Research Paper

Therapeutic benefits of pharmacologic and nonpharmacologic treatments for depressive symptoms after traumatic brain injury: a systematic review and network meta-analysis

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Background: Depression is a common morbidity after traumatic brain injury. This network meta-analysis investigated the efficacy and tolerability of pharmacologic and nonpharmacologic interventions for depression after traumatic brain injury. **Methods:** We extracted randomized controlled trials examining pharmacologic or nonpharmacologic interventions with placebo- or active-controlled designs from PubMed, the Cochrane Library and ScienceDirect, from inception to October 30, 2018. We based study selection and extraction of a predefined list of variables on the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines, and conducted meta-analysis procedures using random effects modelling. Primary outcomes were changes in depressive symptom severity after pharmacologic or nonpharmacologic treatment; the secondary outcome was tolerability, reflected in overall patient dropout rates. **Results:** Our analysis of 27 randomized controlled trials (10 pharmacologic, total *n* = 483, mean age = 37.9 yr; 17 nonpharmacologic, total *n* = 1083, mean age = 38.0 yr) showed that methylphenidate had significantly superior efficacy compared to placebo or control (standardized mean difference –0.91, 95% confidence interval [CI] –1.49 to –0.33). Sertraline was associated with significantly lower tolerability (i.e., a higher dropout rate) compared to placebo or control (odds ratio 2.65, 95% CI 1.27 to 5.54). No nonpharmacologic treatment was more effective than the others, and we found no significant differences in tolerability (i.e., dropout rates) among the nonpharmacologic treatments. **Limitations:** Heterogeneity in participant characteristics (e.g., comorbidities), study designs (e.g., trial duration) and psychopathology assessment tools, as well as small trial numbers for some treatment arms, could have been confounders. **Conclusion:** The present network meta-analysis suggests that methylphenidate might be the best pharmacologic intervention for depressive symptoms related to traumatic brain injury. None of the nonpharmacologic interventions was associated with better improvement in depressive symptoms than the others or than control conditions. None of the pharmacologic or nonpharmacologic treatments had inferior tolerability compared to placebo or controls except for sertraline, which had significantly lower tolerability than placebo.

Introduction

Depressive disorders after traumatic brain injury (TBI) are not uncommon, with an estimated incidence of 16% to 60%,[1–3] and the prevalence of post-TBI major depression has been reported to be as high as 25% to 50%.[4,5] Another disturbing finding is that TBI-associated major depressive disorder (MDD) is a long-term condition with a increased prevalence over a person's lifetime, up to 50 years after injury.[6] Not only has TBI-related MDD been associated with impaired executive function[4] and poor functional outcome,[7] it has also been linked to elevated risk of suicide.[8]

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Current clinical treatment for post-TBI depression consists of pharmacologic and nonpharmacologic strategies.[9] In spite of the lack of specific pharmacologic guidelines for the treatment of post-TBI depression, several pair-wise meta-analyses have investigated the efficacy of antidepressants, with mixed results.[10–12] On the other hand, nonpharmacologic treatments encompass psychotherapeutic approaches such as supportive psychotherapy, cognitive behavioural therapy (CBT) and mindfulness-based CBT.[13] Surprisingly, despite the prevalence and severity of post-TBI depression, there is no consensus on standard therapeutic guidelines.[10] This gap may be partly attributable to the diversity of mechanisms underlying the development of depression after TBI. For instance, comorbidities that contribute to the risk of MDD — such as seizures, posttraumatic stress disorder or chronic pain — are common in patients with TBI.[14–16] A body of evidence has shown that post-TBI epilepsy may worsen chronic behavioural outcomes in the emotional, cognitive and psychosocial functioning domains.[17] As well, one study has reported an association between mild TBI and sleep and circadian disturbances, which may aggravate other sequelae of TBI, such as depression.[18]

The other major difficulty in establishing clinical practice guidelines for post-TBI depression is a lack of well-controlled, evidence-based studies.[11] Although previous randomized controlled trials (RCTs) have demonstrated positive effects of sertraline (a selective serotonin reuptake inhibitor [SSRI]) on the prevention[19] and treatment[1] of depression following TBI, recent meta-analyses have shown either borderline[11] or no significant[10] benefits of antidepressants over placebo in the treatment of post-TBI MDD. As well, the reliability of the results of previous meta-analyses was affected by a high degree of bias and heterogeneity,[10] or by a limited number of included studies.[11] Similarly, the clinical benefit of nonpharmacologic approaches remains inconclusive because of a high risk of bias resulting from a lack of blinding of outcome assessors in the majority of RCTs, and wide variability of results.[13] Most importantly, none of the previous meta-analyses was able to provide information about the comparative efficacy of the different interventions.

To address these uncertainties, we used network meta-analysis — which is designed to compare the efficacy of different treatments — to systemically assess the therapeutic benefit and tolerability of pharmacologic and nonpharmacologic treatments for post-TBI depression among eligible RCTs.

Methods

Study guideline and design

Detailed information about the materials and methods used in the present study is presented in Appendix 1, available at jpn.ca/190122-a1. In brief, the layout of the current network meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension guideline (Appendix 1, Table S1).[20] This study is registered with PROSPERO (CRD42020196151).

Literature search and targets of treatment strategy

We reviewed the PubMed, Cochrane Library, ScienceDirect, Web of Science and the clinical trial registration (ClinicalTrials.gov) databases from inception to October 30, 2018, and included published RCTs with either placebo- or active-controlled designs in humans. The targets for treatment strategy were set to include 2 options: pharmacologic treatment or nonpharmacologic treatment for depressive symptoms in patients with TBI. For nonpharmacologic treatment, we included mainly those targeting cognitive or behavioural strategies and excluded invasive strategies such as transcranial magnetic stimulation.

Outcome measures

The primary outcomes were changes in depression rating scale scores before and after pharmacologic or nonpharmacologic treatment in patients with TBI. The secondary outcome was tolerability, reflected by overall dropout rate during pharmacologic or nonpharmacologic treatment in patients with TBI.

Bias assessment

We used the Cochrane risk of bias tool[21] to evaluate risk of bias in the included studies. We then further categorized the studies according to overall risk of bias.

Statistical analysis

We used a random-effects pair-wise meta-analysis model and the frequentist random-effects model of network meta-analysis, which was proposed by Lu and Ades.[22] The network meta-analysis, which consisted of direct and indirect comparisons, was conducted to compare effect sizes between studies with the same type of treatment (i.e., pharmacologic or nonpharmacologic). We undertook 2-tailed statistical tests and set the significance level at $p < 0.05$. We used the surface under the cumulative ranking curve (SUCRA) to rank treatments for an outcome.[23] We used meta-regression to assess the relationship between treatment effectiveness and participant characteristics, including age, sex and treatment duration. We selected trials involving patients with definite diagnosis of MDD to perform a subgroup analysis. Finally, we assessed potential inconsistency between direct and indirect evidence within a loop formed by 3 or more treatments using the loop-specific approach and local inconsistency with the node-splitting method. We used the design-by-treatment model to evaluate global inconsistency for the entire network meta-analysis.[24] We performed the full analytic procedure using STATA version 14.0 (www.stata.com/stata14/).

