

Pharmacotherapy effectiveness in treating depression after traumatic brain injury: A meta-analysis

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**Pharmacotherapy Effectiveness in Treating Depression After
Traumatic Brain Injury: A Meta-Analysis**

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Pharmacotherapy Effectiveness in Treating Depression After Traumatic Brain Injury: A Meta-Analysis

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Abstract

Depression is a highly prevalent neuropsychiatric sequela in those who have suffered a traumatic brain injury (TBI). Despite its high prevalence, there continues to be conflicting evidence surrounding the efficacy of medication for treating depression post-TBI and whether different treatments have distinct effects. The aim of this study is to systematically review and synthesize the available evidence for the effectiveness of pharmacotherapy for depression following a TBI. A meta-analysis was completed using several online databases (PubMed, NICE, HDAS) to search for clinical trials involving various pharmacological treatments for the treatment of depression in the TBI population. Twelve studies met the inclusion criteria and were assessed using their sample size, treatment duration, treatment used, TBI severity, method of assessment and medication response. Standardized mean difference effect sizes (Cohen's d) were calculated for each study using pre-and post-intervention scores and pooled using a random effects model to produce a summary effect size. Fourteen effect sizes were calculated and a mild to moderate pooled effect size ($d = -0.49$, 95% CI; $-0.96, -0.02$, $p = 0.02$) was found. Ten studies demonstrated effect sizes that were statistically significant and four were non-significant. The weighted pooled effect size was higher for single group design studies ($d = -1.35$, 95% CI; $-2.14, -0.56$, $n = 5$) compared to independent groups design ($d = 0.001$, CI; $-0.59, 0.58$ $n = 9$). The current meta-analysis tentatively supports the view that pharmacological treatment may be effective in reducing depressive symptoms in those with depression following TBI. However, evidence from RCTs alone demonstrated no beneficial effect. The limitations are also discussed.

Traumatic brain injury (TBI) is increasingly one of the largest causes of fatalities globally and produces significant pervasive consequences^{1}. The sequelae of TBI often extends beyond the immediate physical injury, to neuropsychiatric and cognitive complaints that have long-term effects on functioning and quality of life. The most commonly reported neuropsychiatric complaint is that of depression, which can occur in up to 77% of people with TBI^{2}.

Depression post-TBI has been associated with extensive adverse outcomes such as impaired psychosocial functioning, impaired cognitive performance and increased risk of other psychiatric disorders such as anxiety disorders^{3}. It is also more common to experience greater post-concussive symptoms (headaches, sleep disturbances, cognitive and memory impairment) in contrast to those who do not develop depression following a TBI^{4}. The heightened need for research into depression post-TBI is highlighted by Bombardier^{5} who found 53.1% of 559 TBI patients developed major depressive disorder within one year. Therefore, early treatment of depression is crucial and essential to meet the needs of the high proportion affected by it.

The evidence for the effectiveness of pharmacotherapy for depression in the TBI population is conflicted and equivocal, with no overall trend extrapolated. Many studies within the current literature lack methodological rigour, with limited sample sizes and non-randomised control groups. Currently, the first line treatment of depression post-TBI is selective serotonin reuptake inhibitors (SSRIs), which may be attributed to the evidence base surrounding their use in major depressive disorder (MDD). SSRIs display a safer and more tolerated side effect profile than tricyclic antidepressants (TCAs). However, the efficacy of different SSRIs and TCAs vary, and TCAs behold an amplified risk of toxicity in overdose and side effects such as sedation and urinary retention, therefore it is largely a second line intervention. Findings by Jorge and

Arciniegas{6} and Fann, Hart and Schomer{7} have suggested SSRIs to be the most effective pharmacotherapy in treating depression post-TBI. However, because of limited evidence and inconsistencies in the quality of research, they cannot establish clinical guidelines on their use. This again emphasizes the need for more statistically powerful, placebo included randomised controlled trials to validate this association, which can further inform the delivery of high quality evidence recommendations.

Kant, Smith-Seemiller and Zeiler{8} highlighted other beneficial features to antidepressant (SSRIs) treatment such as reducing co-morbid irritability, aggression and improving cognitive functioning such as memory. These topographies of treatment increase its usefulness and practicality in those specifically with TBI as it can alleviate additional neuropsychiatric sequelae that frequently co-exist with TBIs.

