

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

Yu-Shian Cheng, MD\*; Ping-Tao Tseng, MD\*; Yi-Cheng Wu, MD; Yu-Kang Tu, MD; Ching-Kuan Wu, MD; Chih-Wei Hsu, MD; Wei-Te Lei, MD; Dian-Jeng Li, MD; Tien-Yu Chen, MD; Brendon Stubbs, MD; Andre F. Carvalho, MD; Chih-Sung Liang, MD; Ta-Chuan Yeh, MD; Che-Sheng Chu, MD; Yen-Wen Chen, MD; Pao-Yen Lin, MD; Ming-Kung Wu, MD<sup>†</sup>; Cheuk-Kwan Sun, MD, PhD<sup>†</sup>

**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 pre-defined 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%,<sup>1-3</sup> and the prevalence of post-TBI major depression has been reported to be as high as 25% to 50%.<sup>4,5</sup> Another disturb-

ing 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.<sup>6</sup> Not only has TBI-related MDD been associated with impaired executive function<sup>4</sup> and poor functional outcome,<sup>7</sup> it has also been linked to elevated risk of suicide.<sup>8</sup>

**Correspondence to:** C.K. Sun, Department of Emergency Medicine, E-Da Hospital, I-Shou University School of Medicine for International Students, Kaohsiung, Taiwan; lawrence.c.k.sun@gmail.com; ed105983@edah.org.tw

\*These authors contributed equally to this work.

<sup>†</sup>These authors contributed equally to this work.

Submitted Jun. 26, 2019; Revised Jul. 19, 2020; Accepted Sep. 4, 2020

DOI: 10.1503/jpn.190122

Current clinical treatment for post-TBI depression consists of pharmacologic and nonpharmacologic strategies.<sup>9</sup> 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.<sup>10–12</sup> On the other hand, nonpharmacologic treatments encompass psychotherapeutic approaches such as supportive psychotherapy, cognitive behavioural therapy (CBT) and mindfulness-based CBT.<sup>13</sup> Surprisingly, despite the prevalence and severity of post-TBI depression, there is no consensus on standard therapeutic guidelines.<sup>10</sup> 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.<sup>14–16</sup> A body of evidence has shown that post-TBI epilepsy may worsen chronic behavioural outcomes in the emotional, cognitive and psychosocial functioning domains.<sup>17</sup> 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.<sup>18</sup>

The other major difficulty in establishing clinical practice guidelines for post-TBI depression is a lack of well-controlled, evidence-based studies.<sup>11</sup> Although previous randomized controlled trials (RCTs) have demonstrated positive effects of sertraline (a selective serotonin reuptake inhibitor [SSRI]) on the prevention<sup>19</sup> and treatment<sup>1</sup> of depression following TBI, recent meta-analyses have shown either borderline<sup>11</sup> or no significant<sup>10</sup> 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,<sup>10</sup> or by a limited number of included studies.<sup>11</sup> 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.<sup>13</sup> 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](http://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).<sup>20</sup> 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<sup>21</sup> 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.<sup>22</sup> 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.<sup>23</sup> 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.<sup>24</sup> We performed the full analytic procedure using STATA version 14.0 ([www.stata.com/stata14/](http://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

