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Review article

The effects of cognitive behavioral and mindfulness-based therapies on psychological distress in patients with multiple sclerosis, Parkinson's disease and Huntington's disease: Two meta-analyses

Ghielen Ires[a,b,*], Rutten Sonja[a], Boeschoten Rosa E.[c], Houniet-de Gier Marieke[d], van Wegen Erwin E.H.[g], van den Heuvel Odile A.[a,b], Cuijpers Pim[e,f]

[a] Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Psychiatry, Amsterdam Neuroscience, de Boelelaan 1117, Amsterdam, The Netherlands
[b] Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Anatomy & Neurosciences, Amsterdam Neuroscience, de Boelelaan 1117, Amsterdam, The Netherlands
[c] Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Psychiatry, Amsterdam Public Health, de Boelelaan 1117, Amsterdam, The Netherlands
[d] Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Medical Psychology, Amsterdam, The Netherlands
[e] Amsterdam Public Health Research Institute, Department of Clinical Psychology, Faculty of Behavioral and Movement Sciences, Vrije Universiteit Amsterdam, The Netherlands
[f] Department of Clinical, Neuro & Developmental Psychology, VU University, Amsterdam, The Netherlands
[g] Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Rehabilitation Medicine, MOVE Research Institute Amsterdam, de Boelelaan, 1118, Amsterdam, The Netherlands

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ABSTRACT

Objective: Psychological distress has a high impact on quality of life in patients with multiple sclerosis (MS), Parkinson's disease (PD), and Huntington's disease (HD). Studies have shown that cognitive behavioral therapy (CBT) and mindfulness-based therapies (MBTs) are successful in reducing psychological distress in patients with anxiety, depressive, and chronic somatic disorders. We aimed to investigate the effectiveness of these therapies in MS, PD, and HD patients.

Methods: We performed a comprehensive literature search in PubMed, PsycINFO, Embase and the Cochrane Central Register of Controlled Trials up to March 2018. Randomized controlled trials (RCTs) investigating a CBT or MBT and reporting psychological outcome measures were included. Two separate meta-analyses were performed; one on studies comparing psychological therapy with a treatment as usual or waitlist condition and one on studies with active treatment control conditions.

Results: The first meta-analysis (N = 12 studies, 8 in MS and 4 in PD populations) showed a significant effect size of g = 0.51 in reducing psychological distress. The second meta-analysis (N = 7 studies, in MS populations) showed a mean effect size of g = 0.36. No RCTs were found in HD populations. The overall quality of the included studies was low and considerable heterogeneity was found. No evidence was found for publication bias.

Conclusion: CBT and MBTs have a small to moderate effect on reducing psychological distress in patients with PD and MS. However, more research with better methodological quality and larger study samples is warranted, especially in HD patient populations.

1. Introduction

Progressive neurological disorders, such as Multiple Sclerosis (MS), Parkinson's disease (PD) and Huntington's disease (HD), are often accompanied by psychological distress [1–3]. Psychological distress can be defined as negative mental health states and includes anxiety and depressive symptoms. Psychological distress has a higher impact on the quality of life of both the patients and their caregivers as compared to the physical symptoms that accompany the diseases [4,5].

The resemblance between MS, PD and HD includes the progressive nature of the disease, uncertainty on disease course, and incurability (only symptom reduction is possible), which contribute to psychological distress. In addition to these factors, psychological distress can arise from physical symptoms such as spasms, rigidity, and autonomic dysregulation, resulting in a vicious circle where physical and psychological symptoms reinforce one another. On the neurobiological level, frontostriatal circuits are affected by the disease, causing disruptions in cognition, affect, motivation, behavior, and stress regulation [6,7].

* Corresponding author at: PO Box 7057, 1007 MB Amsterdam, The Netherlands.
E-mail address: i.ghielen@vumc.nl (I. Ghielen).

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Because of these similarities, it is likely that these three patient populations can equally benefit from psychological treatments. This hypothesis is supported by the finding that a standardized psychosocial self-management program proved to be effective in a variety of chronic diseases, including MS, PD, and HD [8].

A considerable number of studies has investigated potential effective treatments for psychological distress reduction. These treatments are cognitive behavioral and mindfulness-based. In an extensive review and meta-analysis, Hofmann and colleagues [9], showed that cognitive behavioral therapy (CBT) is an effective treatment for psychological distress and, more specifically, anxiety symptoms in patients with psychiatric and medical conditions. Besides classical CBT, problem solving and self-management therapies are also considered CBT-based since these interventions are based on the same principles. In PD patients, CBT also showed positive effects in treating anxiety and depressive symptoms [10–12]. In MS, Dennison and colleagues [13] concluded that CBT is effective in improving the management of somatic symptoms and psychological distress. According to Novak and Tabrizi [14], depression and anxiety are usually treated with medication in HD patients, but CBT is also effective in well-selected patients that experience mild symptoms and who have insight in their psychological problems. However, no controlled studies have been performed in this patient group.

Besides CBT, mindfulness-based treatments (MBTs) receive increasing attention in clinical practice. Mindfulness involves 'paying attention in a particular way: on purpose, in the present moment, and non-judgmentally' [15]. MBTs include mindfulness-based stress reduction, mindfulness-based cognitive therapy, meditation, and acceptance and commitment therapy. MBTs have been proven to be effective in reducing anxiety and depressive symptoms in patients with anxiety and depressive disorders [16], and patients with chronic pain [17]. Also, small to moderate effect sizes in improving mental health were found in populations with different chronic somatic diseases [18,19], and medium effect sizes were found in MBTs for MS patients [20].