There are alternative pharmacotherapy options, such as monoamine oxidase inhibitors (MAOIs) and Serotonin Noradrenaline Reuptake Inhibitors (SNRIs), that are less established but may offer new avenues of treatment. These are not often used because of the strict guidelines the patient must adhere to while taking them, including strict diet restriction. This is problematic in the TBI population as the common cognitive consequences often impact medication compliance. SNRIs have a dual action on serotonin and noradrenaline reuptake inhibition and could have potential. However, these class of antidepressant are currently considered a second or third line treatment in MDD, and there is limited evidence for their use specifically for depression post-TBI. This highlights the critical need for more comprehensive research into other antidepressants such as SNRIs and MAOIs into their potential effectiveness for treating depression post-TBI.

Evidence for the use of psychostimulants in TBI patients with depression is lacking, with more focus on the treatment of cognitive deficits following a TBI. Gaultiere and Evans{9} found methylphenidate to show some symptomatic relief, but some participants developed a tolerance to its administration over the time.

Anticonvulsants such as lamotrigine have also shown specific benefit in treating the depressive symptoms in bipolar disorder, which may be generalised to future research in its potential in MDD{10}. There is a larger evidence base for the use of anticonvulsants such as valproate, carbamazepine and phenytoin in treating other neuropsychiatric sequelae of TBI, including aggression, agitation and behavioural issues. However, there are also contradictory results by Smith et al{11). which showed they produced negative effects on cognition and motor performance.

There are a limited number of studies examining pharmacotherapy effectiveness in treating depression in those with TBI in comparison to studies examining MDD in the general population. A recent meta-analysis investigating pharmacological interventions for MDD in primary care found 66 eligible RCTs{12}. This meta-analysis totalled 15,161 participants, which is vastly larger than the total sample size investigated in the TBI population. This emphasizes the imbalance of research in contrast to MDD and the insufficient amount of studies focussing on effects in the TBI sample.

The methodological rigor of research should also be considered when evaluating the evidence base for the effectiveness of pharmacotherapy in the treatment of depression in the TBI population. One way to assess the quality of studies is by grading them using systems such as the Cochrane suggested GRADE (Grading recommendations assessment, development and

evaluation) criteria. This can evaluate for methodological flaws such as small sample sizes and lack of randomised control. Subsequently, it is useful in research because it can assist in producing evidence-based guidelines. A systematic review by Fann et al {7} found only one study with the highest grade of research (assessed using American Academy of Neurology criteria). This drastically highlights not just the need for more research, but studies that are conducted at a higher level of quality.

Overall, the current studies examining the treatment for depression post-TBI all implement different outcome measures, varying sample sizes, periods of treatment, TBI severity and time between TBI and the onset of depression. This makes comparison across studies especially difficult. As such, there is a need to amalgamate the current research to provide clear guidelines that inform the treatment of depression following TBI. Subsequently, the aim of the current meta-analysis is to converge existing studies and provide a synthesized effect size in order to measure the effectiveness of pharmacotherapy for depression following a TBI.

Methodology

Search Strategy

Online searches of published studies were conducted through several databases with the criteria of being peer-reviewed, written in English, published after 1980 and including only human participant studies. The searches were performed through PubMed, Cochrane Database, Google Scholar and using the NICE HDAS to search through the following simultaneously: AMED, BNI, CINAHL, EMBASE, HBE, HMIC, Medline and PsychINFO. The following terms were used “antidepressants”, “depression treatment”, “depression”, “traumatic brain injury” and

“TBI”. Author AS independently reviewed all abstracts and full texts and extracted the relevant data. This process was overseen by author RC to ensure objectivity.

Inclusion Criteria

To ensure the relevant articles were selected the following inclusion criteria was chosen to refine the studies obtained. This included studies whereby the depressive symptoms were measured as a secondary outcome to enable a larger number of studies to be incorporated in the already depleted area of research. Unpublished and ongoing studies were not searched for and therefore not included. Research was not contained to a specific setting such as secondary care. The inclusion criteria for the current meta-analysis were:

- I. Including adults above 18 years of age.
- II. Clinical trials measuring the effect of all pharmacological treatments (i.e. all drug types) for depression following a TBI.
- III. Have a diagnosis of depression before the study initiation.
- IV. Sample to include participants with a TBI of any severity (mild, moderate, severe).