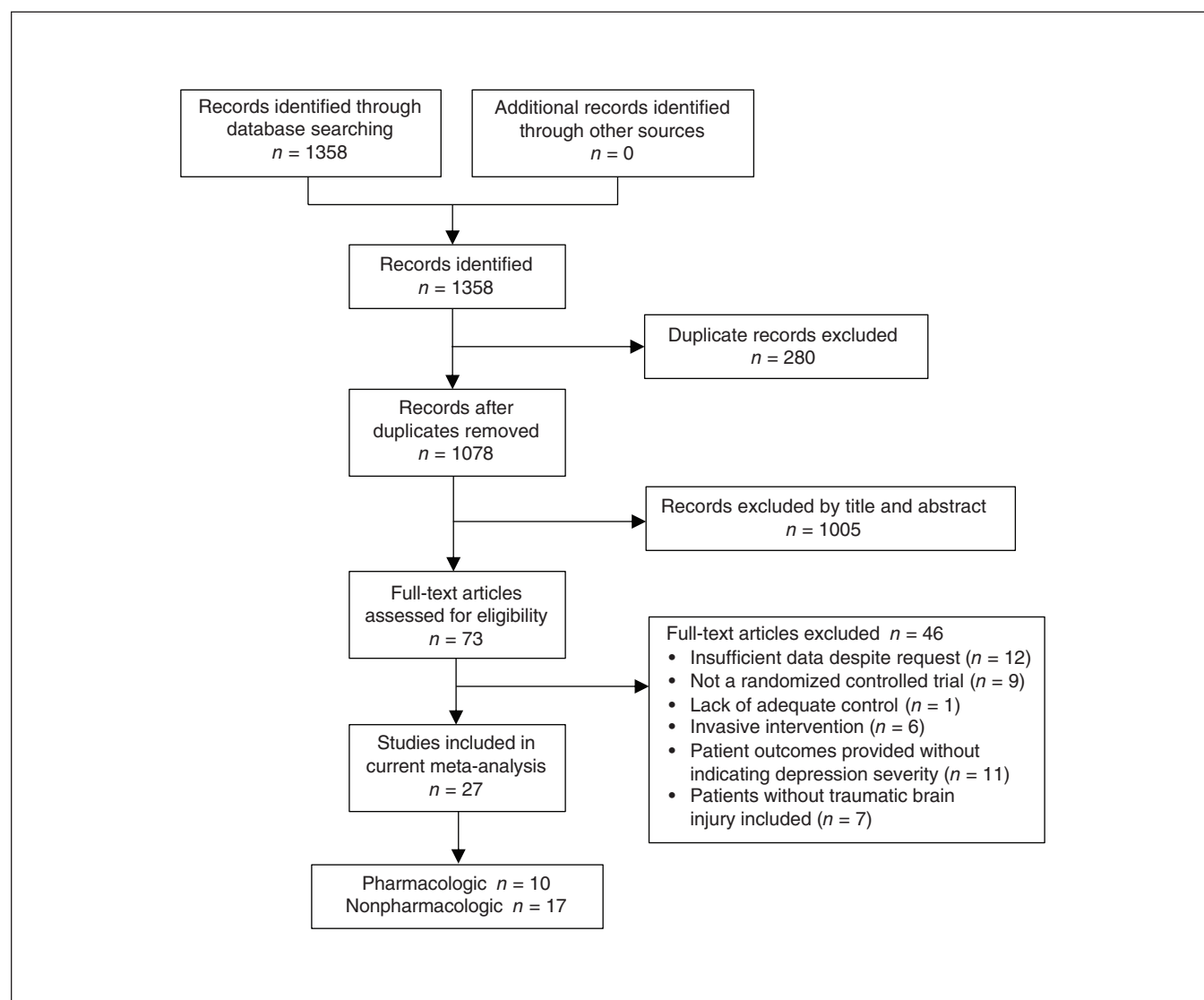
(see Figure 1 and Appendix 1, Table S2, for detailed information). The final number of articles included in the current study was 27 (Table 1).<sup>1,25-50</sup> Of the 27 articles, 10 assessed the effects of pharmacologic treatments and 17 assessed the effects of nonpharmacologic treatments. The geometric 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 Neuro-

behavioural 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.

