study	*n* = 44 MS (23 intervention and 21 control group) Mean age = 45 years; 34 females Scored 16 or higher on the BDI-II Medication: • MS medication (disease modifying and symptoms relief; *n* = 40, 90.90%) • Psychotropic medication (*n* = 21, 47.72%)	5/w web-based iPST, 2 hours a week (5 modules), individual, weekly e-mails support	Depression BDI-II Secondary measures: HADS- A SF-36 EQ-5D EQ-VAS SPSI-R Baseline, post	Depressive symptoms decreased a mean of 3.9 points in all patients (mean at baseline = 20.1, mean at post = 16.2; $d = 0.51$, $p = .01$). There was a significant difference in BDI-II change scores between completers (mean = −7.9) and non-completers (mean = 0.61) ($p = .001$). Completers analyses revealed a significant decrease on anxiety (mean at baseline = 9.4 ± 3.1; mean HADS-A at post 7.2 ± 3.1; d = 0.71, $p = .004$) and on negative problem orientation in whole sample (18.0 ± 5.4, 15.6 ± 6.3; d = 0.41; $p = .004$) larger for the patients who completed the intervention (mean at baseline 19.5 ± 4.8; mean at post 15.3 ± 6.0; d = 0.77, $p = .001$).	68% Not used a comparison group and sample size reduced

TABLE 1 (Continued)

Authors, year, and country	Criteria (type, time since MS diagnosis)	Study design	Sample	Intervention (type, frequency, time and mode of deliverable)	Main outcomes, measurement tools and periods	Main findings	Quality assessment (%)
Moss-Morris, et al., 2012 (England)[21]	Diagnosis of MS from neurologist Years since diagnosis: intervention = 21 (9,05), control group = 16 (7,88) MS type: RRMS 22 SPMS 9 PPMS 2 Unsure 7	RCT, two arms (intervention, usual care)	$n = 40$ MS (intervention group 23, control group 17) 32 females, mean age = 40 Fatigue Scale score>4 Ambulation ability (self-report EDSS): • Able to walk 500 m or more without aid or rest (47.5%) • Able to walk 100 m without aid or rest 15% • Require unilateral or bilateral aid to walk 20 to 100 m 32.5% • Missing data 5%	8-10/w Internet-based CBT (MS Invigor8), weekly sessions (on average, sessions took 25 to 50 min)+three telephone support sessions 30–60′ Homework tasks	Fatigue scale MFIS Secondary measures: HADS Baseline, post	The intervention group showed significant reductions when compared to the control group on both the Fatigue Scale (mean at baseline = 21.39 ± 4.30; mean at post = 12.39 ± 6.84; d = 1.19, $p < .001$) and the Modified Fatigue Impact Scale (mean at baseline = 13.17 ± 3.81; mean at post = 9.00 ± 3.75: d = 1.22, $p < .001$). There were significant differences between the groups on anxiety at baseline (8.26 ± 4.31) and at post (6.44 ± 3.91, $p = ·001$); and on depression at baseline (7.96 ± 3.64) and at post (5.18 ± 3.38, $p = .001$), with the MS Invigor8 group showing significantly greater reductions on both scales.	85% Sample size insufficient and interventional and blinding of investigators were not reported
Bogosian et al., 2015 (England)[32]	Diagnosis of PPMS or SPMS PPMS = 17 (42%) SPMS = 23 (57,5%) Median years since diagnosis = 12 (1–38)	RCT, two arms (CCBT online and wait list)	$n = 40$ MS (19 intervention, 21 control group) Mean age = 52,7 (9,5), 22 females Mean EDSS = 6,5 (1,5) Distress (GHQ-12) score 3 or greater	8/w MBCT (Mindfulness), once a week, 1 hour-long sessions, group videoconference (Skype) Homework tasks	GHQ-12 Secondary measures: HADS MSIS-29 Pain intensity (0–10) FSS Baseline, post, 3-month follow-up	Mean GHQ-12 (distress) total scores were lower in the Mindfulness group compared to waiting-list group at the post-intervention (−3,72 ± 1.76; d = −0.67, $p = .035$), and three-month follow-up (−5.45 ± 1.66, d = 0.97, $p = .005$). Significant reduction in the Mindfulness group compared to waiting-list at post-intervention on: HADS depression (mean at baseline = 6–24 ± 3.51; mean at post = 5.12 ± 3.20; $p = .017$), MSIS psychological (23.09 ± 6.39; at post = 19.19 ± 6.00; $p = .000$) and MSIS physical scores (mean at baseline = 64.52 ± 19.80; mean at post = 58.19 ± 17.56; $p = .016$); and three-month follow-up on HADS depression (5.13 ± 4.27; $p = .026$). HADS anxiety (4.84 ± 3.21; $p = .012$), MSIS psychological (18.72 ± 6.31: $p = .001$), MSIS physical scores (60.54 ± 20.52; $p = .005$); and pain (1.73 ± 2.09; $p = .034$).	96% Exposure measure(s) partial well defined (answer options and number of items were not reported)

(Continues)

TABLE 1 (Continued)