Results

Studies eligible for network meta-analysis

After initial screening, 73 articles were eligible for full-text review, but 46 were excluded at this stage for various reasons

(see Figure 1 and Appendix 1, Table S2, for detailed information). The final number of articles included in the current study was 27 (Table 1).[1,25–50] Of the 27 articles, 10 assessed the effects of pharmacologic treatments and 17 assessed the effects of nonpharmacologic treatments. The geometric distribution of the treatment arms is provided in Figure 2.

Characteristics of the included studies

Among the 10 RCTs that investigated the effects of pharmacologic treatment on depressive symptoms in patients with TBI, 483 participants (mean age 37.9 yr; mean proportion of female participants 23.9%; mean treatment duration 12.3 w) were included at baseline. The rating scales for the evaluation of depression varied widely across the included trials: the Hospital Anxiety and Depression Scale, the Beck Depression inventory, the Hamilton Depression Rating Scale, the Neurobehavioural Functioning Inventory-Depression, the Patient Health Questionnaire-9, the Montgomery–Åsberg Depression Rating Scale and the Affect/Mood scale.

Among the 17 RCTs that assessed the therapeutic effects of nonpharmacologic treatments against depressive symptoms in patients with TBI, 1083 participants (mean age 38.0 yr; mean proportion of female participants 24.3%; mean treatment duration 17.5 w) were included at baseline. The rating scales for the evaluation of depression varied widely across the included trials: the Patient Health Questionnaire-9, the Beck Depression inventory, the Hospital Anxiety and Depression Scale, the Depression and Anxiety Stress Scale–Depression, the Center for Epidemiologic Studies Depression Scale, the Hamilton Depression Rating Scale 17 items, the Authentic Happiness Inventory, the Neurobehavioural Functioning Inventory-Depression, the Profile of Mood States–Depression and the Symptom Checklist–90–Revised.

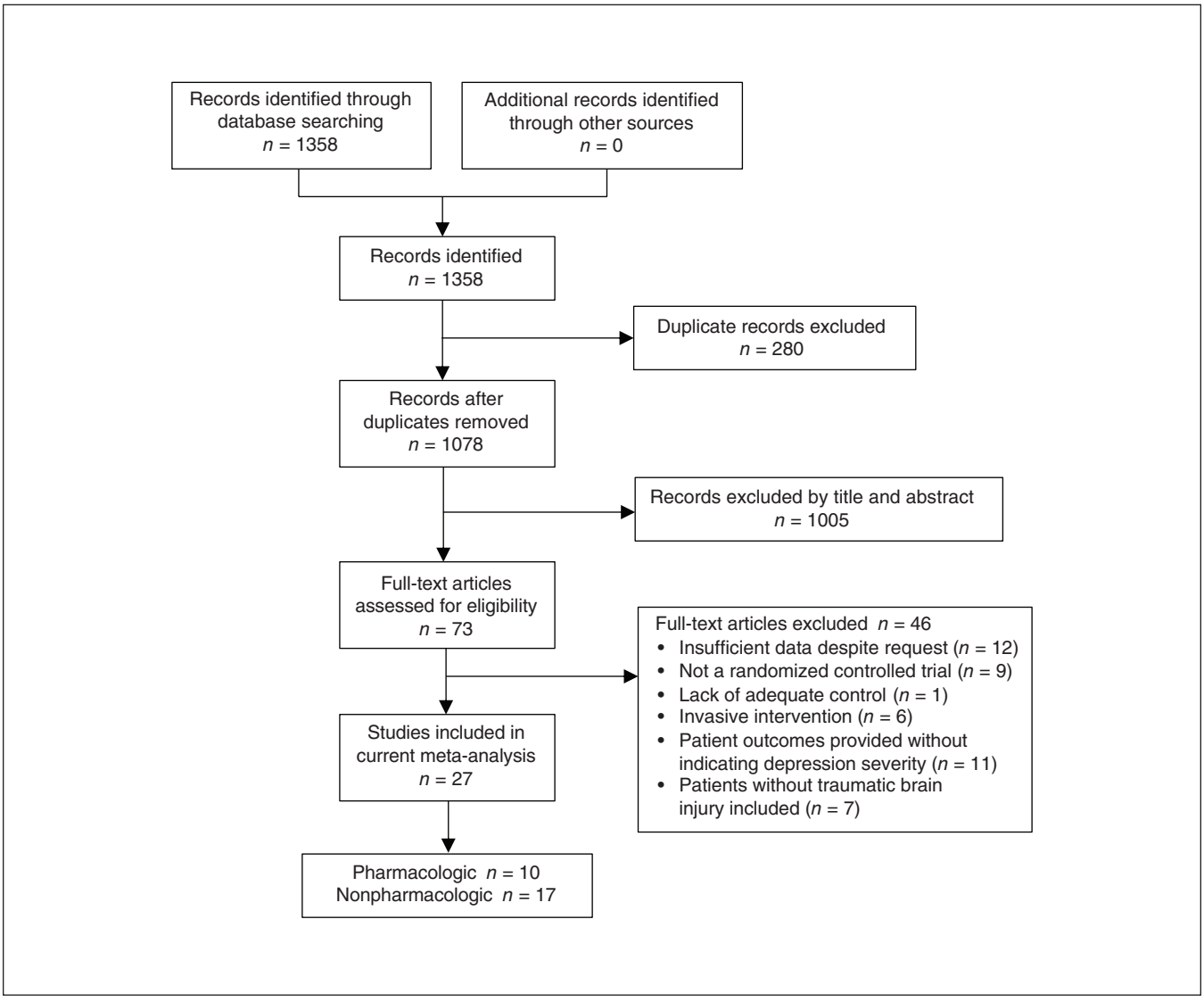

Fig. 1: Flowchart identifying eligible studies for the network meta-analysis.