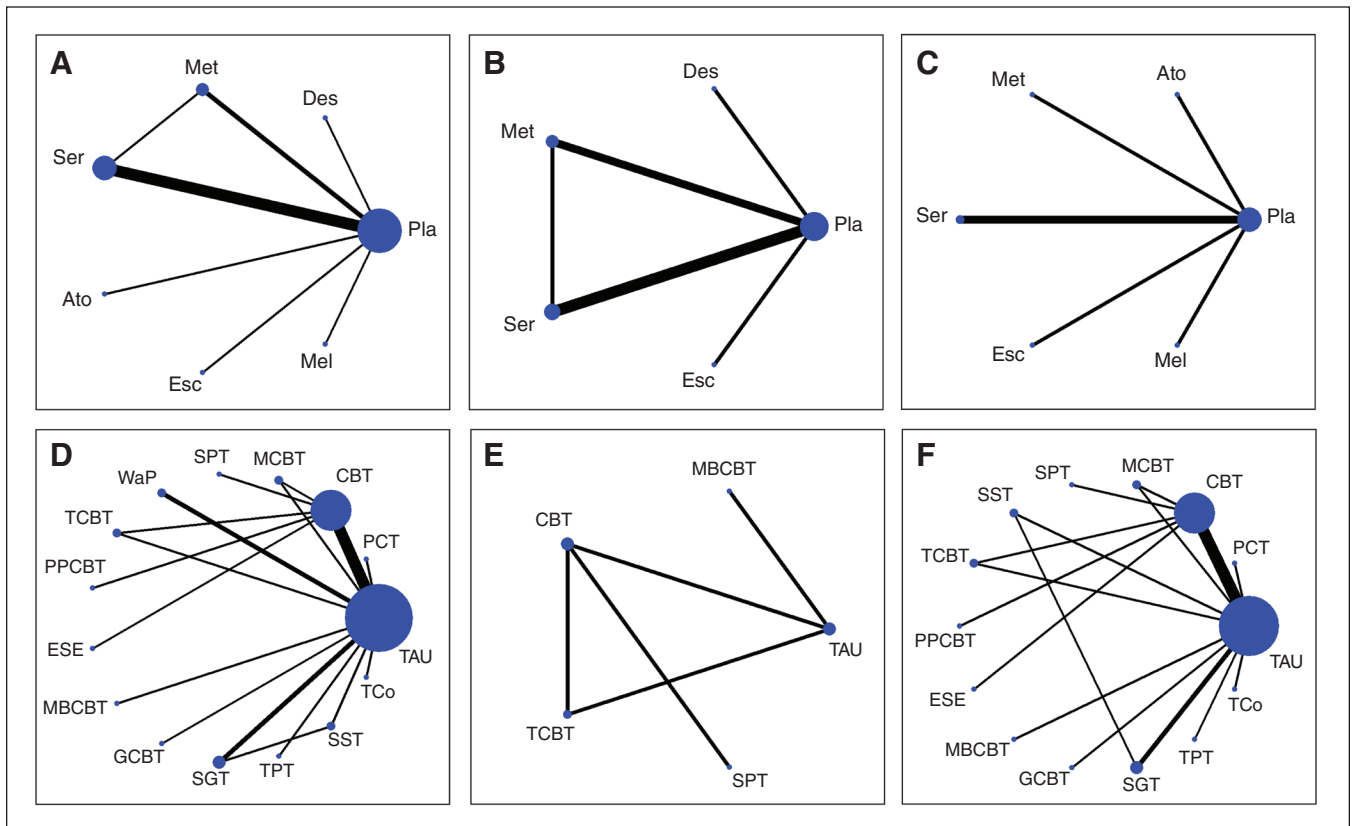
Table 1: Characteristics of included studies (part 1 of 2)