Authors, year, and country	Criteria (type, time since MS diagnosis)	Study design	Sample	Intervention (type, frequency, time and mode of deliverable)	Main outcomes, measurement tools and periods	Main findings	Quality assessment (%)
Fischer et al., 2015 (Germany)[20]	Diagnosis MS Disease duration in years = 8,30 RRMS 40 SPMS 21 Clinically isolated symptom 6 PPMS11 Unclear 12	RCT, two arms (intervention and wait list)	*n* = 90 MS (45 intervention group and 45 control group) Intervention group: mean age = 45,36(12,64). 34 females Control group: mean age = 45.20(810,56), 36 females Medication: • Disease modifying treatment (68% none) • Antidepressant treatment (84.4% none) • Symptomatic treatment (55.5% none, pain 7'8%, muscle relaxant 14.44%, bladder control 5.55%, other 4.44%).	9/w online CBT ('Deprexis'), 10 modules, (60 min)	Depression BDI Secondary measures: WHO-QoL BREF HAQUAMS FSMC Baseline, post, 6-month follow-up	Statistically significant treatment effect was showed in intervention group on BDI total score (mean at baseline = 19.44 ± 9.02; mean at post 16.24 ± 8.66; $p = .01$) and on BDI subscale subdomains of negative attitude towards self (mean at baseline = 9.58 ± 5.47; mean at post 7.83 ± 5.36; $p = .03$) and somatic symptoms (mean at baseline = 2.02 ± 1.56; mean at post 1.57 ± 1.07; $p = 001$). There was statically significant difference on psychological well-being subscale from WHO-Qol BREF (mean at baseline = 47.13 ± 18.84; mean at post 52.22 ± 20.39; $p = .04$); and on motor fatigue subscale from FSMC (mean at baseline = 38.51 ± 6.82; mean at post 36.17 ± 8.45; $p = .03$). At 6-month follow-up, mean BDI intervention group were lower than at baseline (mean BDI at baseline = 19·37 ± 9.59; mean BDI at 6 months = 14·80 ± 10.03; $p = ·001$).	96% Exposure measure(s) not well defined (Answer options and number of items were not reported)
Van Kessel, et al., 2015 (New Zealand)[32]	Diagnosis MS by neurologist RRMS- 26 SPMS- 13 Years since diagnosis: MsInvigor8-Only = 4,78 (4,36); MsInvigor8-Plus = 5,12 (4,29)	RCT, two arms (grup MSInvigor8-Only and group MSInvigor8-Plus)	*n* = 39 MS (20 MSInvigor8-Only, 19 MSInvigor8-Plus) Mean age = 45 (8,1) MSInvigor8-Only: mean age = 42,95 (8,16), 18 females MsINvigor8-Plus: mean age = 45,70 (8,39), 11 females Chalder Fatigue Scale score of 4 or greater EDSS: Only: • 0–4: 10 (53,0) • 4,5-5,5: 2 (10,0) • 6–6,5: 6 (31,5) • NR- 1 (5,0) Plus: • 0–4: 8 (40,0) • 4,5-5,5: 7 (35,0) • 6–6,5: 3 (15,0) NR- 2 (10,0)	8-10/w, weekly sessions, 25 to 50 min MSInvigor8-Only (online CBT, without any therapeutic contact) MSInvigor8-Plus (online CBT with therapeutic contact 10 min at week with email support from a clinical psychologist) Both included homework tasks	Chalder Fatigue Scale Modified Fatigue Impact Scale Secondary outcomes: HADS Baseline, post	The MSInvigor8-Plus group showed significantly greater reductions compared with the MSInvigor8-Only group on the Chalder Fatigue Scale (mean at baseline = 22.37 ± 4.39; mean at post = 11.37 ± 6.20; d = 0.99, $p < .01$) and the Modified Fatigue Impact Scale (mean at baseline = 13.58 ± 2.97; mean at post = 10.00 ± 2.71; d = 0.81, $p < .02$).	77% Study design partial inappropriate (not used a control group) and method of subject selection and comparison group was inappropriate

TABLE 1 (Continued)