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were used for the process of conducting the meta-analysis^{13}. Initially, 98 papers were identified. Studies not meeting the inclusion criteria, and duplicates, were omitted leaving 24 studies. If the information in the abstract was not sufficient the full paper was reviewed. Of these, 6 studies were discounted as they did not meet the inclusion criteria; one was study excluded as it was a continuation of a previous study not focussing on depression, and a further 6 studies were excluded because of the use of preventative treatment. However, 2 additional

articles were discovered through independent internet searches and through other journal articles. Of these studies, 1 study was excluded due to insufficient descriptive data provided (after the author was contacted) leaving 12 articles fully meeting the inclusion criteria. A diagram summarising the selection of studies is provided in *Figure 1*.

-----Insert Figure 1 here-----

Figure 1: Flow chart overview of the study selection and exclusion process.

Statistical Analyses

The statistical analysis was calculated using standardized mean differences for both RCTs (two independent groups) and single intervention groups using different calculations for both.

The standardized mean difference was calculated (Cohens d) for the pre- and post-intervention and control scores by using the extracted means and standard deviations from the literature {14}. This resulted in an effect size for each study measuring treatment effectiveness for depression following a TBI. Correlations between the pre- and post-intervention scores were based upon the literature review of the correlation coefficient of the outcome measure (test re-test reliability r value). Where the r value was not derived from the available literature, the recommended value of 0.5 from the Cochrane Handbook was employed {15}. To assess if this would bias results, a sensitivity analysis was conducted using r values of 0.3 and 0.8 to assess impact on effect size. There were no large differences in results and so 0.5 was used in such instances. For example, the test-retest reliability of HAM-D and DSM-III R was set at 0.5 as

there was no appropriate estimate in the TBI population. The Patient Health Questionnaire-9 (PHQ-9) was set at 0.76, which was extracted from a study in the TBI population {16}.

The standard deviation of pooled change scores were not reported by any of the studies. Therefore, this was calculated using the standard deviation of changed scores for both treatment group and placebo/control group. The effect sizes was then calculated as was the standard error, variance and the weight of each effect size. Alternative calculations for the effect size in single group design were also completed. According to Cohen {17} a small effect size is interpreted as ($d=0.25$), medium ($d=0.5$) and large ($d=0.75$). For the purpose of this meta-analysis, a negative effect size (-) would indicate a reduction in depression scores.

Pooled analysis

All effect sizes were weighted and pooled to obtain an average effect size for both the two group and one group designs combined. Subsequently, a 95% confidence interval was calculated for the average weighted effect size produced. A random effects model was then applied to the analysis and heterogeneity was assessed using a chi-squared-based Q -statistic test and I^2 value {15}.

When multiple assessments were used, the most reliable and validated method was included. For instance, in cases where both the HAM-D/HDRS (Hamilton Depression Rating Scale) and BDI (Beck Depression Inventory) were used, the HAM-D was included to keep the data extracted as consistent as possible.

In order to assess publication bias, a funnel plot was created and was assessed visually, which is displayed in Figure 3. An asymmetrical funnel plot indicates the presence of publication bias.

Results

Study Characteristics

Out of the twelve studies analysed, four compared pharmacological effectiveness to placebo groups, one compared treatment in the TBI sample to a functional depressive group and two studies included control groups. Five studies compared the pre- and post-treatment effects with no control group. All placebo and control groups contained depressed TBI patients who were either given a placebo or no treatment. Dinan and Moyabed{18} was the only study to compare treatment effectiveness in non-TBI patients, but instead used functionally depressed patients.

There was considerable variation in the measurements of treatment effectiveness, but it was most commonly measured using HAM-D/HDRS scores in nine studies. Depression was diagnosed with the DSM in all but one study, which used the PHQ-9.

(a) Two independent groups

Fann et al. {19} and Zhang and Wang {20} included multiple outcome measures including HAM-D, Maeir subscale and BDI. For consistency the HAM-D pre-and post-scores were assessed.

The Saran{21} study consisted of participants receiving four weeks of amitriptyline and then a washout period of one week, followed by initiation of treatment with phenelzine. To gain separate effect sizes for each drug type (amitriptyline [TCA] and phenelzine [MAOI]), each condition was assessed separately. As this is a cross over trial, there are concerns regarding any possibility of carry over treatment effects{15}.

Dinan and Moyabed{18} were contacted for further data concerning the comparison group of TBI patients to functionally depressed patients. However, as the authors no longer had access to the data the pre-and post-intervention scores were used from a previous meta-analysis{22}.