To reduce psychological distress in patients with progressive neurological disorders, CBTs and MBTs might thus be of potential benefit. Since these interventions are considered treatment options, it is warranted to investigate their effectiveness. In order to establish the efficacy of CBTs and MBTs on reducing psychological distress in PD, HD, and MS patients, we performed a meta-analysis on randomized controlled trials.

2. Method

2.1. Selection of studies

A comprehensive literature search was conducted in PubMed, PsycINFO, the Cochrane library and EMBASE through March 2018. In addition, *ClinicalTrials.gov* was searched for completed but unpublished studies. The following keywords were used: "Parkinson", "Huntington", "Multiple Sclerosis", "psychological distress", "stress reduction", "distress", "depressive symptoms", "anxiety symptoms" (see the supplementary material for the complete search string). Besides the database searches, recent meta-analyses [21–23] were read to find additional studies. Two researchers (IG, SR) independently selected the studies for inclusion and when they disagreed a consensus was made.

Inclusion criteria for the meta-analyses were:

- Patients: a study population of MS, PD, or HD patients.
- Intervention: the examination of a CBT- or MBT-based intervention.
- Comparison: the intervention was compared with a waitlist or treatment-as-usual (TAU) condition, or with another active form of therapy. Only randomized controlled trials (RCTs) were included in this meta-analysis.
- Outcome: availability of questionnaires that measure anxiety and/or depressive symptoms, or general mental health. These data should allow the calculation of standardized mean differences (post-treatment means, standard deviations, and number of participants; or other statistics that allowed to calculate effect sizes).

The study abstract or manuscript should be available in English or Dutch.

2.2. Data extraction

All decisions on the inclusion of outcome measures for psychological distress, including depressive and anxiety symptoms, or/and general mental health outcome measures, were based on consensus between two researchers (IG, SR). Outcome measures of psychological distress were extracted by these two researchers, independently. Post-treatment measurements were collected to examine the immediate effect of the interventions. When data were not available, the study researchers were contacted. In addition, two independent researchers (RB, MH) rated the type of interventions (CBT or MBT) investigated in the studies, based on the treatment components described in the manuscript.

2.3. Quality assessment

The methodological quality of the included studies was assessed with seven criteria of the risk of bias assessment tool, developed by Cochrane [24] to assess sources of bias in RCTs:

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and researchers (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Other bias

When questionable or unclear risk of bias was found, this was considered a risk of bias.

Again, quality assessment was performed by two independent researchers (IG, SR).

2.4. Meta-analyses

The Hedges' *g* effect sizes were calculated for each study and pooled with Comprehensive Meta-analysis (CMA; version 3 for Windows). Post-treatment means and corresponding standard deviations measures were used to calculate Hedges' *g*. Means and standard deviations from anxiety, depression, and general mental health outcome measures within each study were pooled within the CMA program so that one 'psychological distress' measure for each study was included in the meta-analyses. Two separate main meta-analyses were conducted: the first to investigate CBTs and MBTs that were compared with waitlist or TAU conditions, the second to investigate CBTs and MBTs that were compared with other active interventions (such as supportive listening, relaxation, and psycho-education).

Within the first main meta-analysis, besides the combined psychological distress measure, the individual effect sizes on anxiety, depression, and general mental health outcomes were investigated using separate smaller meta-analyses. Subgroup analyses were conducted for disease type, control condition, and high vs low risk of bias. In addition, the relationship between risk of bias and effect size was investigated with a regression analysis. Within the second main meta-analysis, the different types of interventions of interest (CBTs and MBTs) were investigated by performing two separate meta-analyses. There were too few studies to perform further subgroup analyses.

As considerable heterogeneity was expected, all analyses were conducted using the random effects model. The I^2 statistic was

calculated as an indicator of heterogeneity. We calculated the 95% confidence intervals (95% CI) around I^2 [25] using the non-central chi-squared based approach within the heterogi module for Stata [26]. When the I^2 estimate reached 40%, this was classified as considerable heterogeneity [27].

Subgroup analyses were conducted according to the mixed-effects model [28], and the meta-regression analysis was conducted according to the procedures developed by Borenstein et al. [28].

Publication bias was examined with Duval and Tweedie's trim and fill procedure which estimates how many studies are missing in the meta-analyses and then imputes these [29], as well as Egger's test for the asymmetry of the funnel plot.

The protocol of this meta-analysis was not pre-registered.

3. Results

3.1. Selected studies

After removing duplicate studies, 156 records were found. After inspection of the titles and abstracts, 24 full-text articles were retrieved. In addition, four studies were included from past meta-analyses, resulting in 28 full-text articles that were read. Fig. 1 presents the flowchart of the inclusion process with reasons for exclusion, following the PRISMA statement [30]. Eventually, 19 studies were included, of which 12 were included in the first meta-analysis, and seven in the second meta-analysis.

3.2. Characteristics of included studies

Table 1 shows the characteristics of the included studies, displayed separately for the two main meta-analyses. Within the first analysis, eight studies included MS patients [31–38], four studies included PD patients [39–42], and no RCTs were found investigating HD populations. Nine studies examined a CBT-based intervention [31,33–37,39,41,42] and three studies investigated an MBT [32,38,40].