Authors, year, and country	Criteria (type, time since MS diagnosis)	Study design	Sample	Intervention (type, frequency, time and mode of deliverable)	Main outcomes, measurement tools and periods	Main findings	Quality assessment (%)
Boeschoten, et al., 2017 (Netherlands)[29]	Diagnosis MS (>3 months) Years since MS onset = 11,2 (8,1) Benign 2.3 Relapsing remitting 55.0 Secondary progressive 28.1 Primary progressive 9.9 Relapsing progressive 3.5 Missing 1.2	RCT, two arms (intervention and wait list)	*n* = 171 MS (85 intervention and 86 wait list) Mean age = 48,9 ± 10,5 137 females EDSS: 0–1.5 = 3.5 2–4 = 50.0 4.5–6 = 17.5 ⩾6.5 = 27.5 Score BDI-II (<20) Medication: • Disease modifying treatment (32.9%) • Symptoms relief (52.0) Antidepressant (12.9%)	5/w iPST ('Worry Less') 5 modules, once a week Contact therapeutic weekly via email	Depression BDI-II Secondary measures: HADS BAI FSS MSNQ MSIS-29 EQ-5D SPSI-R Pearlin Mastery Scale Baseline, post (5–10 weeks), 4-month follow-up,	Both groups showed a high within-group effect size in depressive symptoms after intervention (IPST = −7.9; wait list = −6.2), and at follow-up (IPST = −7-4: wait list control = − 7.1). There was no difference between groups on BDI-II after intervention and at follow-up.	100%
Alschuler et al., 2018 (USA)[23]	Self-reported physician diagnosis of MS Mean disease duration = 20 years RRMS- 19 SPMS- 5 PPMS – 4	RCT, two arms (intervention, wait-list control)	*n* = 28 MS (12 intervention and 16 control group) Intervention group: 10 females, mean age = 59.8 (7.7); Control group: 16 females, mean age = 59.8 (6.5) PDDS: • Mild disability 6 • Moderate disability 4 • Gait disability 3 • Early cane 02 • Late cane 4 • Bilateral support 4 • Wheelchair/scooter 5	6/w positive psychology intervention (Everyday Matters Intervention), 90-min sessions, delivered via group teleconference Private web-based group page among facilitators and participants	CD-RISC Secondary outcomes: Neuro-QoL SES PROMIS SHS Baseline, post	Significant group effect in the treatment group reporting higher resilience (mean at baseline = 25.70 ± 10.3 and at post-test = 31.66 ± 2.26; d = 1.16, *p* = .02). Significant group effect in the intervention group for satisfaction with social roles (mean PROMIS at baseline = 39.95 ± 9.44; at post = 47.55 ± 2.92; d = 1.06, *p* = .02), and a marginal effect for positive affect and well-being (mean Neuro-QoL at baseline = 50.01 ± 7.62; at post = 54.82 ± 3.45; d = 0.72, *p* = .09) and for depressive symptoms severity (57.43 ± 9.14 45.22 ± 3.93; d = 0.72, *p* = .09)	95% Some estimate of variance (e.g. confidence intervals, standard errors) were insufficient reported for the main results

(Continues)

TABLE 1 (Continued)

Authors, year, and country	Criteria (type, time since MS diagnosis)	Study design	Sample	Intervention (type, frequency, time and mode of deliverable)	Main outcomes, measurement tools and periods	Main findings	Quality assessment (%)
Pöttgen, et al., 2018 (England)[25]	Diagnosis MS confirmed by neurologist RRMS 98 (70.5) SPMS 21 (15,1) PPMS 8 (5,8) Unknown 12 (8,6) RRMS 102 (75,0) SPMS 19 (14,0) PPMS 3 (2.2) Unknown 12 (8.8)	RCT, two arms (intervention, wait list)	*n* = 275 MS (139 intervention and 136 control group) Intervention group: mean age = 40,80(11,1), 114 females Control group: mean age = 41,90 (9,4), 108 females FSMC (>43) Impairment (PDDS): • Not impaired 9.81% • Mild impairment 36.36% • Moderate impairment 17.81% • Walking aid/ wheelchair 28.36% • Unclear 7.63% Medication: • Disease modifying treatment (24% none, 76% yes) • Symptomatic therapies (67.6% none, 22.1% antidepressant, fatigue medication 1.09%, other 9.09%)	12/w Internet-based CBT (ELEVIDA), once to twice a week, modules Included homework tasks	Chalder Fatigue Scale Secondary measures: FSMC, HADS-A, HADS-D HAQUAMS MSNQ FAI Baseline, post, 12-week follow-up	Both groups showed a decreased in Chalder Scale, but this decline was more pronounced in the ELEVIDA group (mean difference = −2.74, d = 0.53, $p = .0007$). There were significant reductions in group intervention on fatigue (FSMC: −3.47, $p = .0034$), as well as its subscales for motor fatigue (−1.71, $p = .0064$) and cognitive fatigue (−1.78, $p = .0092$), and on anxiety (HADSA-A: −0.64, $p = .0406$). Domain-specific QoL was significantly increased for three of the HAQUAMS subscales: fatigue (−0.39, $p = <.0001$), thinking (−0.17, $p = .0458$) and mobility lower extremities (−0.13, $p = .0397$), favouring ELEVIDA. Treatment effects remained statistically significant at 12-week follow-up on Chalder Fatigue scale (−2.19, $p = .008$). Group differences also remained significant for the secondary endpoints FSMC (−3.47, $p = .00049$) and HAQUAMS subscales fatigue (−0.25, $p = .01$) and thinking (−0.19, $p = .0459$).	100%
Tietjen et al., 2018 (USA)[26]	Diagnosis of MS	RCT, two arms (intervention MS, intervention people with other chronic diseases)	*n* = 47 participants (11 MS and 36 others chronic diseases) MS group: 10 female, 1 male; mean age = 45 (10,07); Without MS group: 30 female, 6 male; mean age = 47,15 (13,57). Antidepressant medication: 91% (10/11)	8/w CBT online program ('Think Clearly About Depression'), self-directed, contents in a web Homework tasks	PHQ-8 Health Distress Scale Self-Rated Health Scale Chronic Disease Self-Efficacy Scales Baseline, Week 4 and Week 8 (post)	Greater improvement in MS patients in intervention group on depressive symptoms (PHQ-8) compared with control group (mean at baseline = 22.80±3.63; at post = 15.20±4.49), on health distress scores (mean at baseline = 4.35±0.72; at post = 3.25±1.48), on self-efficacy measures of exercising regularly (mean at baseline = 3.40±3.00; at post = 4.67±2.22), on social/recreational activities (mean at baseline = 2.00±1.84; at post = 5.50±3.48; and on controlling/managing depression (mean at baseline = 1.40±1.62; at post = 2.40±1.70).	92% Study design inappropriate (not used a control group) and sample size insufficient