(b) Single treatment groups

In the study by Fann, Uomoto, and Katon{23}, all participants initially received one-week of placebo before switching to receiving sertraline (after no significant drop of more than 50% in HAM-D scores). However, the baseline scores were given before the placebo and no additional data was included. Therefore calculations used the baseline score and the post intervention scores given at study end.

In the trial by Wroblewski, Josephand and Cornblatt{24} ten patients were randomised to either start with placebo or desipramine and then evaluated using two different measures. However, there was various missing data for both outcomes. Only eight participants had complete data that could be evaluated using DSM-III criteria and seven for the affect/mood scale. Therefore, the measure with the most data (DSM-III) was used. The means and standard deviations were calculated from the patient-level data provided.

In the Perino et al. {25} study, the participants received both carbamazepine and citalopram and were split into two groups according to time elapsed since TBI. The global pre- and post-scores for both groups were combined.

Rapoport et al. {26} continued the study for ten weeks, from the initial six weeks, for twenty-six of the fifty-four participants. However, the most complete data (six-week stage) was used in the analysis.

Kanetani, Kimura and Endo {27} post-intervention scores were not provided in the study, but were taken from a previous meta-analysis {22}.

Meta-analysis

The results of pre-to post-treatment differences are presented in *Table 1*, showing the effect size for each study (Cohen's d), standard error, 95% confidence interval and weights (inverse of the variance). These analyses are presented in *Figure 2* in the form of a forest plot, which demonstrates the effect size, 95% confidence intervals and includes the overall synthesised effect size for all studies.

Most of the studies had a negative effect size. The weighted effect size for all studies was $d = -0.49$ (SE=0.24, 95% CI; -0.96, -0.02). The calculated Z score was -2.04 ($p=0.02$), which determined that the mean effect size was larger than zero. The studies were highly heterogenous ($I^2 = 91.94\%$; Tau squared = 0.68). Studies without a control/placebo group were lower in heterogeneity ($I^2 = 81.45\%$; Tau squared = 0.19).

When additional analyses were performed, the mean effect size for studies that included a comparison group were non-significant ($d = 0.001$, CI; -0.59, 0.58) when compared to single

group design studies ($d = -1.35$, 95% CI; -2.14, -0.56). This should be interpreted in the context that these studies included no control/placebo.

-----**Insert table 1 here**-----

Table 1: The total sample size (n), effect size (Cohen's d), standard error (SE), 95% confidence intervals (CI) and weight of each study with the mean effect size below.

(a) Study administered carbamazepine with citalopram.

The 95% confidence intervals of the overall effect size do not cross the zero threshold. Therefore the results of the current meta-analysis are considered statistically significant. However, it should be highlighted that the margin is very close. The null hypothesis can be rejected and the alternative hypothesis that there is an effect can be accepted. Although there is a large variation in the studies included and very small sample sizes, ten studies have shown statistically significant results with their effect sizes being larger than the pooled estimate. Four studies are statistically non-significant. The non-significant studies included very small sample sizes, were non-randomised and had no control groups; apart from the RCT by Fann et al. {29}.

-----**Insert Figure 2 here**-----

Figure 2: Forest plot of effect size (ES) and 95% confidence intervals (CI) of studies with the summary effect size displayed below. (a) Study administered carbamazepine with citalopram.

The forest plot (Fig. 2) demonstrates the pharmacological treatment that had the greatest effect size was for was Fann et al. {23} study, which examined sertraline. Although this study was non-randomized, it had very large confidence intervals and the lowest weight, which indicates that it lacks precision.

The largest number of studies was performed on sertraline ($n = 5$), of which all produced large effect sizes apart from the most recent study by Fann et al. {19}. In Fann et al. {19} both treatment and placebo group had significant changes in depressive symptoms. The variation in results could be from the underpowered studies ranging from 20 to 80 participants, the varying dosage from 25mg/day up to 200mg/day and the period of treatment ranging from 4 weeks up to 12 weeks. Fann et al. {19} had the longest period of treatment, highest dosage and second largest sample size of 62 TBI patients. However, their sample contained a larger amount of severe TBI patients with high levels of psychiatric co-morbidity. However, when the pooled effect size was calculated for sertraline it produced a large effect size $d = -1.02$ (95% CI, -1.76, -0.28, $p = 0.004$).

Both studies looking at amitriptyline produced non-significant effect sizes with larger confidence intervals, which were more positive than the pooled estimate. Citalopram and methylphenidate only included two trials each but both showed large effect sizes and therefore significantly reduced depressive symptoms.