Within the second analysis, only MS patients were investigated in the included studies. Regarding the treatments of interest, four studies investigated a CBT-based treatment [43–46] and three examined an MBT [47–49].

Overall, the quality of the included RCTs was low, based on the scores on the risk of bias assessment tool. Blinding of participants/researchers was impossible due to the nature of studies on psychotherapeutic interventions, and was therefore always considered as risk of bias. As allocation concealment was often not well reported, two studies had a risk of detection bias [41,47]. The study by Okai and colleagues [41] also showed an attrition bias, as did the study by Calleo and colleagues [39]. In the first analysis, four studies showed good quality [31,33,38,42], as shown by a total risk of bias of 1 (only risk of performance bias). In the second analysis, only the study by Carletto and colleagues had good quality (score of 1 on the risk of bias assessment tool: only blinding of participants was not achieved) [49].

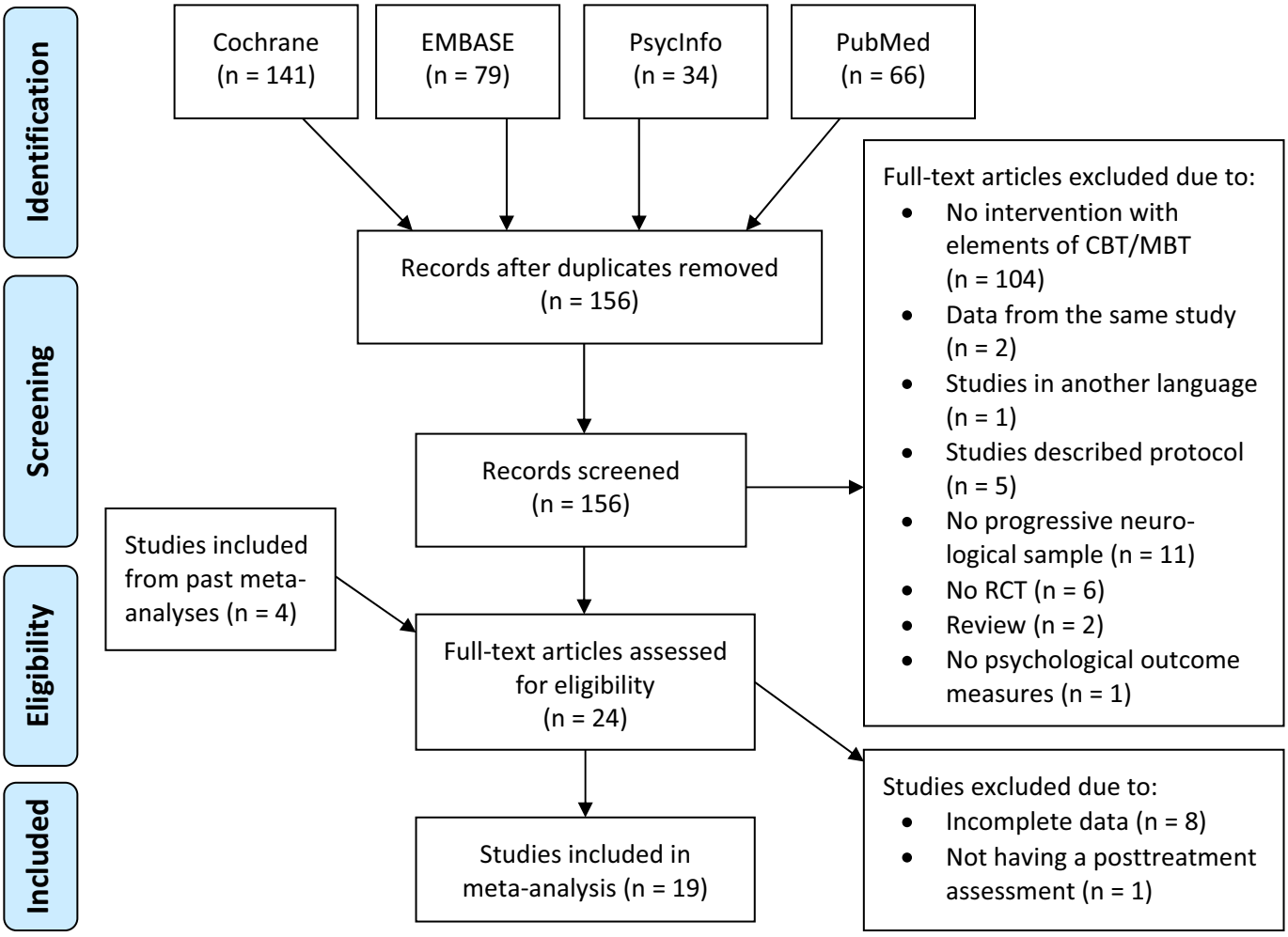

Fig. 1. PRISMA flow chart of selection and inclusion process. CBT = Cognitive Behavioral Therapy, MBT = Mindfulness Based Therapy; RCT = randomized controlled trial.

Table 1
Study characteristics.

