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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Introduction

Depressive disorders after traumatic brain injury (TBI) are not uncommon, with an estimated incidence of 16% to 60%, and the prevalence of post-TBI major depression has been reported to be as high as 25% to 50%. 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. Not only has TBI-related MDD been associated with impaired executive function and poor functional outcome, it has also been linked to elevated risk of suicide.

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.
Current clinical treatment for post-TBI depression consists of pharmacologic and nonpharmacologic strategies. 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. On the other hand, nonpharmacologic treatments encompass psychotherapeutic approaches such as supportive psychotherapy, cognitive behavioural therapy (CBT) and mindfulness-based CBT. Surprisingly, despite the prevalence and severity of post-TBI depression, there is no consensus on standard therapeutic guidelines. 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. A body of evidence has shown that post-TBI epilepsy may worsen chronic behavioural outcomes in the emotional, cognitive and psychosocial functioning domains. 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.

The other major difficulty in establishing clinical practice guidelines for post-TBI depression is a lack of well-controlled, evidence-based studies. Although previous randomized controlled trials (RCTs) have demonstrated positive effects of sertraline (a selective serotonin reuptake inhibitor [SSRI]) on the prevention and treatment of depression following TBI, recent meta-analyses have shown either borderline or no significant 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, or by a limited number of included studies. 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. 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). 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 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. 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. 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. 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.
of 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          | 24          | PHQ-9 (+) | > 18              | 0         | NA              | India       |
| Ashman et al.1               | TBI          | NA                   | Yes | RCT          | Sertraline 25–200 mg/d Placebo | 22          | 10          | HAM-D (-) | 49.1 ± 10.9        | 41.5      | NA              | Australia   |
| Fann et al.26                | TBI          | NA                   | Yes | RCT          | Sertraline 25–200 mg/d Placebo | 31          | 12          | HAM-D (-) | 37.5 ± 12.5        | 24.2      | 32.0            | United States |
| Grima et al.27               | TBI          | Mild to severe       | NA  | RCT (crossover) | Melatonin 2 mg/d Placebo  | 18          | 4           | HAM-D (-) | 37 ± 11             | 33.3      | 0.0             | Australia   |
| Lee et al.28                 | TBI          | Mild to moderate     | Yes | RCT          | Methylphenidate 20 mg/d Placebo | 10          | 4           | HAM-D (+) | 35.3 ± 8.0          | 20        | NA              | Korea       |
| Novack et al.29              | TBI          | Moderate to severe   | No  | RCT          | Sertraline 50 mg/d Placebo  | 49          | 12          | NFI-D (+) | 35.3 ± 16.7         | 27.3      | 40.8            | United States |
| Rao30                        | TBI          | NA                   | Yes | RCT          | Escitalopram 10–20 mg/d Placebo | 7           | 12          | MADRS    | 34.5 ± 15.6         | 35.7      | 11.4            | United States |
| Ripley et al.31              | TBI          | Attention problems   | NA  | RCT (crossover) | Atomoxetine 80 mg/d Placebo  | 26          | 2           | NFI-D (-) | 40.6 ± 11.8         | 25.5      | 3.9             | United States |
| Wroblewski et al.32          | TBI          | Severe               | Yes | RCT          | Desipramine 150 mg/d Placebo | 6           | 4           | Affect/Mood scale (-) | 32.2 ± 8.51 | 30        | NA             | United States |
| Zhang et al.33               | TBI          | Mild to moderate     | Yes | RCT          | Methylphenidate 20 mg/d Placebo | 18          | 30          | BDI (+)   | 36.3 ± 10.9          | 25        | 5.6             | China       |
| Nonpharmacologic interventions|              |                      |     |              |                             |             |             |          |                  |           |                 |             |
| Andrewes et al.34            | TBI          | NA                   | NA  | RCT          | Positive psychology interventions | 5           | 12          | AHI (+)   | 38.3 ± 5.9          | 10        | 20.0            | United Kingdom |
| Ashman et al.35              | TBI          | NA                   | Yes | RCT          | CBT                          | 39          | 12          | BDI (-)   | 47.1 ± 10.6          | 54.5      | 43.6            | United States |
| Bedard et al.36              | TBI          | NA                   | Yes | RCT          | Supportive cognitive therapy  | 38          | 10          | BDI (+)   | 46.8 ± 13.4          | 33.3      | 20.8            | Canada      |
| Bell et al.37                | TBI          | Mild                 | NA  | RCT          | Telephone problem-solving Usual care | 178         | 24          | PHQ-9 (-) | 29.4 ± 7.2          | 6.74      | 22.0            | United States |
| Bellon et al.38              | TBI          | NA                   | NA  | RCT (crossover) | Walking program Nutrition program | 28          | 12          | CES-D (-) | 43.7 ± 15.8         | 41        | 0.0             | United States |
| 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.   | TBI                                 | Mild to severe      | NA  | RCT          | Telephone supportive psychotherapy                                         | 62          | 36          | NFI-D (+) | 34.5 ± 13.9      | 25.4      | 27.0            | United States |
|                     |                                    |                     |     | RCT          | Usual care                                                                 | 64          |             |          | 37.1 ± 15.6      |           |                 |               |
| Driver et al.       | TBI                                 | Cognitive impairment| NA  | NA           | RCT                                                                          | 8           | 8           | POMS-D (-) | 38.8 ± 2.5       | NA        | 0.0             | United States |