TABLE 1 (Continued)

Authors, year, and country	Criteria (type, time since MS diagnosis)	Study design	Sample	Intervention (type, frequency, time and mode of deliverable)	Main outcomes, measurement tools and periods	Main findings	Quality assessment (%)
Cavalera et al., 2019 (England)	Diagnosis of RR or SP MS by a neurologist RRMS = intervention 51 (94%), control 62 (92%) SPMS = intervention 3 (6%), control group 5 (8%) Years since MS diagnosis = intervention group 11,19 (8,0)/ control group 12,21(7,29)	RCT, two arms: intervention MSBR, active control group (online psychoeducational)	n = 121 MS (54 intervention and 67 active control group) Mindfulness group: 36 females, mean age = 42,26 (8,35); (Control group: 42 females, mean age) 43,19 (9,02) EDSS median = 3 Medication: Disease modifying treatment (85.95%) Antidepressant (4.13%) Anxiolytics (3.30%)	8/w online Mindfulness-based course (MSBR), once a week, group videoconference (Skype) Active control group: online 8/w psychoeducational course and videos Both groups included home exercises	MSQOL-54 Secondary outcomes: HADS MOSS MFIS Baseline, post, 6-month follow-up	MSQOL-54 was significantly higher in the Mindfulness group at the post-intervention assessment (F[1110] = 4.68, p = .033), but no difference was found after 6 months (F[1,95] = 0.018, p = .894). Anxiety and depression were significantly lower at the post-intervention in the mindfulness group compared to the psychoeducation one (respectively, F(1,111) = 3.96, p = .049; F(1,111) = 5.56, p = .020), but the difference between the groups was not maintained at the follow-up (respectively, F(1,95) = 1.033, p = .31; F(1, 95) = 0.169, p = .682). The mindfulness program showed a strong effect on sleep at the post-intervention evaluation (F(1,111) = 16.257, p < .001) but no statistical difference between groups was found after 6 months (F(1,95) = 1.650, p = .202). Fatigue score differences at post-intervention were borderline significant (F(1,111) = 3.674, p = .058) and non-significant at the follow-up (F(1,95) = 0.251, p = .617).	75% No interventional and blinding of investigators No blinding of subjects Outcome and exposure measure partial well defined (information test missing)
Gandy et al., 2020 (Australia)[27]	Formal diagnosis of one of the targeted neurological disorders (epilepsy, multiple sclerosis (MS), Parkinson's disease (PD), or acquired brain injury (ABI)), with clinical management by a GP or neurologist, Duration neuro diagnosis: mean = 7.49, ±7.06	Interventional study (pre–post)	n = 29 participants with MS of 105 adults with neurological disorders Total sample: Mean age = 51.68 (12.07) 74 women; 31 men Medication (total sample): Neurology medication (81.9%) Antidepressant (41.9%) Anxiolytics (7%)	10/w Internet-delivered psychological intervention based on CBT and CRT (six lessons in form of slide show) Weekly contact, via telephone or email with a clinical psychologist	PHQ-9 GAD-7 WHODAS 2.0 Secondary measures PDQ FSS Baseline, post, 3-month follow-up	A significant effect was showed after intervention for depression (mean at baseline = 8.86 ± 5.28; at post = 5.07 ± 3.18; d = 0.94, p < .001); for anxiety (mean GAD-7 at baseline = 6.73 ± 5.49; at post = 3.73 ± 3.50; d = 0.93, p < .001); for disability (mean WHODAS 2.0 at baseline = 16.00 ± 8.29; at post = 11.31 ± 7.11; d = 0.69, p < .001). All of these reductions remained at 3-month follow-up, not prospective memory. An overall time effects was revealed for perceived cognitive difficulties (mean difference) on attention/concentration (−0.17, d = 0.21, p < .01), planning/ organization (−0.14, d = 0.17, p = .01) and prospective memory (−0.16, d = 0.21, p = .04); and for fatigue (−2.62, d = 0.21, p < .05).	77% Study design inappropriate (not used comparison group) and method of subject and comparison group selection were insufficient described Confounding not controlled and may had disturbed the results

(Continues)

TABLE 1 (Continued)

Authors, year, and country	Criteria (type, time since MS diagnosis)	Study design	Sample	Intervention (type, frequency, time and mode of deliverable)	Main outcomes, measurement tools and periods	Main findings	Quality assessment (%)
Dunne et al., 2021 (Australia)[34]	MS diagnosis ´ Years since diagnosis (median [IQR]) = 8 (12)	RCT, three arms (Mindfulness, Chair yoga and wait-list control)	*n* = 55 participants with MS (*n* = 18) group Mindfulness M4MS, 18 Chair Yoga, 19 control group Mean age = 48,4 (±10,9) 45 women, 9 males 1 missing Screened as not highly distressed (Kessler Psychological Distress Scale K10 < 30) Psychotropic drugs (70.1%)	8/w M4MS program (MBCT), weekly two-hour Chair Yoga seated in a chair Both programs were delivered online via live web sessions (Zoom) for one hour every week for eight weeks, group live sessions 10′ of home practice and home tasks	MSQOL-54 BPI Baseline, post	Significant marginal decrease after treatment in M4MS group in two scales of the MSQoL-54 (coefficient); sexual function (15.71, $p = .059$); and role limitations emotional (23.71, $p = .036$).	92% Outcome and exposure measure partial well defined (information test missing) Some estimate of variance (e.g. confidence intervals, standard errors) were not reported for the main results