Study	Medical condition	Comorbidity	Primary outcome	N intervention	Intervention	N control	Control	Outcomes in analysis	Risk of bias (0–7)[a]
Meta-analysis 1									
Boeschoten et al. (2016) [31]	MS	Moderate/severe depressive symptoms	BDI-II	85	IPST	86	WL	BDI-II HADS-A BAI	0–0–1-0-0-0-0 (1)
Bogosian et al. (2015) [32]	MS	Psychological distress	GHQ	19	Mindfulness	21	WL	GHQ HADS-A HADS-D	0-?-1–0–0-0-0 (2)
Fischer et al. (2013) [33]	MS	Depressive symptoms	BDI-II	45	CBT	45	WL	BDI-II	0–0–1-0-0-0-0 (1)
Forman et al. (2010) [34]	MS	Anxiety and/or depressive symptoms	HADS & GHQ	20	CBT	20	WL	HADS-A HADS-D	0-?-1–0–0-0-0 (2)
Kiropoulos et al. (2016) [35]	MS	Depressive symptoms	BDI-II	15	CBT	15	TAU	BDI-II STAI	0–0–1-1-0-0-0 (2)
Lincoln et al. (2011) [36]	MS	Anxiety and/or depressive symptoms	GHQ	72	CBT	79	WL	BDI GHQ HADS-A HADS-D	0-?-1–0–0-0-0 (2)
Mohr et al. (2000) [37]	MS	Moderate depressive symptoms	POMS-DDS	16	CBT	16	TAU	POMS-DDS	?-?-1-?-0–1-0 (5)
Simpson et al. (2017) [38]	MS	No inclusion criteria	PSS	25	MBSR	25	WL	PSS	0–0–1-0-0-0-0 (1)
Calleo et al. (2015) [39]	PD	Anxiety and/or depressive symptoms	Feasibility & satisfaction	10	CBT	6	TAU	HADS-A HADS-D	0–0–1-0-1-?-0 (3)
Ghielen et al. (2016) [40]	PD	Anxiety symptoms	GSES	19	ACT + PT	19	TAU (PT)	BAI BDI	0–0–1-0-0-0-1 (2)
Okai et al. (2013) [41]	PD	Impulse control disorder(s)	NPI	28	CBT	17	WL	GHQ	?-0–1–1-1-0-0 (3)
Troeung et al. (2014) [42]	PD	Anxiety and/or depressive symptoms	DASS	11	CBT	7	WL	DASS-A DASS-D DASS-S	0–0–1-0-0-0-0 (1)
Meta-analysis 2									
Ehde et al. (2015) [43]	MS	Fatigue, pain, or depressive symptoms	PHQ	75	Self-management	88	PE	PHQ	0–0–1-0-0-0-1 (2)
Mohr et al. (2001) [44]	MS	Major depressive disorder	HRSD & BDI	20	CBT	22	Supportive expression	BDI HRSD	1-?-1-?-0–0-? (5)
Mohr et al. (2005) [45]	MS	Moderate depressive symptoms	HRSD & BDI-II	62	CBT	65	Supportive expression	BDI-II HRSD	1-?-1–0–0-0-0 (3)
Moss-Morris et al. (2013) [46]	MS	Psychological distress	GHQ	48	CBT	46	SL	GHQ	0–0–1-0-0-?-0 (2)
Nordin et al. (2012) [47]	MS	Anxiety and/or depressive symptoms	HADS	11	ACT	10	Relaxation	BDI HADS-A HADS-D	0-?-1–1–0-0-0 (3)
Oreja-Guevera et al. (2015) [48]	MS	Unknown	HADS	21	MBSR	20	PE	HADS-A	Not assessable
Carletto et al. (2017) [49]	MS	Depressive symptoms		43	BAM	45	PE	BDI-II BAI PSS	0–0–1-0-0-0-0 (1)

MS = Multiple Sclerosis, PD = Parkinson's Disease, CBT = Cognitive Behavioral Therapy, MBSR = Mindfulness Based Stress Reduction, ACT = Acceptance & Commitment Therapy, IPST = Internet-based Problem Solving Therapy, BAM = Body-Affective Mindfulness, PT = Physical Therapy, WL = Wait-List, PE = Psycho-Education, SL = Supportive Listening, TAU = Treatment As Usual, HADS = Hospital Anxiety and Depression Scale (A = anxiety, D = depression), BDI = Beck Depression Inventory, PSS = Perceived Stress Scale, GHQ = General Health Questionnaire, PHQ = Patient Health Questionnaire, NPI = NeuroPsychiatric Inventory, POMS = Profile Of Mood Scale, GSES = General Self-Efficacy Scale, BAI = Beck Anxiety Inventory, HRSD = Hamilton Rating Scale for Depression

[a] Risk of bias is derived after assigning a zero (low risk of bias (0)) or one (unclear (?) or high risk of bias (1)) to each one of the following quality criteria: allocation sequence, allocation concealment, blinding of participants and personnel, blinding of assessors, incomplete outcome data, selective reporting, and other sources of bias, and a sum score.

3.3. Treatment effects

- *Meta-analysis 1: CBTs and MBTs versus TAU or waitlist condition*

Fig. 2 displays the forest plot of the standardized effect sizes of psychological therapies on psychological distress in PD and MS patients, compared with a waitlist or TAU condition. The mean effect size (*g*) was 0.51 (95% CI = 0.22–0.80) with a heterogeneity estimate (I^2) of 66 (95% CI = 27–80).

As a post-hoc analysis, the studies of Okai et al. [41], Ghielen et al. [40], and Kiropoulos et al. [35] were excluded in a separate meta-analysis. These studies were considered outliers since the effect sizes with their 95% confidence intervals were outside the 95% confidence interval of the pooled main effect size. The effect size decreased to $g = 0.31$ (95% CI = 0.13–0.48) and heterogeneity decreased to $I^2 = 0$ (95% CI = 0–56) when these three studies were removed (see Table 2).