|                     |                                    |                     |     | NA           | RCT                                                                          | 8           |             |          | 40.8 ± 14.7      |           |                 |               |
| Fann et al.         | TBI                                 | Mild to severe      | Yes | RCT          | Cognitive behavioral therapy                                              | 18          | 16          | HAMD-17 (-) | 45.8 ± 13.3      | 37        | 17.0            | United States |
|                     |                                    |                     |     | RCT          | Telephone CBT                                                               | 18          |             |          | 33.1 ± 11.7      | 23        | 14.0            | United States |
|                     |                                    |                     |     | RCT          | Social skills training                                                       | 17          |             |          | 35.2 ± 11.3      | 25        |                 | United States |
|                     |                                    |                     |     | RCT          | Usual care                                                                  | 16          |             |          |                  | 25.6      |                 |               |
| McDonald et al.     | TBI                                 | Severe              | No  | RCT          | Social skills training                                                       | 18          | 12          | DASS-D (-) | 36.3 ± 10.7      | 21.6      | 22.2            | United States |
|                     |                                    |                     |     | RCT          | Social group                                                                 | 17          |             |          | 33.1 ± 11.7      | 23.5      |                 | United States |
|                     |                                    |                     |     | RCT          | Usual care                                                                  | 16          |             |          | 35.2 ± 11.3      | 25.0      |                 | United States |
| Nguyen et al.       | TBI                                 | Mild to severe      | NA  | RCT          | Cognitive behavioral therapy                                              | 13          | 8           | HADS-D (+) | 43.9 ± 13.0      | 33.3      | 15.3            | Australia     |
|                     |                                    |                     |     | RCT          | Usual care                                                                  | 11          |             |          |                  |           |                 |               |
| Ponsford et al.     | TBI                                 | Mild to severe      | NA  | RCT          | Cognitive behavioral therapy                                              | 26          | 12          | DASS-D (+) | 42.2 ± 14.5      | 26.7      | 15.3            | Australia     |
|                     |                                    |                     |     | RCT          | Usual care                                                                  | 26          |             |          |                  |           |                 |               |
|                     |                                    |                     |     | RCT          | Motivational interviewing + CBT                                             | 23          |             |          |                  |           |                 |               |
| Potter et al.       | TBI                                 | NA                  | NA  | RCT          | Cognitive behavioral therapy                                              | 26          | 12          | HADS-D     | 41.4 ± 11.6      | 45.6      | 3.8             | United Kingdom |
| Simpson et al.      | TBI                                 | Severe              | NA  | RCT          | Group-based CBT                                                            | 8           | 10          | HADS-D (-) | 39.4 ± 12.4      | NA        | 0.0             | Australia     |
|                     |                                    |                     |     | RCT          | Usual care                                                                  | 9           |             |          | 44.1 ± 11.7      |           |                 |               |
| Storzbach et al.    | TBI                                 | Mild                | NA  | RCT          | Compensatory cognitive training + CBT                                       | 50          | 10          | BDI (-)   | 35.4 ± 8.4       | 5.0       | 28.0            | United States |
|                     |                                    |                     |     | RCT          | Usual care                                                                  | 69          |             |          | 34.8 ± 7.4       |           |                 |               |
| Struchen et al.     | TBI                                 | NA                  | NA  | RCT          | Social training                                                             | 12          | 12          | CES-D (x) | NA            | NA        | 50.0            | United States |
|                     |                                    |                     |     | RCT          | Usual care                                                                  | 18          |             |          | NA            |           |                 |               |
| Tiersky et al.      | TBI                                 | Mild to moderate    | NA  | RCT          | Cognitive behavioral therapy                                              | 11          | 11          | SCL-90R (+) | 46.9 ± 10.5      | 55        | 21.4            | United States |
|                     |                                    |                     |     | RCT          | Usual care                                                                  | 9           |             |          |                  |           |                 |               |
| Twamley et al.      | TBI                                 | Mild to moderate    | NA  | RCT          | CogSMART + supported employment                                           | 16          | 12          | HAM-D (-) | 29.4 ± 6.2       | 5.9       | 12.5            | United States |
|                     |                                    |                     |     | RCT          | Enhanced supported employment                                              | 18          |             |          | 34.3 ± 7.4       |           |                 |               |