Study	Diagnosis	Head injury severity	MDD	Study design	Comparison	Patients, n	Duration, w	Outcome*	Mean age ± SD, yr	Female, %	Dropout rate, %	Country
<b>Pharmacologic interventions</b>												
Ansari et al. <sup>25</sup>	TBI	Mild to moderate	Yes	RCT	Sertraline 50 mg/d Placebo	40	24	PHQ-9 (+)	> 18	0	NA	India
Ashman et al. <sup>1</sup>	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. <sup>26</sup>	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. <sup>27</sup>	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. <sup>28</sup>	TBI MDD	Mild to moderate	Yes	RCT	Methyphenidate 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. <sup>29</sup>	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 <sup>30</sup>	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. <sup>31</sup>	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. <sup>32</sup>	TBI MDD	Severe	Yes	RCT	Desipramine 150 mg/d Placebo	6 4	4	Affect/Mood scale (-)	32.2 ± 8.51	30	NA	United States
Zhang et al. <sup>33</sup>	TBI MDD	Mild to moderate	Yes	RCT	Methyphenidate 20 mg/d Placebo	18 18	30	BDI (+)	36.3 ± 10.9 34.9 ± 12.1	25	5.6 11.1	China
<b>Nonpharmacologic interventions</b>												
Andrews et al. <sup>34</sup>	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. <sup>35</sup>	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. <sup>36</sup>	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. <sup>37</sup>	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. <sup>38</sup>	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. <sup>39</sup>	TBI	Mild to severe	NA	RCT	Telephone supportive psychotherapy Usual care	62 64	36	NFD (+)	34.5 ± 13.9 37.1 ± 15.6	25.4	27.0 25.6	United States
Driver et al. <sup>40</sup>	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. <sup>41</sup>	TBI MDD	Mild to severe	Yes	RCT	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 al. <sup>42</sup>	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	Australia
Nguyen et al. <sup>43</sup>	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. <sup>44</sup>	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. <sup>45</sup>	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. <sup>46</sup>	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. <sup>47</sup>	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. <sup>48</sup>	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. <sup>49</sup>	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
Twarmley et al. <sup>50</sup>	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; HAM-D-17 = Hamilton Depression Rating Scale, 17 items; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; NA = not available; NFD = 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).

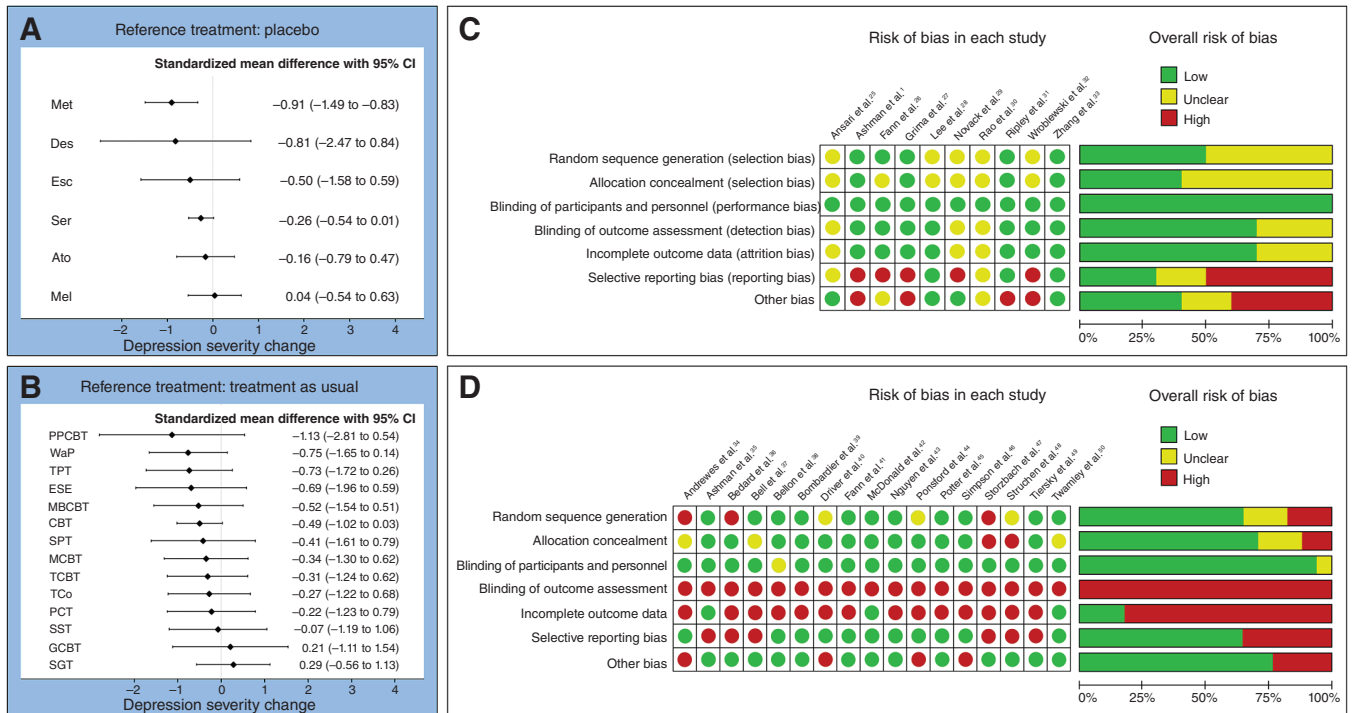
Consistent with the above findings, the network meta-analysis showed that only methylphenidate had a treatment efficacy that was significantly superior to that of placebo or control (SMD  $-0.91$ , 95% CI  $-1.49$  to  $-0.33$ ). In addition, the efficacy of methylphenidate was significantly higher than