HAM-D was the most commonly used outcome measure, but there was variation on the version used (either the 17 or 21 item-scale). Eleven effect sizes were calculated using the reported pre-and post-intervention HAM-D scores. The mean reduction of these scores in the

treatment groups is 10.17 and standard deviation 4.46. Six of the studies reported a statistically significant decrease in HAM-D scores.

Publication bias

The funnel plot seen in *Figure 3*. demonstrates large asymmetry and therefore publication bias. When applying the Orwin fail-safe N formula, the number of studies needed to decrease the effect size to less than ($d= 0.2$) is 48. All but four studies are clustered in the top area, which means these studies have more precise estimated effects. However, 95% of studies do not lie between the 95% confidence intervals and therefore show between trial heterogeneity.

----- **Insert Figure 3 here**-----

Figure 3: Funnel plot to assess publication bias. Summary effect size indicated by the straight line and dashed diagonal lines represent the 95 per cent confidence interval around the summary effect size.

Discussion

These results indicate that pharmacological treatment may be mildly to moderately effective in treating depression post-TBI. Specifically, treatment such as citalopram, sertraline and methylphenidate may be effective in reducing depressive symptoms in TBI patients. The overall small to moderate effect size ($d = -0.49$) suggests that there is a significant reduction in symptoms from pre-to post-intervention scores. However, this overall result should be interpreted with caution as there is a lack of evidence in the form of large RCTs, but rather includes a small sample of studies with poor methodological quality.

The findings from the current meta-analysis are supported by a previous meta-analysis {28} who found similar results. They evaluated antidepressant treatment effectiveness in nine studies treating depression, finding significant effects in favour of anti-depressants. Although, the authors could not draw definite conclusions on treatment efficacy due to the limited number of studies available in the literature.

This stance is reflected in another meta-analysis conducted by Barker-Collo et al. {22} who analysed both pharmacological and non-pharmacological treatments and found that treatment did decrease depressive symptoms. They came to a similar conclusion that there is insufficient evidence to conclusively recommend treatment options to TBI patients. The current meta-analysis does offer an expansion on the included literature, but still consists of limitations and so interpretation of the results should acknowledge this.

Whilst the current meta-analysis was under review, the authors were made aware of a newly published meta-analysis by Kreitzer et al {29}. Although the overall conclusions slightly differ, the results of both meta-analyses are very similar. This is encouraging from a scientific replicability standpoint. For example, Kreitzer et al. {29} acknowledge significant reductions in depression scores for individuals after pharmacotherapy (mean change in HADS scores of -11.2). However, similar to the current meta-analysis, Kreitzer et al. {29} found no significant reduction in depression scores when considering the evidence from RCT alone, for which Kreitzer et al. {29} derived their conclusion. In contrast, the current meta-analysis derived its conclusion from the entire evidence base, including both RCT and single-group design studies, which indicated a small to medium effect for pharmacological treatments for depression following TBI. In addition

to an overall omnibus effect size for all studies, the current meta-analysis also provided separate effect sizes for both single-group design studies and RCTs for the readers consideration.

The most consistent modest effect size was for sertraline followed by methylphenidate and citalopram. A pooled estimate calculated for the sertraline studies $d = -1.02$ produced a large effect size, even with the included outlier. Therefore, these findings suggest that sertraline, with the largest number of studies included and effect size, is potentially the most efficacious pharmacotherapy in treating depression following a TBI. Furthermore, the results from methylphenidate and milnacipran could have further implications in guiding potential pharmacological options. Especially with the additional benefits on cognitive impairments and tolerability.

The studies which had non-significant effect sizes consisted of control groups such as in Fann et al. {19}. In their paper, Fann et al. {19} discuss several possibilities for such non-significant effect sizes. One hypothesis is that the control group had more contact with staff, which may have produced the reduction in depressive symptoms. Fann et al. {19} highlight the high prevalence of social isolation in the TBI population and hypothesise that frequent contact with healthcare staff may have reduced social isolation and decreased depression scores. Subsequently, this could be important in the context of rehabilitation by researching what non-pharmacological mechanism cause reductions in reported depression, thus potentially leading to subsequent application in non-pharmacological therapies.