AHI = Authentic Happiness Inventory; BDI = Beck Depression Inventory; CBT = cognitive behavioral 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; NFID = 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.
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...
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
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

| Intervention    | Estimate SMD (95% CI) | Estimate SMD (95% CI) |
|-----------------|-----------------------|-----------------------|
| PPCBT            | -0.64 (-1.94 to -0.38) | -0.90 (-2.30 to -0.50) |
| (−2.66 to 1.51) |                       |                       |
| -0.40           | -0.26 (-2.17 to -0.16) | -0.38 (-2.35 to -1.11) |
| (−2.35 to 1.54) |                       |                       |
| -0.45           | -0.24 (-2.30 to -0.12) | -0.45 (-2.30 to -1.15) |
| (−2.41 to 1.52) |                       |                       |
| -0.64           | -0.19 (-2.35 to -1.13) | -0.45 (-2.80 to -1.06) |
| (−2.23 to 0.95) |                       |                       |
| -0.61           | -0.21 (-2.30 to -1.15) | -0.52 (-2.98 to -1.06) |
| (−2.58 to 1.35) |                       |                       |
| -0.72           | -0.32 (-2.80 to -1.17) | -0.22 (-2.02 to -1.01) |
| (−2.64 to 1.20) |                       |                       |
| -0.79           | -0.35 (-2.30 to -1.16) | -0.22 (-2.02 to -1.01) |
| (−2.65 to 1.06) |                       |                       |
| -0.82           | -0.38 (-2.30 to -1.19) | -0.22 (-2.02 to -1.01) |
| (−2.67 to 1.02) |                       |                       |
| -0.79           | -0.42 (-2.30 to -1.16) | -0.22 (-2.02 to -1.01) |
| (−2.79 to 1.06) |                       |                       |
| -0.91           | -0.51 (-2.30 to -1.19) | -0.22 (-2.02 to -1.01) |
| (−2.87 to 1.04) |                       |                       |
| -1.07           | -0.62 (-2.30 to -1.17) | -0.22 (-2.02 to -1.01) |
| (−2.81 to 0.54) |                       |                       |
| -1.13           | -0.69 (-2.30 to -1.17) | -0.22 (-2.02 to -1.01) |
| (−2.81 to 0.54) |                       |                       |
| -1.35           | -0.73 (-2.30 to -1.17) | -0.22 (-2.02 to -1.01) |
| (−3.48 to 0.79) |                       |                       |
| -1.42           | -0.77 (-2.30 to -1.17) | -0.22 (-2.02 to -1.01) |
| (−3.29 to 0.46) |                       |                       |

*Statistically significant (p < 0.05).
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 improvements in 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 a definite MDD diagnosis. We find that nonpharmacologic treatments were superior to usual care, but because most of the evidence supporting the benefit of these measures was derived from small trials, we could not reach a firm conclusion based on the current analysis. 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.

**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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