Abbreviations: BAI, Beck Anxiety Inventory; BDI-II-, Beck Depression Inventory Second Edition; BPI, Brief Pain Inventory; CBT, cognitive behavioural therapy; CD-RISC, Connor-Davidson Resilience Scale; CRT, compensatory cognitive rehabilitation therapy; CSRI, Client Service Receipt Inventory; EDSS, Expanded Disability Status Scale; EQ-5D, EuroQol quality of life measure; EQ-VAS, Visual analogue self-rating scale; FAI, Frenchay Activity Index; FIS, Fatigue Impact Scale; FSMC, Fatigue Scale For Motor And Cognitive Function; FSS, Fatigue Severity Scale; GAD-7, Generalized Anxiety Disorder Scale; GHQ, General Health Questionnaire; HADS, Hospital Anxiety and Depression scale; HAQUAMS, Hamburg Quality of Life Questionnaire for Multiple Sclerosis; IPST, Internet-based problem-solving treatment; MFIS, Modified Fatigue Impact Scale; MOSS, Medical Outcomes Study Sleep; MS, Multiple Sclerosis; MSIS-29, Physical and psychological impact of MS; MSNQ, Multiple Sclerosis Neuropsychological Screening Questionnaire; MSQOL-54, Multiple Sclerosis Quality of Life-54; NeuroQoL, Quality of Life in Neurological Disorders; PDDS, Patient Determined Disease Steps; PDQ, Perceived Difficulties Questionnaires; PHQ-8, Personal Health Questionnaire Depression Scale; PPMS, primary progressive; PRMS, primary relapsing; PROMIS, Patient-Reported Outcomes Measurement Information System; RRMS, relapsing remitting; SES, Self-Efficacy Scale for MS–Short Form; SF-36, Medical Outcome Study Short Form 36; SHS, Subjective Happiness Scale; SPMS, secondary progressive; SPSI-R, Social Problem-Solving Inventory Revised; WHODAS (2.0), World Health Organisation Disability Assessment Schedule; WHO-QoL, WHO Quality of Life scale.

problem-solving treatment (IPST) ('Worry Less') that was adjusted for MS patients; (f) Gandy et al. (2020)[27] examined an Internet-delivered psychological intervention tailored specifically for neurological disorders which integrates principles of CBT and compensatory cognitive rehabilitation therapy (CRT); (g) Tietjen et al. (2018)[26] evaluated an Internet-based CBT (iCBT), self-directed programme for depressive symptoms; (h) Calavera et al (2018) used mindfulness-based stress reduction (MSBR); (i) Bogosian et al. (2015)[32] and Dunne et al. (2021)[34] used mindfulness-based cognitive therapy (MBCT) which includes most of the MBSR syllabus with additional cognitive therapy exercises; (j) Alschuler et al. (2018)[23] used a positive psychology programme specific for pwMS; (k) while Finlayson et al. (2011)[30] examined a group-based, fatigue management programme based on CBT contents.

Most studies involved an individual format (8/13) and used time-limited interventions, whereas the remaining studies used a group format (5/13). The individual treatments involved five to ten modules delivered on a weekly basis. Two of these studies[20,25] used the technique of a 'simulated dialogue', an interactive exercise that imitates a real conversation and tailors the subsequent options to the patient's responses. Two studies[21,31] used a website with interactive sessions and included self-assessments to allow the intervention to be tailored to the individual user. Two studies[26,27] used educational videos and interactive activities. Two other studies[28,29] used an intervention with modules containing text, exercises and examples. Group format trials (5/13) were conducted by an expert who was connected through a videoconference system to the group participants.[23,30,32,33,34]

Group sizes ranged from five to seven participants, with one or two instructors. Most studies included homework tasks and therapeutic contact via e-mail or telephone, although three studies did not report therapist support.[20,25,26] Duration of the studies ranged from five to 12 weeks, but the average was about 8 weeks, and the sessions lasted between one and 2 h. All the studies assessed the participants immediately after intervention, except for one study [26] that also includes an assessment at week four (middle of the intervention). Others' follow-up periods varied between trials. Long-term follow-up was reported in seven trials and ranged between three and 6 months.[20,25,27,29.30,32,33]

3.6 | Main outcomes and intervention effectiveness

From 13 articles, nine studies[21,25,27,28,29,30,31,32,33] examined physical functioning, which included pain and fatigue; 12 studies[20,21,25–34] examined socio-affective symptoms, specifically depression, anxiety and distress; three studies[25,27,29] examined cognitive function and eight studies examined QoL.[20,23,25,28,29,33,34] Details about variables and measurement tools are shown in Table 1.