In comparison, a recent by Cipriani et al. {30} investigated the efficacy of twenty-one different antidepressants in treating MDD, which showed modest effect sizes for all antidepressants in reducing depressive symptomology. Although this exhibits a significant

difference in response compared to depression post-TBI, there was a substantial evidence base to converge data from, which is severely lacking in regard to the TBI population. Consequently, it is likely that similar results of treatment efficacy may be found if there was further comprehensive research into depression post-TBI.

In contrast, Saran {21} found that both amitriptyline and phenelzine had greater effects in reducing HAM-D scores in those without a minor closed head injury. Similarly, Dinan and Moyabed {18} reported an 85% response to amitriptyline in those with just MDD compared to 31% responding to treatment in those with depression post-TBI. Cipriani et al. {29} found amitriptyline to produce the greatest effect size in non-TBI MDD, which is interesting when comparing the response to amitriptyline in TBI patients. These findings connote that depression in TBI may respond differently to treatment compared to the non-TBI population. However, the studies in the TBI population had very low methodological quality, lacking large sample size and included a cross-over trial so assumptions cannot be conclusive.

A meta-analysis by Price et al. {31} assessing treatment of depression in neurological disorders (stroke, Parkinson's disease, multiple sclerosis, epilepsy and TBI) found statistically significant effects of antidepressants compared to placebo. Additionally, the meta-analysis also found a small difference in antidepressant responsiveness in this neurological sample when compared to non-neurological depressed population. Although, as there was only one TBI study included, these conclusions cannot be applied to the whole TBI population. This was acknowledged by the authors who stated that lack of trials only permitted evidence on Parkinson's disease and stroke.

The current meta-analysis only evaluated pharmacological treatments and it is important to note that pharmacological treatments alone are not the only options in treating depression in TBI patients. Future research could investigate medication effectiveness in the setting of other interventions such as cognitive behavioural therapy, magnetic field stimulation and psychoeducation. This is because vitally, treating neuropsychiatric sequelae such as depression in TBI patients requires a multi-factorial approach in order to assist TBI patients in their recovery and increase their quality of life.

While considering the proposed effectiveness of the antidepressants it is also imperative to look at the population to whom the treatment will be administered to. Their existing co-morbidities and current medication use will inevitably affect which treatment they receive. This is further complicated by the possibility that the characteristics of depression post-TBI and related co-morbidities could affect treatment effectiveness. For example, most depressed patients post-TBI also experience executive dysfunction, although the causation for this is not clear-cut (either it is due to the TBI damage and/or specific symptoms from the depression). Goryln et al. {32} found deficits in executive function could influence their treatment adherence and predict their response to SSRIs. This also presents the idea of neuropsychological testing to enable identification of those who are at risk of not responding to treatment.

A potential limitation to this meta-analysis is the incorporation of single group designs. This makes it challenging to delineate the treatment effectiveness from the natural course of depression in the context of TBI rehabilitation and recovery. This is also highlighted by Kreitzer et al. {29}. Incidentally, single group design studies produced a large pooled effect size ($d = -1.35$). However, this is limited in the context of the Cochrane recommendations that results

from non-randomized studies should be interpreted with caution. This is because it results in a higher risk of selection bias and can produce effect size estimates that indicate the more extreme ends of the effects of treatment than randomized trials.

Another limitation is the inability to control for the variation in the time since injury or the type and severity of TBI, which otherwise might produce more meaningful results to TBI patients. This undoubtedly contributed to the high heterogeneity including the different outcome measures and length of treatment. For example; the time from injury varied from 30 days to 18.6 years, and the period of treatment varied from four to thirty weeks. The main concern of the shorter administration periods is not allowing for the optimal dosage and adjustment needed for therapeutic levels, such as in the Saran{21} study. For instance; the SSRI sertraline generally shows a latency period of two weeks before having an effect and perhaps more significant results could be found if periods of treatment were longer.

A strength of this current meta-analysis is that it has, to the authors knowledge, the most up-to date inclusion and largest compilation of studies. Therefore, this is the largest comprehensive meta-analysis conducted so far on pharmacological treatment options, and importantly not just inclusion of antidepressants. This can give a wider scope on other pharmacological interventions and their potential effects on depression post-TBI.

To conclude, this meta-analysis suggests that pharmacological treatment may be mildly to moderately effective in treating depression following a TBI. It also demonstrates that sertraline may be the most effective pharmacological treatment option. However, there is still a need for higher quality studies with lower heterogeneity in order to draw less preliminary and more conclusive inferences concerning TBI treatment. This is important in the context of Fann et

al. {7} who found untreated depression in TBI patients is associated with poorer psychosocial functioning, cognition and integration into the community. Consequently, if more comprehensive research is established, especially with pharmacotherapy in conjunction with non-pharmacological therapies, it can help future clinical application and rehabilitation of TBI patients.