Table 1: Characteristics of included studies (part 1 of 2)

Study	Diagnosis	Head injury severity	MDD	Study design	Comparison	Patients, *n*	Duration, w	Outcome*	Mean age ± SD, yr	Female, %	Dropout rate, %	Country
Pharmacologic interventions												
Ansari et al.[25]	TBI	Mild to moderate	Yes	RCT	Sertraline 50 mg/d Placebo	40 40	24	PHQ-9 (+)	> 18	0	NA	India
Ashman et al.[1]	TBI MDD	NA	Yes	RCT	Sertraline 25–200 mg/d Placebo	22 19	10	HAM-D (–)	49.1 ± 10.9	41.5	NA	Australia
Fann et al.[26]	TBI MDD	NA	Yes	RCT	Sertraline 25–200 mg/d Placebo	31 31	12	HAM-D (–)	37.5 ± 12.5	24.2	32.0 10.0	United States
Grima et al.[27]	TBI Insomnia	Mild to severe	NA	RCT (crossover)	Melatonin 2 mg/d Placebo	18 15	4	HADS-D (–)	37 ± 11	33.3	0.0 8.6	Australia
Lee et al.[28]	TBI MDD	Mild to moderate	Yes	RCT	Methylphenidate 20 mg/d Sertraline 100 mg/d Placebo	10 10 10	4	HAM-D (+) HAM-D (+)	35.3 ± 8.0 33.6 ± 12.3 35.5 ± 7.2	20	NA	Korea
Novack et al.[29]	TBI	Moderate to severe	No	RCT	Sertraline 50 mg/d Placebo	49 50	12	NFI-D (+)	35.3 ± 16.7 34.5 ± 15.6	27.3	40.8 24.0	United States
Rao[30]	TBI MDD	NA	Yes	RCT	Escitalopram 10–20 mg/d Placebo	7 6	12	MADRS	NA	35.7	11.4 0.0	United States
Ripley et al.[31]	TBI Attention problems	Moderate to severe	NA	RCT (crossover)	Atomoxetine 80 mg/d Placebo	26 29	2	NFI-D (–)	40.6 ± 11.8	25.5	3.9 6.9	United States
Wroblewski et al.[32]	TBI MDD	Severe	Yes	RCT	Despiramine 150 mg/d Placebo	6 4	4	Affect/Mood scale (–)	32.2 ± 8.51	30	NA	United States
Zhang et al.[33]	TBI MDD	Mild to moderate	Yes	RCT	Methylphenidate 20 mg/d Placebo	18 18	30	BDI (+)	36.3 ± 10.9 34.9 ± 12.1	25	5.6 11.1	China
Nonpharmacologic interventions												
Andrewes et al.[34]	TBI	NA	NA	RCT	Positive psychology interventions CBT	5 5	12	AHI (+)	38.3 ± 5.9 46.0 ± 11.1	10	20.0 0.0	United Kingdom
Ashman et al.[35]	TBI MDD	NA	Yes	RCT	CBT Supportive psychotherapy	39 38	12	BDI (–)	47.1 ± 10.6 48.1 ± 10.2	54.5	43.6 44.8	United States
Bedard et al.[36]	TBI MDD	NA	Yes	RCT	Mindfulness-based cognitive therapy Usual care	38 38	10	BDI (+)	46.8 ± 13.4	44.7	33.3 20.8	Canada
Bell et al.[37]	TBI	Mild	NA	RCT	Telephone problem-solving Usual care	178 178	24	PHQ-9 (–)	29.4 ± 7.2	6.74	22.0 17.0	United States
Bellon et al.[38]	TBI	NA	NA	RCT (crossover)	Walking program Nutrition program	28 29	12	CES-D (–)	43.7 ± 15.8	41	0.0 0.0	United States

Table 1: Characteristics of included studies (part 2 of 2)

Study	Diagnosis	Head injury severity	MDD	Study design	Comparison	Patients, *n*	Duration, w	Outcome*	Mean age ± SD, yr	Female, %	Dropout rate, %	Country
Bombardier et al.[39]	TBI	Mild to severe	NA	RCT	Telephone supportive psychotherapy Usual care	62 64	36	NFI-D (+)	34.5 ± 13.9 37.1 ± 15.6	25.4	27.0 25.6	United States
Driver et al.[40]	TBI Cognitive impairment	NA	NA	RCT	Walking program Vocational rehabilitation class	8 8	8	POMS-D (–)	38.8 ± 2.5 40.8 ± 14.7	NA	0.0 0.0	United States
Fann et al.[41]	TBI MDD	Mild to severe	Yes	RCT	CBT Telephone CBT Usual care	18 40 42	16	HAMD-17 (–)	45.8 ± 13.3	37	17.0 7.0 14.0	United States
McDonald et[42]	TBI	Severe	No	RCT	Social skills training Social group Usual care	18 17 16	12	DASS-D (–)	36.3 ± 10.7 33.1 ± 11.7 35.2 ± 11.3	21.6	22.2 23.5 25.0	
Nguyen et al.[43]	TBI Poor sleep	Mild to severe	NA	RCT	CBT Usual care	13 11	8	HADS-D (+)	43.9 ± 13.0	33.3	15.3 9.1	Australia
Ponsford et al.[44]	TBI Anxiety or depressive symptoms	Mild to severe	NA	RCT	CBT (+ non-directive supportive counselling) Motivational interviewing + CBT Usual care	26 26 23	12	DASS-D (+)	42.2 ± 14.5	26.7	15.3 15.4 8.7	Australia
Potter et al.[45]	TBI	NA	NA	RCT	CBT Usual care	26 20	12	HADS-D	41.4 ± 11.6	45.6	3.8 0.0	United Kingdom
Simpson et al.[46]	TBI Suicidal ideation or hopelessness	Severe	NA	RCT	Group-based CBT Usual care	8 9	10	HADS-D (–)	39.4 ± 12.4 44.1 ± 11.7	NA	0.0 11.1	Australia
Storzbach et al.[47]	TBI	Mild	NA	RCT	Compensatory cognitive training Usual care	50 69	10	BDI (–)	35.4 ± 8.4 34.8 ± 7.4	5.0	28.0 26.0	United States
Struchen et al.[48]	TBI	NA	NA	RCT	Social training Usual care	12 18	12	CES-D (x)	NA	NA	50.0 14.3	United States
Tiersky et al.[49]	TBI Cognitive dysfunction Emotional distress	Mild to moderate	NA	RCT	CBT Usual care	11 9	11	SCL-90R (+)	46.9 ± 10.5	55	21.4 40.0	United States
Twamley et al.[50]	TBI	Mild to moderate	NA	RCT	CogSMART + supported employment Enhanced supported employment	16 18	12	HAM-D (–)	29.4 ± 6.2 34.3 ± 7.4	5.9	12.5 5.6	United States

AHI = Authentic Happiness Inventory; BDI = Beck Depression Inventory; CBT = cognitive behavioural therapy; CES-D = Center for Epidemiological Studies–Depression; CogSMART = Cognitive Symptom Management and Rehabilitation Therapy; DASS-D = Depression and Anxiety Stress Scale–Depression; HADS-D = Hospital Anxiety and Depression Scale, Depression subscale; HAM-D = Hamilton Depression Rating Scale; HAMD-17 = Hamilton Depression Rating Scale, 17 items; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = major depressive disorder; NA = not available; NFI-D = Neurobehavioral Functioning Inventory–Depression; PHQ-9 = Patient Health Questionnaire-9; POMS-D = Profile of Mood States–Depression; RCT = randomized controlled trial; SCL-90R = Symptom Checklist 90–Revised; TBI = traumatic brain injury.