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







**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 toler-

ability 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





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.<sup>10-12</sup> 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.<sup>51</sup> Methylphenidate — a stimulant that facilitates dopamine and norepinephrine neurotransmission in the prefrontal cortex<sup>52</sup> 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.<sup>53</sup> Moreover, a previous study has demonstrated that although sertraline alleviated only depressive symptoms in patients with TBI, methylphenidate improved both depressive and cognitive symptoms.<sup>28</sup> Because executive dysfunction is a frequent comorbidity of TBI-related depression,<sup>4</sup> 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 non-response rate between antidepressants and placebo (OR 0.42,

95% CI 0.15 to 1.17).<sup>11</sup> 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<sup>12</sup>; SMD -0.3, 95% CI -0.6 to 0.0<sup>10</sup>). 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.<sup>28</sup> Those findings may need to be judiciously interpreted, because TBI-related depression is frequently associated with comorbid executive dysfunction.<sup>4</sup> As well, some symptoms of depression and those of TBI may overlap (e.g., lethargy),<sup>54</sup> 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,<sup>13</sup> 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 non-pharmacologic 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 non-pharmacologic 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.

**Affiliations:** From the Department of Psychiatry, Tsyrr-Huey Mental Hospital, Kaohsiung Jen-Ai's Home, Kaohsiung, Taiwan (Cheng, Wu); the Institute of Biomedical Sciences, National Sun Yat-sen University, Kaohsiung City, Taiwan (Cheng, Tseng); the WinShine Clinics in Speciality of Psychiatry, Kaohsiung, Taiwan (Tseng); the Prospect Clinic for Otorhinolaryngology & Neurology (Tseng, Chen); the Department of Physical Medicine and Rehabilitation, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan (Wu); the Institute of Epidemiology & Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan (Tu); the Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan (Hsu, Wu, Lin); the Division of Allergy, Immunology, Rheumatology Disease, Department of Pediatrics, Mackay Memorial Hospital, Hsinchu, Taiwan (Lei); the Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan (Li); the Department of Addiction Science, Kaohsiung Municipal Kai-Syuan Psy-

chiatric Hospital, Kaohsiung, Taiwan (Li); the Department of Psychiatry, Tri-Service General Hospital; School of Medicine, National Defense Medical Center, Taipei, Taiwan (Chen); the Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan (Chen); the Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London, UK (Stubbs); Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London, De Crespigny Park, London, UK (Stubbs); the Department of Psychiatry, University of Toronto, Toronto, ON (Carvalho); the Centre for Addiction & Mental Health (CAMH), Toronto, ON (Carvalho); the Department of Psychiatry, Beitou branch, Tri-Service General Hospital; School of Medicine, National Defense Medical Center, Taipei, Taiwan (Liang); the Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan (Liang); the Department of Psychiatry, Tri-Service General Hospital; School of Medicine, National Defense Medical Center, Taipei, Taiwan (Yeh); the Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan (Chu); the Center for Geriatric and Gerontology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan (Chu); the Institute for Translational Research in Biomedical Sciences, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan (Lin); the Department of Chemical Engineering and Institute of Biotechnology and Chemical Engineering, I-Shou University, Kaohsiung, Taiwan (Wu); the Department of Emergency Medicine, E-Da Hospital, Kaohsiung, Taiwan (Sun); the I-Shou University School of Medicine for International Students, Kaohsiung, Taiwan (Sun).