Peer Review Only

References

1. Hyder, A. A., Wunderlich, C. A., Puvanachandra, P., Gururaj, G., & Kobusingye O. C. (2007). The impact of traumatic brain injuries: A global perspective. *NeuroRehabilitation*, 22 (5): 341–353. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/18162698>
2. Varney, N. R., Martzke, J. S., & Roberts, R. J. (1987). Major depression in patients with closed head injury. *Neuropsychology*, 1(1), 7-9. doi:10.1037/h0091773.
3. Whelan-Goodinson, R., Ponsford, J., & Schönberger, M. (2008). Association between psychiatric state and outcome following traumatic brain injury. *J Rehabil Med*, 40(10):850-7. doi: 10.2340/16501977-0271
4. Suhr, J. A., Gunstad, J. (2002). Postconcussive symptom report: the relative influence of head injury and depression. *J Clin Exp Neuropsychol*, 24(8):981-93. doi: 10.1076/jcen.24.8.981.8372
5. Bombardier, C. H., Fann, J. R, Temkin, N. R, Esselman, P. C, Barber, J., & Dikmen, S. S. (2010). Rates of Major Depressive Disorder and Clinical Outcomes Following Traumatic Brain Injury. *JAMA*, 303(19):1938-1945. doi:10.1001/jama.2010.599
6. Jorge, R. E., & Arciniegas, D.B. (2014). Mood disorders after TBI. *Psychiatr Clin North Am*, 37(1): 13-29. doi:10.1016/j.psc.2013.11.005
7. Fann, J. R., Hart, T., & Schomer, K. G. (2009) Treatment for Depression after Traumatic Brain Injury: A Systematic Review. *J Neurotrauma*, 26(12): 2383-402. doi:10.1089/neu.2009.1091

8. Kant, R., Smith-Seemiller, L., & Zeiler, D. (1998). Treatment of aggression and irritability after head injury. *Brain Inj*, 12(8):661-6. doi: 10.1080/026990598122223
9. Gaultiere, C. T., & Evans R. W. (1988). Stimulant treatment for the neurobehavioural sequelae of traumatic brain injury. *Brain Inj*, 2(4): 273–290.
doi:10.3109/02699058809150898
10. Cascade, E., Kalali, A. H., & Weisler, R. H. (2008). Varying Uses of Anticonvulsant Medications. *Psychiatry (Edgmont)*, 5(6): 31–33. Retrieved from:
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2695747/>
11. Smith, K., Goulding, P., Wilderman, D., Goldfader, P., Holterman-Hommes, P., & Wei, F. (1994). Neurobehavioral Effects of Phenytoin and Carbamazepine in Patients Recovering From Brain Trauma: A Comparative Study. *Archives Of Neurology*, 51(7): 653-660. doi:10.1001/archneur.1994.00540190029012
12. Linde, K., Kriston, L., Rucker, G., Jamil, S., Schumann, I., Meissner, K., Sigterman, K., & Schneider, A. (2015). Efficacy and Acceptability of Pharmacological Treatments for Depressive Disorders in Primary Care: Systematic Review and Network Meta-Analysis. *Ann Fam Med*, 13(1): 69-79. doi: 10.1370/afm.1687
13. Liberati, A., Altman, D., Tetzlaff, J., Mulrow, C., Gotzsche, P., & Ioannidis, J., ... & Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*, 339: b2700. doi:10.1136/bmj.b2700
14. Lipsey, M. W., & Wilson, D. B. (2001). *Applied social research methods series; Vol. 49. Practical meta-analysis*. Thousand Oaks, CA, US: Sage Publications, Inc.