Respect to physical functioning, one trial[32] of four studies that specifically assessed physical functioning reported significant reduction in the mindfulness group compared to the waiting-list control group on the physical scale [(Physical and psychological impact of MS [MSIS-29]: 64.52 ± 19.80)] at post-intervention (MSIS-29: 58.19 ± 17.56, $p = .016$). Only one study,[32] of two that examined pain, showed a significant reduction of symptoms of pain through a MBI at 3-month follow-up (1.73 ± 2.09; $p = .034$). Of eight studies that assessed fatigue, significant changes were reported in all studies except three.[29,31,33] Finlayson et al. (2011)[30] revealed a significant reduction of fatigue in the intervention group immediately after intervention compared to a waiting-list control group [(Fatigue impact scale (FIS): Cognitive: −3.12 ± 6.10, $p = .001$; Physical: −2.53 ± 6.47, $p = .014$; Social: −6.01 ± 12.06, $p = .002$)]. These changes were maintained with large effect sizes in all FIS subscales at the 3- and 6-month follow-up. Moss-Morris et al. (2012)[21] revealed a similar improvement at post-intervention iCBT in the fatigue score (Modified Fatigue Impact Scale) (MFIS) (mean at baseline = 13.17 ± 3.81; at post = 9.00 ± 3.75; $p < .001$). Pöttgen et al. (2012)[25] using an iCBT programme showed a more pronounced decline in the intervention group compared with the waiting-list control group (Chalder Fatigue Scale: −2.74, $p = .0007$) and a significant reduction on the fatigue [(Fatigue Scale for motor and cognitive function [FSMC]: −3.47, $p = .0034$)], as well as its subscales for motor fatigue (−1.71, $p = .006$) and cognitive fatigue (−1.78, $p = .009$). Van Kessel et al. (2015)[31] compared CBT without any therapeutic contact (MSinvigor-Only) and with therapeutic contact (MSinvigor-Plus), the latter receiving email support from a skilled clinical psychologist with extensive CBT experience, and they reported significant reductions in both groups, although greater reductions were achieved in MSInvigor-Plus (Chalder Fatigue Scale: mean at baseline = 22.37 ± 4.39; mean at post = 11.37 ± 6.20; $p < .01$) (MFIS: mean at baseline = 13.58 ± 2.97; at post = 10.00 ± 2.71; $p < .02$). Gandy et al. (2020)[27] found a significant decrease in fatigue at both post-intervention (−2.62, $p < .05$) and 3-month follow-up [(Fatigue severity scale [FSS]: −2.5, $p < .05$)].

In reference to socio-affective symptoms, that 11 studies that examined depressive symptoms, only three no reported significant reductions.[25,29,31] Boeschoten et al. (2012)[28] found a significant difference in change scores among completers and non-completers using a web-based iPST (BDI-II: −3.9, $p = .001$). Fischer et al. (2015)[20] showed a statistically significant treatment effect in the intervention group [(Beck Depression Inventory [BDI]: mean at baseline = 19.44 ± 9.02; mean at post 16.24 ± 8.66; $p = .01$)]. Moss-Morris et al. (2012)[21] found significantly greater reductions of 2.78 points of depressive and anxiety symptoms in the intervention group compared to a control group [(Hospital Anxiety and Depression Scale [HADS]: mean at baseline = 7.96 ± 3.64; and at post = 5.18 ± 3.38, $p = .001$)]. Pöttgen et al. (2018)[25] showed that an iCBT program reduced anxiety (HADS) in the intervention group (−0.64, $p = .0406$). Bogosian et al. (2015)[32] found a significant reduction in the mindfulness group compared to the waiting-list control group at post-intervention of depression (HADS: −1.12, $p = .017$), and at 3-month follow-up, the effect was also significant for anxiety (HADS: −2.12, $p = .012$). Cavalera et al. (2018) reported that a MBI delivered via videoconference reduced depressive (HADS: −3.46, $p = .049$) and anxiety symptoms (HADS: −5.56, $p = .020$) at the end of the intervention compared to psychoeducation, but the difference between the groups was not maintained at the follow-up (respectively, $p = .312$; $p = .682$). Tietjen et al. (2018)[26] assessed depression and observed a significant reduction compared with the control group

[(Personal Health Questionnaire Depression Scale [PHQ] mean at baseline = 22.80 ± 3.63; at post = 15.20 ± 4.49)]. Gandy et al. (2020)[27] reported an overall time effect for depressive and anxiety symptoms at post-intervention [(PHQ-9: −9: −3.79, $p = p < .001$; GAD-7: −3, $p < .001$)] and at follow-up (PHQ-9: −3.86, $p < .001$; GAD-7; −3-39, $p < .001$). Only one study[32] evaluated distress (General Health Questionnaire: GHQ-12) and scores were lower in the mindfulness group compared to the waiting-list control group at the post-intervention (−3,72 ± 1.76; $p = .035$) and three-month follow-up (−5.45 ± 1.66; $p = .005$).

Of the three studies that assessed cognitive functions[25,27,29]; only one study[27] showed a significant effect for difficulties in attention/concentration (−0.17, $p < .01$), in planning/organization (−0.14, $p < .01$) and in prospective memory (−0.16, $p = .04$). Attention and planning ability remained stable at three-month follow-up (−0.29; $p < .01$; −0.23, $p < .01$, respectively).