*(+) = intervention group significantly better than control group; (–) = no significant difference between intervention group and control group; (x) = intervention group significantly worse than control group.

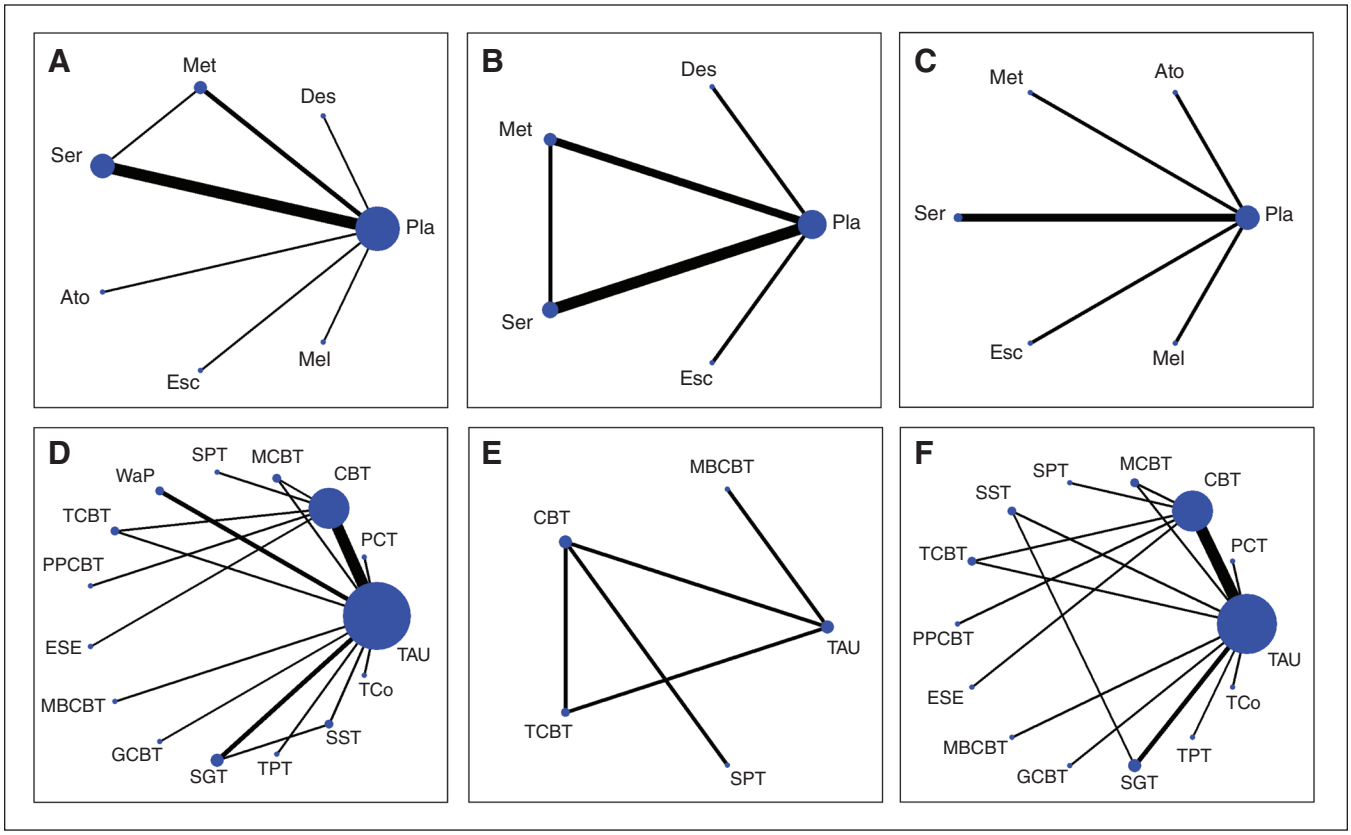

Fig. 2: Whole geometric distribution of the treatment arms of the network meta-analysis. Network structure of the treatment effects of pharmacologic interventions on (A) depression severity change, (B) the subgroup with a definite diagnosis of MDD and (C) dropout rate. Network structure of the treatment effects of nonpharmacologic interventions on (D) depression severity change, (E) the subgroup with a definite diagnosis of MDD and (F) dropout rate. The lines between nodes represent direct comparisons in various trials, and the size of each circle is proportional to the size of the population involved in each treatment. The thickness of the line is proportional to the number of trials connected to the network. Ato = atomoxetine; CBT = cognitive behavioural therapy; Des = desipramine; Esc = escitalopram; ESE = enhanced supported employment; GCBT = group-based cognitive behavioural therapy; MBCBT = mindfulness-based cognitive behavioural therapy; MCBT = motivational training plus cognitive behavioural therapy; Mel = melatonin; Met = methylphenidate; PCT = psychotherapy with compensatory cognitive training; Pla = placebo; PPCBT = positive psychological cognitive behavioural therapy; Ser = sertraline; SGT = social group training; SPT = supportive psychotherapy; SST = social skills training; TAU = treatment as usual; TCBT = telephone cognitive behavioural therapy; TCo = telephonic counselling; TPT = telephone supportive psychotherapy; WaP = walking program.

Pharmacologic treatment for depressive symptoms in patients with TBI

Efficacy

Ten articles addressed the efficacy of pharmacologic treatments for depressive symptoms in patients with TBI, including 7 treatment arms: placebo/control, desipramine, methylphenidate, sertraline, atomoxetine, melatonin and escitalopram (Fig. 2A and Table 2). Pair-wise meta-analysis demonstrated that only methylphenidate and sertraline showed treatment efficacies superior to those of placebo or control (SMD –0.91, 95% confidence interval [CI] –1.55 to –0.28; and SMD –0.28, 95% CI –0.54 to –0.02, respectively).