To investigate the treatment effects on the different types of outcome measure separately, three meta-analyses were conducted on anxiety, depression, and general psychological distress outcome measures. The treatment effect on general mental health outcomes was highest ($g = 0.79$, 95% CI = 0.32–1.25 with $I^2 = 66$, 95% CI = 0–85), followed by the effect on anxiety symptoms ($g = 0.36$, 95% CI = 0.03–0.66 with $I^2 = 59$, 95% CI = 0–79), and depressive symptoms ($g = 0.33$, 95% CI = 0.05–0.62 with $I^2 = 60$, 95% CI = 0–78) (see Table 2).

In addition, subgroup analyses were conducted (Table 2) to investigate differences in effect size for disease type, control condition,

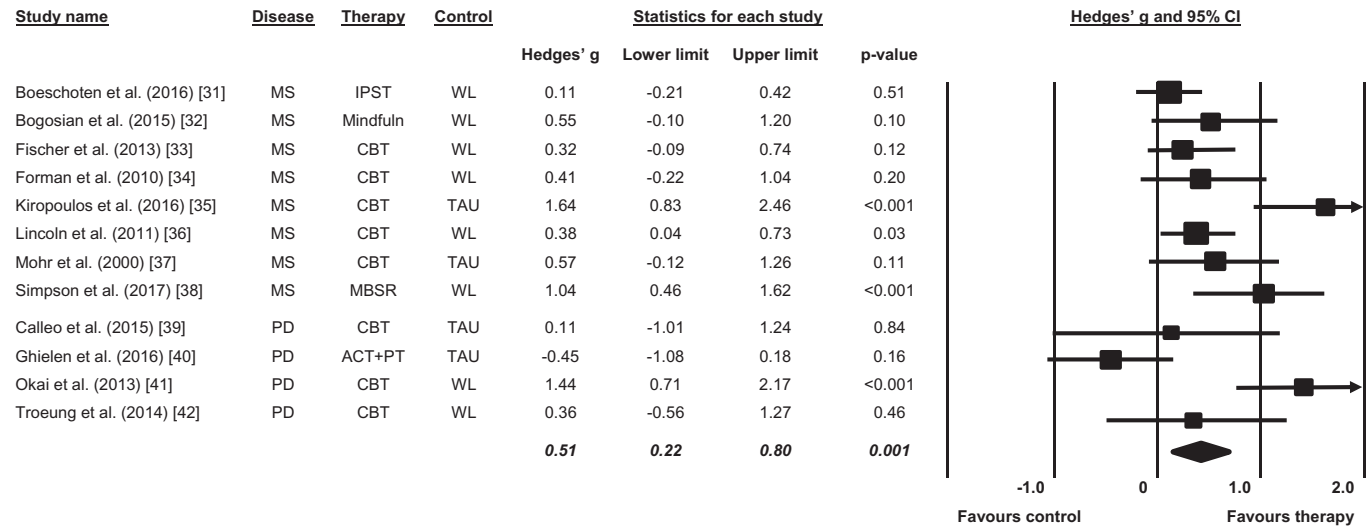

Fig. 2. Forest plot of studies comparing CBTs and MBTs with TAU or WL conditions (meta-analysis 1). MS = Multiple Sclerosis; PD = Parkinson's disease; IPST = Internet-based Problem Solving Therapy; Mindfuln = Mindfulness; CBT = Cognitive Behavioral Therapy; MBSR = Mindfulness Based Stress Reduction; ACT = Acceptance & Commitment Therapy; PT = Physical Therapy; TAU = treatment as usual; WL = waitlist.

Table 2
Effect sizes and heterogeneity measures for CBTs and MBTs in improving psychological distress in PD and MS patients, including subgroup analyses.

	N (studies)	Hedges'*g*	95% CI	I^2	95% CI	*p*-value	NNT[a]
Meta-analysis 1							
All	12	0.51	0.22–0.80	66	27–80	< 0.001	3.55
Excluding outliers[@]	8	0.31	0.13–0.48	0	0–56	0.008	5.75
Outcome							
Depression	10	0.33	0.05–0.62	60	0–78	0.042	5.43
Anxiety	8	0.36	0.03–0.68	59	0–79	0.038	5.00
Psychological distress	5	0.79	0.32–1.25	66	0–85	0.015	2.36
Subgroup analyses							
Disease type							
MS	8	0.54	0.26–0.82	45	0–72	0.003	3.36
PD	4	0.37	−0.55–1.29	80	16–91		4.85
Control condition							
Waitlist	7	0.39	0.18–0.60	26	0–68	0.006	4.59
TAU	5	0.67	−0.16–1.49	82	49–91		2.75
Risk of Bias [#]							
High	8	0.57	0.14–0.99	71	22–84	0.003	3.18
Low	4	0.42	0.02–0.81	61	0–85		4.27
Meta-analysis 2							
All	7	0.36	0.13–0.58	40	0–74	0.002	5.00
Treatment type							
CBTs	4	0.45	0.26–0.64	0	0–73	0.004	3.55
MBTs	3	0.06	−0.56–0.68	68	0–89	0.72	29.41

MS = Multiple Sclerosis; PD = Parkinson's Disease; CBTs = Cognitive Behavioral Therapies; MBTs = Mindfulness Based Therapies; NNT = Number Needed to Treat; TAU = treatment as usual. [a]according to Kraemer & Kupfer [50].[@] outliers include Okai et al. [41], Kiropoulos et al. [35], Ghielen et al. [40]. [#] low risk of bias include studies scoring 1 according to the risk of bias assessment tool, developed by Cochrane [24], a score > 1 is considered high risk of bias.

and risk of bias (high vs low). Significantly larger effect sizes were found in MS patient populations, TAU control condition, and studies with a high risk of bias.