**Competing interests:** None declared.

**Contributors:** Y.-S. Cheng, P.-T. Tseng, M.-K. Wu and C.-K. Sun designed the study and acquired the data, which all authors analyzed. Y.-S. Cheng, P.-T. Tseng, M.-K. Wu and C.-K. Sun wrote the article, which all authors reviewed. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

**Content license:** This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-NC-ND 4.0) license, which permits use, distribution and reproduction in any medium, provided that the original publication is properly cited, the use is non-commercial (i.e. research or educational use) and no modifications or adaptations are made. See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

1. Ashman TA, Cantor JB, Gordon WA, et al. A randomized controlled trial of sertraline for the treatment of depression in persons with traumatic brain injury. *Arch Phys Med Rehabil* 2009;90:733-40.
2. Jorge RE, Robinson RG, Arndt SV, et al. Depression following traumatic brain injury: a 1 year longitudinal study. *J Affect Disord* 1993;27:233-43.
3. Kreutzer JS, Seel RT, Gourley E. The prevalence and symptom rates of depression after traumatic brain injury: a comprehensive examination. *Brain Inj* 2001;15:563-76.
4. Jorge RE, Robinson RG, Moser D, et al. Major depression following traumatic brain injury. *Arch Gen Psychiatry* 2004;61:42-50.
5. Vaishnavi S, Rao V, Fann JR. Neuropsychiatric problems after traumatic brain injury: unraveling the silent epidemic. *Psychosomatics* 2009;50:198-205.
6. Holsinger T, Steffens DC, Phillips C, et al. Head injury in early adulthood and the lifetime risk of depression. *Arch Gen Psychiatry* 2002;59:17-22.
7. Haagsma JA, Scholten AC, Andriessen TM, et al. Impact of depression and post-traumatic stress disorder on functional outcome and health-related quality of life of patients with mild traumatic brain injury. *J Neurotrauma* 2015;32:853-62.
8. Brooks N, Campsie L, Symington C, et al. The five year outcome of severe blunt head injury: a relative's view. *J Neurol Neurosurg Psychiatry* 1986;49:764-70.
9. Juengst SB, Kumar RG, Wagner AK. A narrative literature review of depression following traumatic brain injury: prevalence, impact, and management challenges. *Psychol Res Behav Manag* 2017;10:175-86.