Consistent with the above findings, the network meta-analysis showed that only methylphenidate had a treatment efficacy that was significantly superior to that of placebo or control (SMD –0.91, 95% CI –1.49 to –0.33). In addition, the efficacy of methylphenidate was significantly higher than that of sertraline and melatonin (SMD –0.65, 95% CI –1.26 to –0.03; and SMD –0.95, 95% CI –1.77 to –0.12, respectively; Table 2 and Figure 3A). A SUCRA ranking of the efficacies of the pharmacologic treatments for depressive symptoms in patients with TBI also demonstrated that methylphenidate had the best efficacy (Appendix 1, Table S3A). We performed a meta-regression using restricted maximum likelihood estimators to examine the potential effect of age, sex distribution (i.e., proportion of female participants) and treatment duration on treatment effectiveness. The results of this meta-regression did not reveal a significant effect on treatment effectiveness.

We performed further subgroup analyses focusing on trials that recruited participants with a definite diagnosis of MDD; this analysis included 5 treatment arms (placebo/control, desipramine, methylphenidate, sertraline and escitalopram; Figure 2B). Both pair-wise and network meta-analyses showed that only methylphenidate had a treatment efficacy

Table 2: League table of association between pharmacologic treatments and changes in depressive symptom severity

Methylphenidate				–0.86 (–1.77 to 0.04)			–0.91 (–1.55 to –0.28)*
–0.09 (–1.84 to 1.66)	Desipramine						–0.82 (–2.44 to 0.81)
–0.41 (–1.64 to 0.82)	–0.32 (–2.29 to 1.66)	Escitalopram					–0.50 (–1.53 to 0.54)
–0.65 (–1.26 to –0.03)*	–0.55 (–2.23 to 1.12)	–0.24 (–1.35 to 0.88)	Sertraline				–0.28 (–0.54 to –0.02)*
–0.74 (–1.60 to 0.11)	–0.65 (–2.42 to 1.12)	–0.33 (–1.59 to 0.92)	–0.10 (–0.79 to 0.59)	Atomoxetine			–0.16 (–0.71 to 0.39)
–0.95 (–1.77 to –0.12)*	–0.86 (–2.61 to 0.90)	–0.54 (–1.77 to 0.69)	–0.30 (–0.95 to 0.35)	–0.20 (–1.06 to 0.66)	Melatonin		0.04 (–0.45 to 0.53)
–0.91 (–1.49 to –0.33)*	–0.81 (–2.47 to 0.84)	–0.50 (–1.58 to 0.59)	–0.26 (–0.54 to 0.01)	–0.16 (–0.79 to 0.47)	0.04 (–0.54 to 0.63)	Placebo	

CI = confidence interval; SMD = standardized mean difference.
Results of pair-wise (right side of row) and network (left side of row) meta-analysis are presented as estimate effect sizes for postintervention depressive severity. Interventions are reported in order of mean ranking of treatment effect, and outcomes are expressed as SMD (95% CI). For pair-wise meta-analyses, an SMD of less than 0 indicates that the treatment specified in the row led to better improvement in depressive severity than the treatment specified in the column. For network meta-analysis, an SMD of less than 0 indicates that the treatment specified in the column led to better improvement in depressive severity than the treatment specified in the row.
*Statistically significant ($p < 0.05$).

that was significantly superior to placebo/control (SMD –0.91, 95% CI –1.55 to –0.28; and SMD –0.85, 95% CI –1.38 to –0.31, respectively; Appendix 1, Table S4A and Figure S1A). The efficacy of methylphenidate was also significantly higher than that of sertraline (SMD –0.80, 95% CI –1.39 to –0.20). A SUCRA ranking of the efficacies of the pharmacologic treatments for depressive symptoms in patients with TBI and MDD demonstrated that methylphenidate still had the best efficacy (Appendix 1, Table S3B).

Tolerability

Four eligible articles and 1 trial provided data related to dropout rates across 5 treatment arms (placebo/control, methylphenidate, sertraline, atomoxetine and escitalopram; Figure 2C and Appendix 1, Table S4B). Both pair-wise and network meta-analyses demonstrated that only the dropout rate of sertraline was significantly higher than that of placebo/control (odds ratio [OR] 2.65, 95% CI 1.27 to 5.54; and OR 2.65, 95% CI 1.27 to 5.54, respectively). A forest plot for dropout rates across the pharmacologic treatment groups relative to those of placebo/control is presented in Appendix 1, Figure S1B. A SUCRA ranking of the relative tolerability based on dropout rate (i.e., a lower likelihood of early dropout from study) among the pharmacologic treatments showed that melatonin had the best overall tolerability (i.e., the lowest dropout rate; Appendix 1, Table S3C). The results of for meta-regression revealed that age, sex distribution and treatment duration did not significantly influence tolerability.

Nonpharmacologic treatment for depressive symptoms in patients with TBI

Efficacy

Seventeen articles addressed the efficacy of nonpharmacologic treatments for depressive symptoms in patients with TBI, including 15 treatment arms: usual care, CBT, positive psychological CBT, telephone supportive psychotherapy, enhanced supported employment, mindfulness-based CBT, supportive psychotherapy, motivational training plus CBT, a walking program, telephone CBT, psychotherapy with compensatory cognitive training, social group training, group-based CBT program, social skills training and telephonic counselling (Table 3 and Figure 2D). Pair-wise meta-analysis showed that the efficacies of CBT, mindfulness-based CBT, telephone supportive psychotherapy and telephonic counselling were significantly better than usual care (SMD –0.45, 95% CI –0.85 to –0.06; SMD –0.52, 95% CI –0.98 to –0.06; SMD –0.73, 95% CI –1.11 to –0.35; and SMD –0.27, 95% CI –0.50 to –0.03, respectively).

For the network meta-analysis, Figure 3B shows the efficacies of nonpharmacologic treatments for depressive symptoms relative to those of usual care. None of the investigated nonpharmacologic treatments was more effective than the others. A SUCRA ranking demonstrated that positive psychological cognitive behavioural therapy had the highest efficacy among the investigated nonpharmacologic treatments for depressive symptoms (Appendix 1, Table S3D). According to meta-regression analysis, age, sex distribution and treatment duration had no significant effect on efficacy.