Meta-regression analyses on risk of bias (β = 0.08, 95% CI = −0.18–0.33, $p > .05$) did not show a significant relationship with effect size.

- *Meta-analysis 2: CBTs and MBTs versus active control condition*

Fig. 3 shows the forest plot of the standardized effect sizes of psychological therapies on psychological distress in MS patients, compared with an active control condition. The mean effect size (*g*) was 0.36 (95% CI = 0.13–0.58) with a heterogeneity estimate (I^2) of 40 (95% CI = 0–74).

To investigate the treatment effects for the types of investigated intervention, two separate meta-analyses were conducted on CBT-based treatments and MBTs. The treatment effect for CBT-based treatments was highest ($g = 0.45$, 95% CI = 0.26–0.64 with $I^2 = 0$, 95% CI = 0–73), followed by a small effect for MBTs ($g = 0.06$, 95% CI = −0.56–0.68 with $I^2 = 68$, 95% CI = 0–89) (see Table 2).

- *Publication bias*

No evidence for publication bias was found in both meta-analyses.

Study name	Disease	Therapy	Control	Statistics for each study			
				Hedges' g	Lower limit	Upper limit	p-value
Ehde et al. (2015) [43]	MS	Self-management	PE	0.35	0.04	0.66	0.03
Mohr et al. (2001) [44]	MS	CBT	Supportive expression	0.51	-0.10	1.11	0.10
Mohr et al. (2005) [45]	MS	MBSR	PE	0.39	0.03	0.74	0.03
Moss-Morris et al. (2013) [46]	MS	CBT	SL	0.69	0.27	1.12	0.001
Nordin et al. (2012) [47]	MS	ACT	Relaxation	-0.10	-0.93	0.73	0.81
Oreja-Guevera et al. (2015) [48]	MS	MBSR	PE	-0.37	-0.98	0.23	0.23
Carletto et al. (2017) [49]	MS	BAM	SL	0.53	0.11	0.96	0.01
				0.36	***0.13***	***0.58***	***0.002***

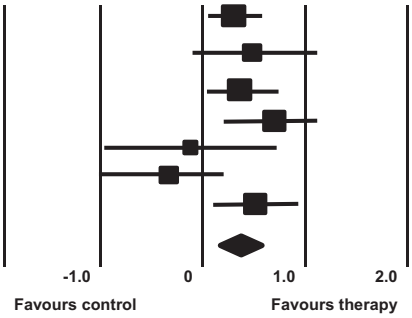

Fig. 3. Forest plot of studies comparing CBTs and MBTs with active control conditions (meta-analysis 2). MS = Multiple Sclerosis; CBT = Cognitive Behavioral Therapy; MBSR = Mindfulness Based Stress Reduction; ACT = Acceptance & Commitment Therapy; PE = Psycho-Education; SL = Supportive Listening.

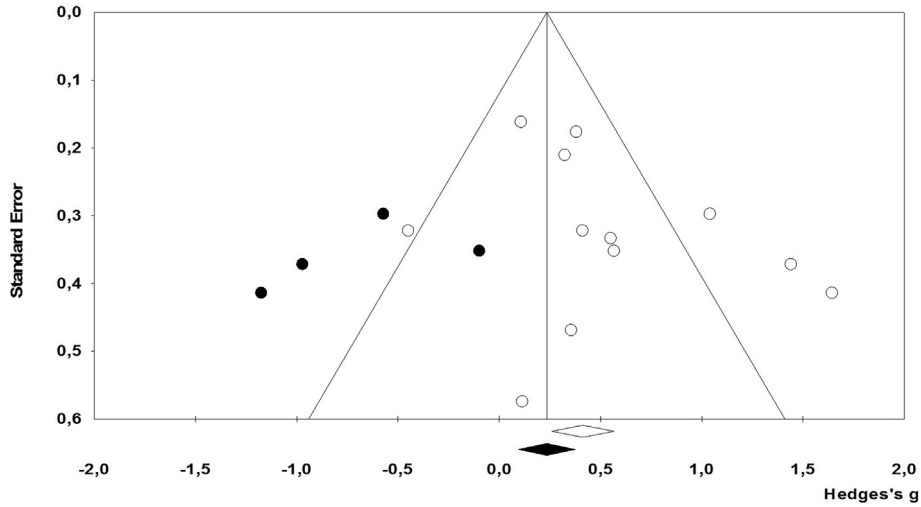

Fig. 4. Funnel plot of meta-analysis 1: CBTs and MBTs versus TAU or WL conditions. CBT = Cognitive Behavioral Therapy; MBT = Mindfulness Based Therapy; TAU = treatment as usual; WL = waitlist. The imputed studies are shown in black.