10. Kreitzer N, Ancona R, McCullumsmith C, et al. The effect of antidepressants on depression after traumatic brain injury: a meta-analysis. *J Head Trauma Rehabil* 2018;34:E47-E54.
11. Paraschakis A, Katsanos AH. Antidepressants for depression associated with traumatic brain injury: a meta-analytical study of randomised controlled trials. *East Asian Arch Psychiatry* 2017;27:142-9.
12. Salter KL, McClure JA, Foley NC, et al. Pharmacotherapy for depression posttraumatic brain injury: a meta-analysis. *J Head Trauma Rehabil* 2016;31:E21-32.
13. Gertler P, Tate RL, Cameron ID. Non-pharmacological interventions for depression in adults and children with traumatic brain injury. *Cochrane Database Syst Rev* 2015;12:CD009871.
14. Blakey SM, Wagner HR, Naylor J, et al. Chronic pain, TBI, and PTSD in military veterans: a link to suicidal ideation and violent impulses? *J Pain* 2018;19:797-806.
15. Juengst SB, Wagner AK, Ritter AC, et al. Post-traumatic epilepsy associations with mental health outcomes in the first two years after moderate to severe TBI: a TBI model systems analysis. *Epilepsy Behav* 2017;73:240-6.
16. Nampiarampil DE. Prevalence of chronic pain after traumatic brain injury: a systematic review. *JAMA* 2008;300:711-9.
17. Semple BD, Zamani A, Rayner G, et al. Affective, neurocognitive and psychosocial disorders associated with traumatic brain injury and post-traumatic epilepsy. *Neurobiol Dis* 2019;123:27-41.
18. Wickwire EM, Schnyer DM, Germain A, et al. Sleep, sleep disorders, and circadian health following mild traumatic brain injury in adults: review and research agenda. *J Neurotrauma* 2018;35:2615-31.
19. Jorge RE, Acion L, Burin DI, et al. Sertraline for preventing mood disorders following traumatic brain injury: a randomized clinical trial. *JAMA Psychiatry* 2016;73:1041-7.
20. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777-84.
21. Higgins J, Green S, editors. *Cochrane handbook for systematic reviews of interventions*. Version 5.0.2. London: Cochrane Collaboration; 2009.
22. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004;23:3105-24.
23. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64:163-71.
24. Higgins JP, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a network meta-analysis. *Value Health* 2014;17:A324.
25. Ansari A, Jain A, Sharma A, et al. Role of sertraline in posttraumatic brain injury depression and quality-of-life in TBI. *Asian J Neurosurg* 2014;9:182-8.
26. Fann JR, Bombardier CH, Temkin N, et al. Sertraline for major depression during the year following traumatic brain injury: a randomized controlled trial. *J Head Trauma Rehabil* 2017;32:332-42.
27. Grima NA, Rajaratnam SMW, Mansfield D, et al. Efficacy of melatonin for sleep disturbance following traumatic brain injury: a randomised controlled trial. *BMC Med* 2018;16:8.
28. Lee H, Kim SW, Kim JM, et al. Comparing effects of methylphenidate, sertraline and placebo on neuropsychiatric sequelae in patients with traumatic brain injury. *Hum Psychopharmacol* 2005;20:97-104.
29. Novack TA, Banos JH, Brunner R, et al. Impact of early administration of sertraline on depressive symptoms in the first year after traumatic brain injury. *J Neurotrauma* 2009;26:1921-8.
30. Rao V. Lexapro for the treatment of traumatic brain injury (TBI) depression and other psychiatric conditions. *ClinicalTrials.gov*: NCT01368432; 2016. Available: <https://clinicaltrials.gov/ct2/show/NCT01368432> (accessed 2020 Dec. 16).
31. Ripley DL, Morey CE, Gerber D, et al. Atomoxetine for attention deficits following traumatic brain injury: results from a randomized controlled trial. *Brain Inj* 2014;28:1514-22.
32. Wroblewski BA, Joseph AB, Cornblatt RR. Antidepressant pharmacotherapy and the treatment of depression in patients with severe traumatic brain injury: a controlled, prospective study. *J Clin Psychiatry* 1996;57:582-7.
33. Zhang WT, Wang YF. Efficacy of methylphenidate for the treatment of mental sequelae after traumatic brain injury. *Medicine (Baltimore)* 2017;96:e6960.
34. Andrewes HE, Walker V, O'Neill B. Exploring the use of positive psychology interventions in brain injury survivors with challenging behaviour. *Brain Inj* 2014;28:965-71.