We conducted a subgroup analysis focusing on trials that recruited patients with a definite diagnosis of MDD, which included 5 treatment arms: usual care, mindfulness-based

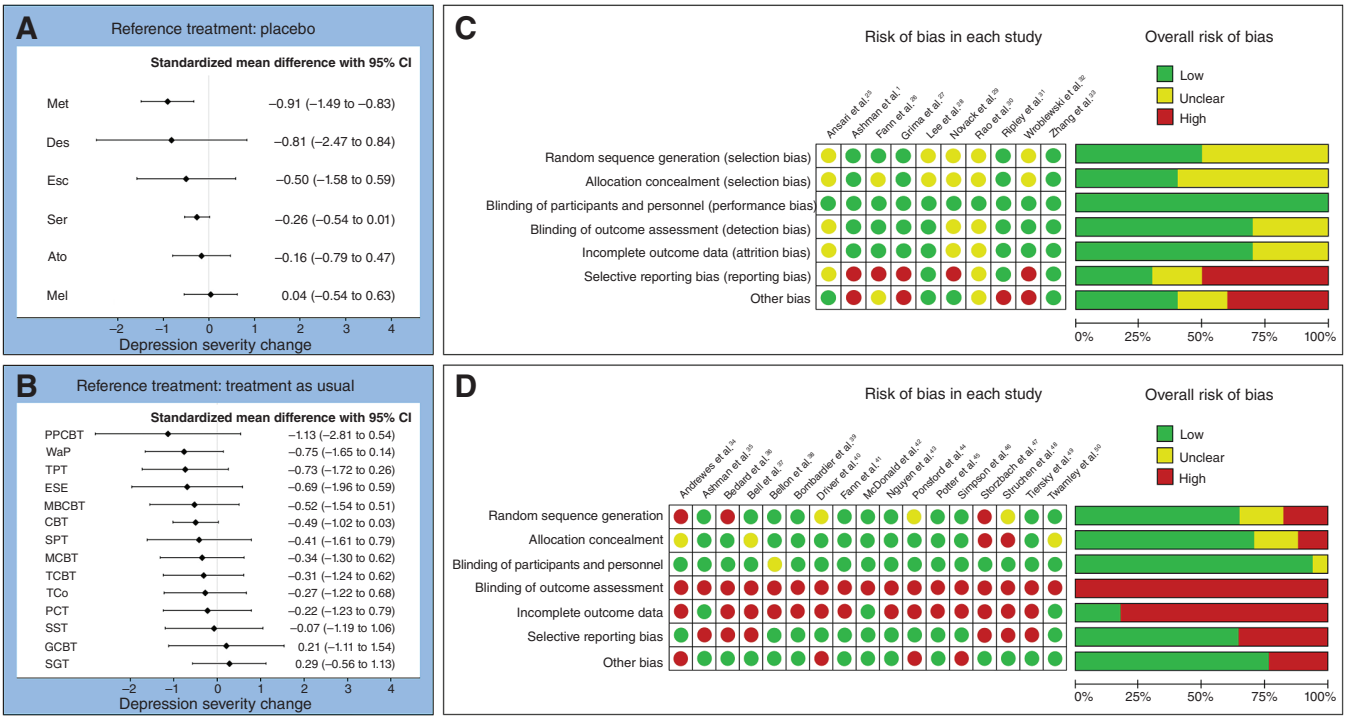

Fig. 3: Forest plot of the current network meta-analysis on (A) pharmacologic and (B) nonpharmacologic interventions for the treatment of depression after traumatic brain injury versus usual care; effect size greater than 0 indicates more improvement following interventions compared to placebo or usual care. Risk of bias arising from each study and the overall bias in literature for (C) pharmacologic and (D) nonpharmacologic interventions. Ato = atomoxetine; CBT = cognitive behavioural therapy; CI = confidence interval; Des = desipramine; EET = enhanced supported employment; Esc = escitalopram; GCBT = group-based cognitive behavioural therapy; MBCBT = mindfulness-based cognitive behavioural therapy; MCBT = motivational training plus cognitive behavioural therapy; Mel = melatonin; Met = methylphenidate; PCT = psychotherapy with compensatory cognitive training; PPCBT = positive psychological cognitive behavioural therapy; Ser = sertraline; SGT = social group training; SPT = supportive psychotherapy; SST = social skills training; TAU = treatment as usual; TCBT = telephone cognitive behavioural therapy; TCo = telephonic counselling; TPT = telephone supportive psychotherapy; WaP = walking program.

CBT, CBT, telephone CBT and supportive psychotherapy (Figure 2E and Appendix 1, Table S4C). Pair-wise meta-analysis and network meta-analysis showed that only mindfulness-based CBT had significantly better efficacy than usual care (SMD –0.52, 95% CI –0.98 to –0.06 for pair-wise meta-analysis and SMD –0.52, 95% CI –0.98 to –0.06 for network meta-analysis; Appendix 1, Table S4C and Figure S1C). A SUCRA ranking showed that mindfulness-based CBT had the highest efficacy against depressive symptoms among the nonpharmacologic treatments investigated (Appendix 1, Table S3E).

Tolerability

Fifteen articles provided evidence on dropout rates for the different nonpharmacologic treatments, including 14 treatment arms: usual care, positive psychological treatments, telephone supportive psychotherapy, enhanced supported employment, mindfulness-based cognitive therapy, CBT, supportive psychotherapy, motivational training plus CBT, telephone CBT, psychotherapy with compensatory cognitive training, social group training, group-based CBT, social skills training and telephonic counselling (Figure 2F and Appendix 1, Table S4D). We found no nominally significant differences in tolerability measured by dropout rate according to pair-wise meta-analysis or network meta-analysis. The forest plot for dropout rates among the different nonpharmacologic treatments relative to those of usual care is shown in Appendix 1, Figure S1D. A SUCRA ranking showed that telephone CBT had the lowest likelihood of dropouts among the nonpharmacologic strategies examined (Appendix 1, Table S3F). According to meta-regression analysis, age, sex distribution and treatment duration did not moderate tolerability.

Risk of bias and publication bias

Among the pharmacologic treatments, 57.1%, 30.0% and 12.9% of studies had an overall low, unclear and high risk of bias, respectively. We frequently observed an unclear risk of bias because of unclear reporting of randomization procedures, allocation or blindness (Figure 3C). Among the nonpharmacologic treatments, 55.4%, 5.9% and 38.7% of studies had overall low, unclear and high risk of bias, respectively. Unclear risk of bias because of unclear reporting of randomization procedures or allocation frequently occurred (Figure 3D).