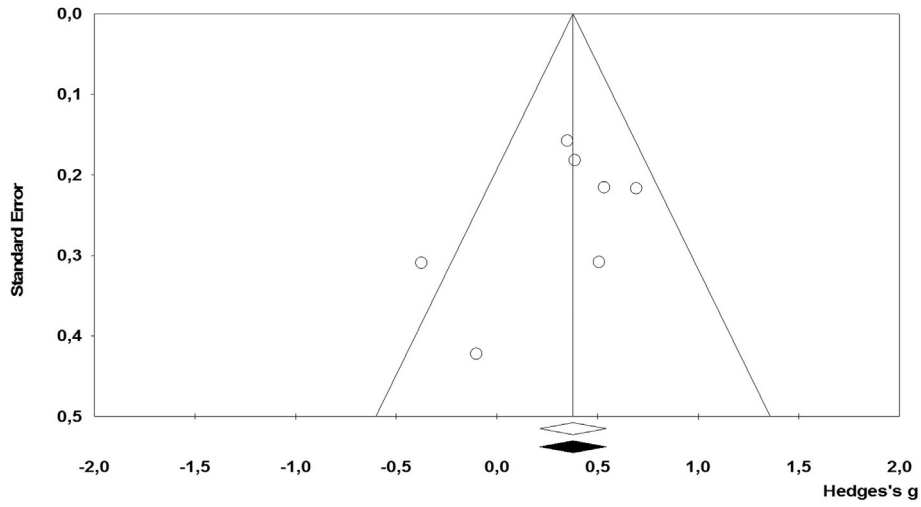

Fig. 5. Funnel plot of meta-analysis 2: CBTs and MBTs versus active control conditions. CBT = Cognitive Behavioral Therpay; MBT = Mindfulness Based Therapy.

Inspection of the funnel plots did not indicate significant publication bias (Figs. 4 & 5). Duval & Tweedie's trim-and-fill procedure resulted in the imputation of four studies in the first meta-analysis, and no imputations in the second meta-analysis, according to a random model. Egger's regression intercept indicated no significant publication bias ($p > .05$ in both analyses).

4. Discussion

In this study, we investigated the effectiveness of CBT and MBT on psychological distress in patients with PD and MS by conducting two main meta-analyses of randomized controlled trials. There were no RCTs found studying these therapies in HD populations. Nineteen studies were included in the analyses, of which twelve compared the treatment of interest with a TAU or waitlist condition (meta-analysis 1), and seven studies compared the treatment of interest with an active control condition (meta-analysis 2). A moderate effect size ($g = 0.51$) was found in the first meta-analysis, and a small effect size ($g = 0.36$) was found in the second meta-analysis. In both meta-analyses there was considerable heterogeneity, which was probably due to the variability in hours of treatment (range: 5–16 h), different delivery forms (for example by telephone or face-to-face), differences in comorbidity in the included subjects over all included studies, and specific elements that varied between the interventions (such as psycho education in the study of Okai et al. [41]). The heterogeneity decreased when 1) outliers were removed; 2) depression and anxiety outcomes were analyzed separately; 3) only looking at MS patient samples; 4) studies with waitlist control conditions were analyzed; and 5) studies with a low risk of bias were analyzed. In these post-hoc analyses, the effect sizes decreased to small ($g = 0.31$, $g = 0.33$, $g = 0.36$, $g = 0.39$, $g = 0.42$, respectively). No evidence was found for publication bias.

The small to moderate main effect sizes suggest that CBT and MBT are beneficial in reducing psychological distress, but only to a certain extent. Biological approaches, e.g. pharmacotherapy, showed a reduction of depressive symptoms in MS patients with an effect size of 0.63 (standardized mean difference) [22]. According to the review and meta-analysis by Fiest et al. [22], current research is insufficient to determine the effectiveness of pharmacotherapy for anxiety in MS as no controlled studies were found. In PD, the meta-analysis of Bomasang and colleagues [51] on antidepressant medication showed an effect size of 0.54 in reducing depressive symptoms. The effect of pharmacotherapy on reducing symptoms of anxiety in PD patients has insufficiently been studied. Although the effect sizes of pharmacotherapy on depressive symptoms appear to be larger than those of psychological treatment, regarding anxiety and global mental health the effect is not yet investigated properly. One can imagine that pharmacological interventions show larger effect sizes compared to psychotherapeutic interventions, since the latter requires cognitive abilities to learn and apply the methods that are taught. Although patients with dementia were excluded in most studies, it is possible that these populations have reduced cognitive abilities as a result of the neurodegenerative process, and are therefore unable to optimally benefit from CBT and MBT. It is also argued that a combination of psychotherapy and pharmacotherapy might be most beneficial, at least for outpatients with chronic forms of depression [52,53] and panic disorder [53]. In adults with an anxiety or depressive disorder without neurological comorbidity, a meta-analysis of Cuijpers and colleagues [54] showed that CBT is probably effective. Although effect sizes were larger (around $g = 0.80$) compared to our results, the quality of the included studies was low and publication bias was present. Large effect sizes were also found for MBTs in the treatment of anxiety and depressive symptoms in participants without neurological comorbidity [55]. Here, no publication bias was present but study quality was again unsatisfactory. CBT and MBT appear to be more effective in patients without compared to patients with neurodegenerative disorders. However, the methodological quality is insufficient to draw definite conclusions.

MS patients seem to benefit more from CBT and MBT than PD patients as is represented by the significant subgroup difference in effect size regarding disease type. However, considerable heterogeneity was present in both subgroups and all therapies described here were adapted to the respective study sample. The MS population is best represented in these meta-analyses, including fifteen RCTs of which eight were included in the first meta-analysis. The second meta-analysis included only studies in MS populations. Overall, the mean age of MS patient groups was lower compared to the PD patient groups. One can imagine that having a progressive neurological disorder in an earlier or later phase of life results in different psychosocial issues and cognitive abilities to benefit from therapy.