Of the eight studies that quantified health-related QoL, seven indicated significant improvements in this domain.[20,23,25,28–30,33,34] Fischer et al. (2015)[20] showed significant improvement in the psychological well-being subscale measured (WHO-Qol BREF: mean at baseline = 47.13 ± 18.84; mean at post 52.22 ± 20.39; $p = .04$) in the intervention group. Alschuler et al. (2012)[23] found a significant improvement in satisfaction with social roles (mean PROMIS at baseline = 39.95 ± 9.44; at post = 47.55 ± 2.92; $p = .02$). Pöttgen et al. (2018)[25] revealed a significant increase in domain-specific QoL in the intervention HAQUAMS subscales: fatigue (−0.39, $p < .0001$), thinking (−0.17, $p = .046$) and lower extremity mobility (−0.13, $p = .004$), and this difference remained statistically significant at a 12-week follow-up, except for lower extremity mobility. Finlayson et al. (2011)[30] found that a fatigue management programme significantly improved QoL in the intervention group in the SF-36 subscales (Mental Health: 5.32 ± 13.38, $p = .012$; Social Function: 7.54 ± 25.35, $p = .05$; Role Physical: 18.06 ± 30.49, $p = .000$). Cavalera et al. (2018)[33] observed that the QoL (Multiple Sclerosis Quality of Life-54: MSQOL-54) was significantly higher in the mindfulness group at the post-intervention ($p = .033$), but no difference was found after 6 months ($p = .894$). Dunne et al. (2021)[34] compared a MBI against Chair Yoga and against wait-list control group found no statistically significant main effects for either intervention on any of the MSQoL-54 scales, except two: sexual function (15.71, $p = .059$) and role limitations emotional (23.71, $p = .036$) in favour of the mindfulness group. Boeschoten et al. (2012)[28] found a decrease of 2.4 points on negative problem orientation in the whole sample (18.0 ± 5.4, 15.6 ± 6.3; $p = .004$) that was larger for the patients who completed the intervention (mean at baseline 19.5 ± 4.8; mean at post 15.3 ± 6.0; $p = .001$).

4 | DISCUSSION

4.1 | Main findings

To our knowledge, this is the first systematic review that has comprehensively analysed online psychological interventions (13 studies) and examined their impact on reducing physical, socio-affective and cognitive symptoms and to improve QoL in pwMS. This study also explores the mode of delivery in order to know which the most efficient format is to design online interventions in a future.

Findings indicate that online-based CBT and MBI used in pwMS may show changes in socio-affective symptoms, QoL and physical symptoms like fatigue, and slight changes in cognitive symptoms, specifically in executive functions. Moreover, data on how the intervention was applied show two main enablers of online physiological interventions: being in touch with the therapist and the importance of group sessions (rather than individual ones).

4.2 | Effectiveness of online psychological interventions

The data reviewed suggest that iCBT interventions showed mainly improvement in depression, anxiety, fatigue and QoL, and slight improvement in cognitive functioning in pwMS. Previous findings suggest that people with less severe depression could benefit more from low-intensity interventions than people with severe depression.[28,29,35] However, most studies included in this review were focused on mild-to-moderate depression. Although no studies focused on anxiety symptoms, four studies assessed anxiety as a secondary outcome. In three of these studies, the interventions proved to be successful, showing a reduction in anxiety after the intervention. It was unclear whether these benefits remained significant at follow-up. The moderate effect sizes of iCBT that we found were similar to those reported in other trials for depression and anxiety for pwMS.[36] Also, iCBT interventions were effective treating MS-related fatigue. Besides, in most studies, this reduction maintained at follow-up. Five studies showed that iCBT led to clinically significant decreases in MS-associated fatigue, whereas only one study failed to report a significant effect in fatigue This result is in line with the findings from a meta-analysis conducted by Phyo et al. (2018),[37] who concluded that CBT was effective in the treatment of MS-related fatigue but found moderate heterogeneity between studies. This might be associated with the ways in which CBT was delivered, as these were slightly different across the studies. Finally, iCBT-based intervention also showed a significant improvement in QoL in most studies. However, it is important to analyse how QoL was measured, as it is a multidimensional concept that encompasses several domains. It is usually concerned with physical and mental well-being, and thus was associated with depression, anxiety, fatigue and cognitive impairment. This is consistent with the systematic review conducted by Gil-González (2020),[38] which concluded that fatigue, cognitive impairment and pain are associated with lower QoL.[14,38,39,40] Cognitive functioning was not included in most CBT studies. Even though perceived cognitive difficulties were common in pwMS, only three of the studies reviewed took them in account.[13] Only one study reported benefits in some cognitive components such as attention, concentration, planification and organization, and all of these remained at 3 months after the intervention. This finding

suggests that attention and executive function were areas where CBT could potentially benefit pwMS, which is also supported by other studies.[41,42]

With regard to MBIs, we found two different approaches, MBCT ($n = 2$) and MBSR ($n = 1$), both of which reported benefits in depression, anxiety, stress and QoL, and, to a lesser extent, in fatigue. MBSR intervention was associated with decreased depression and anxiety and improvement in QoL, even though these changes did not remain at follow-up. MBCT intervention also showed an improvement in depression, anxiety and QoL, but these effects also remained at follow-up. The main results in depression are consistent with other findings.[43–47] Likewise, a meta-analysis led by Simpson et al. (2019)[14] concluded that MBIs were at least moderately effective in treating depression in pwMS. However, there is low evidence on the effectiveness of mindfulness interventions for anxiety reduction.[14] This is consistent with our review; although we found an apparent benefit for anxiety reduction, few studies examined this. Several previous trials of mindfulness interventions have shown positive effects on stress-management in pwMS.[47] In our review, only one trial focused on this through a mindfulness intervention, but it reported a medium-large effect post-intervention and a large effect at 3 months. Therefore, more studies examining interventions for stress-management for pwMS are needed, as this factor has been related to a worsening or exacerbation of MS.[48] In addition, we only found one study that treated fatigue or chronic pain. Neither showed significant improvement after intervention, but improvements in pain were significant at follow-up. More studies with a robust methodology and greater sample size needed to verify the effect of mindfulness-based interventions to manage chronic pain and fatigue in pwMS.[18] In addition, the results of the reviewed studies suggest that online mindfulness interventions may have significant though not large effects right after the treatment. Furthermore, long-term psychological effects can disappear, at least if not properly supported.[49]