35. Ashman T, Cantor JB, Tsoulosides T, et al. Comparison of cognitive behavioral therapy and supportive psychotherapy for the treatment of depression following traumatic brain injury: a randomized controlled trial. *J Head Trauma Rehabil* 2014;29:467-78.
36. Bedard M, Felteau M, Marshall S, et al. Mindfulness-based cognitive therapy reduces symptoms of depression in people with a traumatic brain injury: results from a randomized controlled trial. *J Head Trauma Rehabil* 2014;29:E13-22.
37. Bell KR, Fann JR, Brockway JA, et al. Telephone problem solving for service members with mild traumatic brain injury: a randomized, clinical trial. *J Neurotrauma* 2017;34:313-21.
38. Bellon K, Kolakowsky-Hayner S, Wright J, et al. A home-based walking study to ameliorate perceived stress and depressive symptoms in people with a traumatic brain injury. *Brain Inj* 2015;29:313-9.
39. Bombardier CH, Bell KR, Temkin NR, et al. The efficacy of a scheduled telephone intervention for ameliorating depressive symptoms during the first year after traumatic brain injury. *J Head Trauma Rehabil* 2009;24:230-8.
40. Driver S, Ede A. Impact of physical activity on mood after TBI. *Brain Inj* 2009;23:203-12.
41. Fann JR, Bombardier CH, Vannoy S, et al. Telephone and in-person cognitive behavioral therapy for major depression after traumatic brain injury: a randomized controlled trial. *J Neurotrauma* 2015;32:45-57.
42. McDonald S, Tate R, Togher L, et al. Social skills treatment for people with severe, chronic acquired brain injuries: a multicenter trial. *Arch Phys Med Rehabil* 2008;89:1648-59.
43. Nguyen S, McKay A, Wong D, et al. Cognitive behavior therapy to treat sleep disturbance and fatigue after traumatic brain injury: a pilot randomized controlled trial. *Arch Phys Med Rehabil* 2017;98:1508-17.e2.
44. Ponsford J, Lee NK, Wong D, et al. Efficacy of motivational interviewing and cognitive behavioral therapy for anxiety and depression symptoms following traumatic brain injury. *Psychol Med* 2016;46:1079-90.
45. Potter SD, Brown RG, Fleming S. Randomised, waiting list controlled trial of cognitive-behavioural therapy for persistent post-concussional symptoms after predominantly mild-moderate traumatic brain injury. *J Neurol Neurosurg Psychiatry* 2016;87:1075-83.
46. Simpson GK, Tate RL, Whiting DL, et al. Suicide prevention after traumatic brain injury: a randomized controlled trial of a program for the psychological treatment of hopelessness. *J Head Trauma Rehabil* 2011;26:290-300.
47. Storzbach D, Twamley EW, Roost MS, et al. Compensatory cognitive training for Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn veterans with mild traumatic brain injury. *J Head Trauma Rehabil* 2017;32:16-24.
48. Struchen MA, Davis LC, Bogaards JA, et al. Making connections after brain injury: development and evaluation of a social peer-mentoring program for persons with traumatic brain injury. *J Head Trauma Rehabil* 2011;26:4-19.
49. Tiersky LA, Anselmi V, Johnston MV, et al. A trial of neuropsychologic rehabilitation in mild-spectrum traumatic brain injury. *Arch Phys Med Rehabil* 2005;86:1565-74.
50. Twamley EW, Jak AJ, Delis DC, et al. Cognitive Symptom Management and Rehabilitation Therapy (CogSMART) for veterans with traumatic brain injury: pilot randomized controlled trial. *J Rehabil Res Dev* 2014;51:59-70.
51. Lipsey JR, Robinson RG, Pearlson GD, et al. Nortriptyline treatment of post-stroke depression: a double-blind study. *Lancet* 1984;1:297-300.
52. Stahl SM. *Stahl's essential psychopharmacology: neuroscientific basis and practical applications*. 3rd ed. Cambridge, United Kingdom: Cambridge University Press; 2008.
53. Briars L, Todd T. A review of pharmacological management of attention-deficit/hyperactivity disorder. *J Pediatr Pharmacol Ther* 2016;21:192-206.
54. Whelan-Goodinson R, Ponsford J, Schonberger M. Validity of the Hospital Anxiety and Depression Scale to assess depression and anxiety following traumatic brain injury as compared with the Structured Clinical Interview for DSM-IV. *J Affect Disord* 2009;114:94-102.