Funnel plots for publication bias across the included studies (Appendix 1, Figure S2A to L) revealed general symmetry. As

Table 3: League table of association between nonpharmacologic interventions and changes in depressive symptom severity

PPCBT				−0.64 (−1.94 to 0.66)										
−0.38 (−2.26 to 1.51)	WaP											−0.90 (−2.30 to 0.50)		
−0.40 (−2.35 to 1.54)	−0.02 (−1.36 to 1.31)	TPT										−0.73 (−1.11 to −0.35)*		
−0.45 (−2.41 to 1.52)	−0.07 (−1.61 to 1.47)	−0.04 (−1.66 to 1.57)	ESE	−0.19 (−0.90 to 0.52)										
−0.64 (−2.23 to 0.95)	−0.26 (−1.27 to 0.75)	−0.24 (−1.36 to 0.89)	−0.19 (−1.35 to 0.97)	CBT		−0.09 (−0.65 to 0.48)	−0.10 (−0.65 to 0.44)	0.06 (−0.50 to 0.62)				−0.45 (−0.85 to −0.06)*		
−0.61 (−2.58 to 1.35)	−0.24 (−1.60 to 1.13)	−0.21 (−1.64 to 1.22)	−0.17 (−1.80 to 1.47)	0.02 (−1.13 to 1.17)	MBCBT							−0.52 (−0.98 to −0.06)*		
−0.72 (−2.64 to 1.20)	−0.35 (−1.82 to 1.13)	−0.32 (−1.88 to 1.24)	−0.28 (−1.86 to 1.31)	−0.09 (−1.16 to 0.99)	−0.11 (−1.69 to 1.47)	SPT								
−0.79 (−2.65 to 1.06)	−0.42 (−1.72 to 0.89)	−0.39 (−1.77 to 0.99)	−0.35 (−1.85 to 1.16)	−0.16 (−1.12 to 0.81)	−0.18 (−1.59 to 1.23)	−0.07 (−1.51 to 1.37)	MCBT					−0.29 (−0.85 to 0.28)		
−0.82 (−2.67 to 1.02)	−0.45 (−1.72 to 0.83)	−0.42 (−1.78 to 0.94)	−0.38 (−1.87 to 1.11)	−0.19 (−1.13 to 0.75)	−0.21 (−1.59 to 1.17)	−0.10 (−1.53 to 1.33)	−0.03 (−1.32 to 1.26)	TCBT				−0.11 (−0.54 to 0.33)		
−0.86 (−2.79 to 1.06)	−0.48 (−1.79 to 0.82)	−0.46 (−1.83 to 0.91)	−0.42 (−2.00 to 1.17)	−0.23 (−1.31 to 0.86)	−0.25 (−1.64 to 1.15)	−0.14 (−1.67 to 1.39)	−0.07 (−1.42 to 1.28)	−0.04 (−1.36 to 1.29)	TCo			−0.27 (−0.50 to −0.03)*		
−0.91 (−2.87 to 1.04)	−0.53 (−1.89 to 0.82)	−0.51 (−1.93 to 0.91)	−0.47 (−2.09 to 1.16)	−0.28 (−1.41 to 0.86)	−0.30 (−1.74 to 1.14)	−0.19 (−1.76 to 1.38)	−0.12 (−1.52 to 1.28)	−0.09 (−1.46 to 1.28)	−0.05 (−1.44 to 1.34)	PCT		−0.22 (−0.65 to 0.21)		
−1.07 (−3.08 to 0.95)	−0.69 (−2.12 to 0.75)	−0.66 (−2.16 to 0.83)	−0.62 (−2.32 to 1.08)	−0.43 (−1.67 to 0.81)	−0.45 (−1.97 to 1.07)	−0.34 (−1.98 to 1.30)	−0.27 (−1.75 to 1.20)	−0.24 (−1.70 to 1.21)	−0.20 (−1.67 to 1.26)	−0.15 (−1.66 to 1.36)	SST	−0.31 (−1.09 to 0.46)		−0.11 (−0.87 to 0.66)
−1.13 (−2.81 to 0.54)	−0.75 (−1.65 to 0.14)	−0.73 (−1.72 to 0.26)	−0.69 (−1.96 to 0.59)	−0.49 (−1.02 to 0.03)	−0.52 (−1.54 to 0.51)	−0.41 (−1.61 to 0.79)	−0.34 (−1.30 to 0.62)	−0.31 (−1.24 to 0.62)	−0.27 (−1.22 to 0.68)	−0.22 (−1.23 to 0.79)	−0.07 (−1.19 to 1.06)	TAU	−0.22 (−1.17 to 0.74)	−0.29 (−1.25 to 0.68)
−1.35 (−3.48 to 0.79)	−0.97 (−2.57 to 0.63)	−0.94 (−2.60 to 0.71)	−0.90 (−2.74 to 0.94)	−0.71 (−2.13 to 0.71)	−0.73 (−2.41 to 0.94)	−0.62 (−2.41 to 1.16)	−0.55 (−2.19 to 1.08)	−0.52 (−2.14 to 1.09)	−0.48 (−2.11 to 1.14)	−0.43 (−2.10 to 1.23)	−0.28 (−2.02 to 1.45)	−0.21 (−1.54 to 1.11)	GCBT	
−1.42 (−3.29 to 0.46)	−1.04 (−2.27 to 0.19)	−1.02 (−2.32 to 0.29)	−0.97 (−2.50 to 0.55)	−0.78 (−1.77 to 0.21)	−0.80 (−2.13 to 0.52)	−0.70 (−2.16 to 0.77)	−0.62 (−1.91 to 0.66)	−0.59 (−1.85 to 0.66)	−0.56 (−1.82 to 0.71)	−0.51 (−1.82 to 0.81)	−0.35 (−1.47 to 0.77)	−0.29 (−1.13 to 0.56)	−0.07 (−1.64 to 1.50)	SGT

CBT = cognitive-behavioural therapy; CI = confidence interval; ESE = enhanced supported employment; GCBT = group-based cognitive behavioural therapy; MBCBT = mindfulness-based cognitive behavioural therapy; MCBT = motivational training plus cognitive behavioural therapy; PCT = psychotherapy with compensatory cognitive training; PPCBT = positive psychological cognitive behavioural therapy; SGT = social group training; SMD = standardized mean difference; SPT = supportive psychotherapy; SST = social skills training; TAU = treatment as usual; TCBT = telephone cognitive behavioural therapy; TCo = telephonic counselling; TPT = telephone supportive psychotherapy; WaP = walking program.

Results of pair-wise (right side of row) and network (left side of row) meta-analysis are presented as estimate effect sizes for post-intervention depressive severity. Interventions are reported in order of mean ranking of treatment effect, and outcomes are expressed as SMD (95% CI). For pair-wise meta-analyses, an SMD of less than 0 indicates that the treatment specified in the row led to better improvement in depressive severity than the treatment specified in the column. For network meta-analysis, an SMD of less than 0 indicates that the treatment specified in the column led to better improvement in depressive severity than the treatment specified in the row.

*Statistically significant ($p < 0.05$).

well, results for Egger's test indicated no significant publication bias among the articles included in the network meta-analysis, for pharmacologic or nonpharmacologic treatments. In general, the network meta-analysis did not demonstrate local inconsistency (evaluated using the loop-specific approach and node-splitting method) or global inconsistency (assessed using the design-by-treatment method; Appendix 1, Tables S5 and S6).