4.3 | Mode of delivery: characteristics, barriers and enablers

Findings suggest that offering a website alone without support or therapeutic contact may contribute to less adherence and probably a higher dropout rate. Therapeutic contact via telephone, mail or videoconference was seen as a key component of the interventio n.[20,21,23,28–34] Dropout probably had an influence on the efficacy of the intervention, and the absence of regular contact with a 'therapist' may have contributed to low levels of engagement. Besides, it was seen that contact with a therapist encouraged socialization and was instrumental in prompting participants to engage in the sessions. Thus, wordance with previous studies, we also observed that group intervention approaches could be more successful than individual self-management.[38] Adherence rates in online-based interventions were substantially lower compared with face-to-face treatments. Furthermore, adding short face-to-face consultations in a blended-care design and small group setting may have positive effects on adherence and outcome of the psychological intervention.[50] Moreover, in pwMS online interventions could help to overcome disability physical barriers.

Technological issues, such as slow Internet connections, interaction with the computer interface and website bugs, and previous experience using the Internet programmes or videoconference, should be considered as they can affect adherence. However, due to the COVID-19 pandemic, the use of video conferencing and calls related to health has become more widespread, and some of these technological issues have been solved or improved.

4.4 | Robustness of the evidence

Generally, study quality was acceptable in most studies. Moreover, some aspects that could influence the quality of evidence are considered to be as limitations because they may influence the results: the lack of information related to the functional impairment, severity of symptoms, medication information, disease history and years since diagnosis. Although most studies included data on disability or functional impairment, few studies stipulated them as an inclusion criterion. Furthermore, the severity of symptoms and associated impairment might influence the results. Some studies had only recruited patients with scores indicative of mild symptoms from baseline and excluded moderate or severe symptoms. Clinical cut-off from baseline could play a crucial role in the level of symptom changes during the intervention.[38] Relatedly, five studies did not report medication information. Also, few studies assessed whether participants started any new or additional treatments (pharmacological or non-pharmacological) after enrolment. In view with the evidence, disease history could be an important factor and could influence intervention response.[38,51] In patients with more years since diagnosis, neurological impairment and physical disability usually increased.[52] In our review, years since diagnosis differ among studies, and it was undervalued in many of the studies when analysing results.

Moreover, some interventions include a large social component, which can promote well-being and could influence the results. Consequently, social components should be evaluated separately because they may lead to improvements in some parameters, such as depression and anxiety. Another important feature is related to the fact that all the sessions in most studies were delivered by the same therapist, which could represent a risk of bias because the therapist's skill may influence treatment effect and intervention adherence.[21]

4.5 | Strengths and limitations

In conducting the systematic review, we adopted rigorous search, appraisal and analysis strategies, using various reviewers for data extraction, and our methods were guided by the PRISMA checklist.[22]

However, this systematic review has several limitations. The limited number of studies ($n = 13$) and the heterogeneity of health

outcomes reported across studies made it difficult to provide a meta-analysis that produced robust conclusions on the effect of online psychological intervention in pwMS. Nevertheless, relatively few studies met the inclusion criteria. In addition, practically all the studies were carried out in women with RRMS or SPMS, so despite being the most common profile of pwMS[4] the results extracted may not be representative for the whole population. It could be useful to carry out more studies with a sample of men. Almost all the studies consider at least one health-related outcome; however, the wide variety of tools used to measure them meant that few studies considered the same factors. Furthermore, it must be considered that the clinical relevance of changes on self-reported symptom-based scales needs to be interpreted in the context of the magnitude of change and severity of symptoms before.[12]

4.6 | Future directions

In line with the data reviewed, future studies should consider tracking therapy participation, empowering incentives that ensure adherence, and evaluating the users experience on intervention quality and therapists' ability. Furthermore, upcoming research should focus on robust RCT comparing a group-based online mindfulness intervention against a similar psychoeducational group with respect to structure and duration or, better still, against a current 'gold standard' treatment, such as iCBT.

5 | CONCLUSION

The findings from this systematic review suggest that online-based psychological interventions, mainly based on CBT and MBI, may produce short-term benefits for fatigue, depression, anxiety, distress and QoL in pwMS. Little evidence supports improvements on physical functioning such as pain and perceived cognitive difficulties. In addition, the studies reviewed suggest that therapeutic contact or group sessions may enable participation therapy engagement. These findings have important clinical implications due to online psychological interventions could reach people who are unable to access physically to the therapy. This, together with the variety of novel and engaging intervention strategies used, highlights the potential online psychological interventions have for promoting physical, cognitive, socio-affective well-being and QoL for pwMS.

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CONFLICTS OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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