A considerably large effect size was found in the pilot study of Okai and colleagues [41]. In this study, all PD patients additionally suffered from impulse control disorders. When the treatment components were critically investigated, it was notable that this was the only CBT-based intervention that included executive dysfunction education. PD patients often show an impairment in executive functioning in an early stage of the disease [56,57]. Since this study showed a great improvement in psychological distress, this might indicate that executive dysfunction plays an important role in regulating negative emotions and cognitions, at least in PD patients with impulse control disorders. This, however, needs confirmation in future research.

The pilot study by Kiropoulos et al. [35] also showed a large effect size ($g = 1.64$). This study included newly diagnosed MS patients (< 5 years since diagnosis) and the age of these patients was lower compared to other studies that investigated MS populations. These patients might be less severely affected compared to other study populations. Comparisons, however, could not be made since studies reported different measures of disease severity. No differences were found concerning treatment components when compared with other CBT-based interventions in MS.

Of great importance is the focus of the treatment types and control conditions. The studies by Ghielen et al. [40], Oreja-Guevera et al. [48], and Nordin et al. [47] investigated MBTs. These three studies showed (non-significant) negative effect sizes of $g = -0.45$, $g = -0.37$, and $g = -0.10$, respectively, favoring the control condition in reducing psychological distress symptoms. These studies all included an active form of control condition: physical therapy (TAU), psycho education, and relaxation, which might have diminished the positive effect. Besides this, the focus of ACT is not on symptom reduction but on coping with the disease despite of the symptoms that are present. This is achieved by improving awareness of ones bodily sensations, thoughts and feelings. As one can imagine, when one is more aware of his/her symptoms, these will also be more often reported, resulting in a higher score on questionnaires.

This leads us into the discussion concerning the suitability of questionnaires to measure treatment effects. Since MBTs are focused on awareness and acceptance, and not aim to reduce symptoms, questionnaires that measure the prevalence or severity of symptoms are less appropriate. The studies by Bogosian et al. [32] and Simpson et al. [38], however, investigated mindfulness interventions and showed effect sizes of $g = 0.55$ and $g = 1.04$, respectively, in improving general mental health. In addition, when overall psychological distress was measured with general mental health questionnaires, a high effect size of $g = 0.79$, although with considerable heterogeneity, was found. The focus of an intervention, type of control condition, and the outcome measures used seem to be of importance in evaluating the effectiveness, and therefore need to be carefully considered when conducting an RCT.

Overall, the included studies had low quality, only three out of seventeen studies reached good quality according to the risk of bias tool. The findings need to be carefully interpreted since risk of bias is present in most of the studies and might have influenced the treatment effects. Each study suffers from different types of bias, except for the performance bias which is always a risk due to the nature of these intervention studies.

4.1. Limitations and implications

First, the effect size is solely based on studies in patients with PD and MS, since there were no RCTs found in HD that investigated the effect of psychological interventions on psychological distress. Second, MS patients might be overrepresented in the meta-analysis since fifteen

out of nineteen RCTs investigated MS populations, resulting in the effect size being driven mostly by MS populations, especially in the second meta-analysis in which only MS populations were included. Heterogeneity estimates were above 40% in most analyses, reflecting high heterogeneity within the meta-analyses, and most studies included small sample sizes, which resulted in low power. Finally, the overall quality of the studies was low and the quality of one study could not be assessed.

It is therefore recommended to study psychological interventions in more detail and in larger patient samples in study designs with higher methodological quality. Especially in HD more research is needed, since no RCTs on the effects of psychological treatment were found in our literature search. It might also be interesting to investigate the addition of psychopharmacological therapies, besides psychotherapy. Besides a primary focus on reducing psychological distress, we recommend to investigate the effect on coping with the disease, quality of life, valued living, or self-efficacy, especially in RCTs studying the effect of MBTs. Since progression of the disease is inevitable, it is therefore important to learn how to cope with the disease instead of focusing on symptom reduction only. Furthermore, caution is warranted in the choice of outcome measures and the type of control conditions as comparators, since these decisions greatly influence the study outcome. Lastly, it might be interesting to include executive dysfunction education in interventions for PD patients with impulse control disorders.

4.2. Conclusion

Despite the abovementioned limitations, we conclude that CBTs and MBTs have a small to moderate effect on reducing psychological distress in patients with PD and MS. However, more research is warranted, especially in HD and PD patient samples. These studies need to have better methodological quality (e.g. lower risk of bias) and study samples should be larger to achieve a sufficient power.

Author's contributions

IG: junior researcher, psychologist, data collection and analysis, manuscript writing. SR: psychiatrist, epidemiologist, data collection, critical revision of the manuscript. REB: psychologist, rating of investigated treatments, critical revision of the manuscript. MHdG: psychologist, rating of investigated treatments, critical revision of the manuscript. EvW: associate professor neurorehabilitation, movement scientist, critical revision of the manuscript. OAvdH: professor of neuropsychiatry, psychiatrist, supervision junior researcher, critical revision of the manuscript. PC: professor of clinical psychology, data analysis, supervision junior researcher, critical revision of the manuscript. All authors read and approved the final manuscript.

Conflicts of interest and source of funding

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

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