Discussion

To the best of our knowledge, the present study is the first network meta-analysis aimed at investigating the efficacy and tolerability of pharmacologic and nonpharmacologic treatments for depressive symptoms after TBI. For pharmacologic treatment, based on our analysis of 10 RCTs with a total of 483 patients, we found that methylphenidate was associated with the best improvement in depressive symptoms among TBI patients, and sertraline had significantly lower tolerability (in terms of dropout rate) than placebo or other pharmacologic treatments. Our network meta-analysis of 17 RCTs on the benefits of nonpharmacologic treatments with a total of 1083 patients showed that none of the treatments investigated was associated with significantly better improvement or worse tolerability than the others.

One of our main findings was that some of the pharmacologic treatments were associated with superior therapeutic benefit for depressive symptoms in patients with TBI compared with placebo/control. This was consistent with the results of previous pair-wise meta-analyses, which addressed the benefits of pharmacologic treatments for post-TBI depressive symptoms.[10–12] In addition, based on the frequentist model of network meta-analysis and the SUCRA method, the present network meta-analysis provided further evidence to support the superiority of individual pharmacologic treatments. Specifically, our findings demonstrated that methylphenidate was associated with the best improvement of all pharmacologic treatments. A previous double-blind study has shown that depression in post-stroke patients may be treated with stimulants, instead of antidepressants, through increasing biogenic amines.[51] Methylphenidate — a stimulant that facilitates dopamine and norepinephrine neurotransmission in the prefrontal cortex[52] by inhibiting the presynaptic dopamine transporters of central adrenergic neurons and in part the norepinephrine transporters — augments synaptic cleft dopamine concentration and amplifies dopaminergic neurotransmission.[53] Moreover, a previous study has demonstrated that although sertraline alleviated only depressive symptoms in patients with TBI, methylphenidate improved both depressive and cognitive symptoms.[28] Because executive dysfunction is a frequent comorbidity of TBI-related depression,[4] methylphenidate may further improve depressive symptoms by enhancing cognitive function.

Another important finding of the current network meta-analysis was the lack of superior effectiveness of antidepressants compared to placebo. This finding was partially consistent with those of a previous meta-analysis based on high-quality RCTs showing an insignificant difference in nonresponse rate between antidepressants and placebo (OR 0.42, 95% CI 0.15 to 1.17).[11] However, our findings contradict those of other 2 meta-analyses based on trials with different study designs and showing significant therapeutic benefit for antidepressants as a whole to treat depressive symptoms in patients with TBI compared to placebo or control (Hedges' *g* 1.17, 95% CI 0.85 to 1.49[12]; SMD –0.3, 95% CI –0.6 to 0.0[10]). The inclusion of some clinical trials of poor quality in those 2 meta-analyses may have contributed to the discrepancy in results.

Although our pair-wise meta-analysis also revealed a positive therapeutic effect of sertraline (a first-line SSRI) for treating depression, the effect became nonsignificant in network meta-analysis. Because our analysis found no inconsistency among the included studies with the design-by-treatment method, the small effect size of sertraline (SMD –0.28) in pair-wise analysis may have contributed to the loss of significance in treatment efficacy after we combined direct and indirect comparisons in the network meta-analysis. A previous study demonstrated that sertraline could improve depressive symptoms but might worsen cognitive functional performance.[28] Those findings may need to be judiciously interpreted, because TBI-related depression is frequently associated with comorbid executive dysfunction.[4] As well, some symptoms of depression and those of TBI may overlap (e.g., lethargy),[54] complicating the interpretation of the therapeutic benefits of sertraline in this setting. Furthermore, the tolerability of sertraline was relatively poor, as reflected by the significantly higher dropout rate in the sertraline group than in the placebo group (OR 2.65, 95% CI 1.27 to 5.54). Although sertraline may be of therapeutic benefit, it failed to show statistical significance when subjected to more comprehensive statistical analysis. Considering its low tolerability and equivocal therapeutic effect, it should be used with caution. Further studies are warranted to provide stronger evidence to support its use for post-TBI depressive symptoms.

In terms of nonpharmacologic treatments, our study included mainly psychotherapy and exercise programs. Interestingly, the findings of the present study did not support superior therapeutic benefit for any nonpharmacologic treatments, compared among themselves or with usual care. Similarly, when we compared the tolerability of the different treatments, we found no significant differences among the different treatment groups, including usual care. These nonsignificant results were similar to those of a previous meta-analysis,[13] which failed to show superiority of CBT to supportive psychotherapy in patients with TBI. The nonsignificant findings indicated that different nonpharmacologic treatment measures may not be superior to usual care in the treatment of post-TBI depressive symptoms.

Limitations

Several limitations of the current network meta-analysis need to be considered for accurate interpretation of its results. First, some of the analyses in this study were limited by underpowered statistics, including heterogeneities in participant characteristics and study designs (e.g., comorbid diseases; baseline cognitive function; placebo-controlled or not; a larger proportion of male participants in most trials; and trial duration);

a small number of total participants for the entire network meta-analysis (n = 483 for pharmacologic and n = 1083 for nonpharmacologic treatments); small trial numbers for some treatment arms; and heterogeneity in psychopathology assessment tools used. Second, most of the evidence supporting the benefit of methylphenidate was derived from 2 RCTs with a total of 66 participants, so we could not reach a firm conclusion based on the current analysis. Third, because the network for pharmacologic treatments was poorly connected, we did not have sufficient direct evidence between arms to support the findings for the entire network meta-analysis. Fourth, many nonpharmacologic studies had a high or unclear risk of bias (38.7% high risk and 5.9% unclear). In particular, we found problems with performance bias and subsequently detection bias; participants were often not blinded to treatment, introducing detection bias in self-rated outcome assessment. Given these circumstances, the results for efficacy would be expected to favour nonpharmacologic treatments. Still, our network meta-analysis did not find that nonpharmacologic treatments were superior to usual care. Fifth, the short durations of nonpharmacologic treatments in most studies did not shed light on the long-term therapeutic effects of these measures. Finally, most of the trials of nonpharmacologic treatments (14/17) did not specifically target participants with TBI and a definite diagnosis of MDD; therefore, our findings for nonpharmacologic treatments may not be applicable to participants with a definite MDD diagnosis.

Conclusion

The current network meta-analysis demonstrated that methylphenidate and positive psychological CBT were associated with the most significant improvement in TBI-related depressive symptoms among the pharmacologic and nonpharmacologic treatments investigated. No pharmacologic or nonpharmacologic treatments were associated with worse tolerability (i.e., higher dropout rate) than placebo/control, except for sertraline, which was associated with a higher dropout rate than placebo. Nevertheless, the limited number of trials from which these results were generated precluded us from drawing robust conclusions for clinical practice. Future large-scale and well-designed (i.e., placebo-controlled) randomized controlled trials are warranted to validate our results and identify the optimal treatment for depressive symptoms after traumatic brain injury.

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