15. Higgins, J., Deeks, J., Altman, D. (Eds.), Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (Eds.), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Retrieved from www.handbook.cochrane.org.
16. Fann, J., Bombardier, C., Dikmen, S., Esselman, P., Warms, C., Pelzer, E., Rau, H., & Temkin, N. (2005). Validity of the Patient Health Questionnaire-9 in Assessing Depression Following Traumatic Brain Injury. *The Journal of head trauma rehabilitation*. 20. 501-11. 10.1097/00001199-200511000-00003.
17. Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates.
18. Dinan, T. G., & Mobayed, M. (1992). Treatment resistance of depression after head injury: A preliminary study of amitriptyline response. *Acta Psychiatrica Scandinavica*, 85(4): 292-294. doi:10.1111/j.1600-0447.1992.tb01472.x
19. Fann, J., Bombardier, C., Temkin, N., Esselman, P., Warms, C., Barber, J., & Dikmen, S. (2017). Sertraline for Major Depression During the Year Following Traumatic Brain Injury. *Journal Of Head Trauma Rehabilitation*, 32(5): 332-342. doi:10.1097/HTR.0000000000000322
20. Zhang, W. T., & Wang, Y. F. (2017). Efficacy of methylphenidate for the treatment of mental sequelae after traumatic brain injury. *Medicine (Baltimore)*, 96(25): e6960. doi:10.1097/MD.00000000000006960
21. Saran, A. (1988). Antidepressants not effective in headache associated with minor closed head injury. *Int J Psychiatry Med*, 18(1):75-83. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/3294202>

22. Barker-Collo, S., Starkey, N., Theadom, A. (2013). Treatment for depression following mild traumatic brain injury in adults: a meta-analysis. *Brain Inj*, 27(10): 1124-33. doi:10.3109/02699052.2013.801513
23. Fann, J., Uomoto, J., & Katon, W. (2000). Sertraline in the Treatment of Major Depression Following Mild Traumatic Brain Injury. *Journal Of Neuropsychiatry*, 12(2): 226-232. doi:10.1176/appi.neuropsych.12.2.226
24. Wroblewski, B. A., Joseph, A. B., & Cornblatt, R. R. (1996). Antidepressant pharmacotherapy and the treatment of depression in patients with severe traumatic brain injury: A controlled, prospective study. *The Journal of Clinical Psychiatry*, 57 (12): 582-587. doi:10.4088/JCP.v57n1206
25. Perino, C., Rago, R., Cicolini, A., Torta, R., & Monaco, F. (2001). Mood and behavioural disorders following traumatic brain injury: Clinical evaluation and pharmacological management. *Brain Inj*, 15(2):139-48. doi:10.1080/02699050120891
26. Rapoport, M. J., Chan, F., Lanctot, K., Herrmann, N., McCullagh, S., & Feinstein, A. (2008). An open-label study of citalopram for major depression following traumatic brain injury. *J Psychopharmacol*, 22(8):860-4. doi:10.1177/0269881107083845
27. Kanetani, K., Kimura, M., & Endo, S. (2003). Therapeutic effects of milnacipran (serotonin noradrenalin reuptake inhibitor) on depression following mild and moderate traumatic brain injury. *J Nippon Med Sch*, 70(4):313-20. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/12928711>
28. Salter, K., McClure, J., Foley, N., Sequeira, K., & Teasell, R. (2016). Pharmacotherapy for Depression Posttraumatic Brain Injury. *Journal Of Head Trauma Rehabilitation*, 31(4): E21-E32. doi:10.1097/htr.0000000000000193

29. Kreitzer, N., Ancona, R., McCullumsmith, C., Kurowski, B., Foreman, B., Ngwenya, L., & Adeoye, O. (2018). The Effect of Antidepressants on Depression After Traumatic Brain Injury: A meta-analysis. *J Head Trauma Rehabil.* doi: 10.1097/HTR.0000000000000439. [Epub ahead of print].
30. Cipriani, A., Furukawa, T., Salanti, G., Chaimani, A., Atkinson, L., & Ogawa, Y., ... & Geddes, J. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *The Lancet*, 391(10128): 1357-1366. doi:10.1016/S0140-6736(17)32802-7
31. Price, A., Rayner, L., Okon-Rocha, E., Evans, A., Valsraj, K., Higginson, I., & Hotopf, M. (2011). Antidepressants for the treatment of depression in neurological disorders: a systematic review and meta-analysis of randomised controlled trials. *Journal Of Neurology, Neurosurgery & Psychiatry*, 82(8), 914-923. doi:10.1136/jnnp.2010.230862
32. Gorlyn, M., Keilp, J. G., Grunebaum, M. F., Taylor, B. P., Oquendo, M. A., Bruder, G. E., ... & Mann, J. J. (2008). Neuropsychological characteristics as predictors of SSRI treatment response in depressed subjects. *J Neural Transm*, 115(8): 1213-1219 doi:10.1007/s00702-008-0084-x

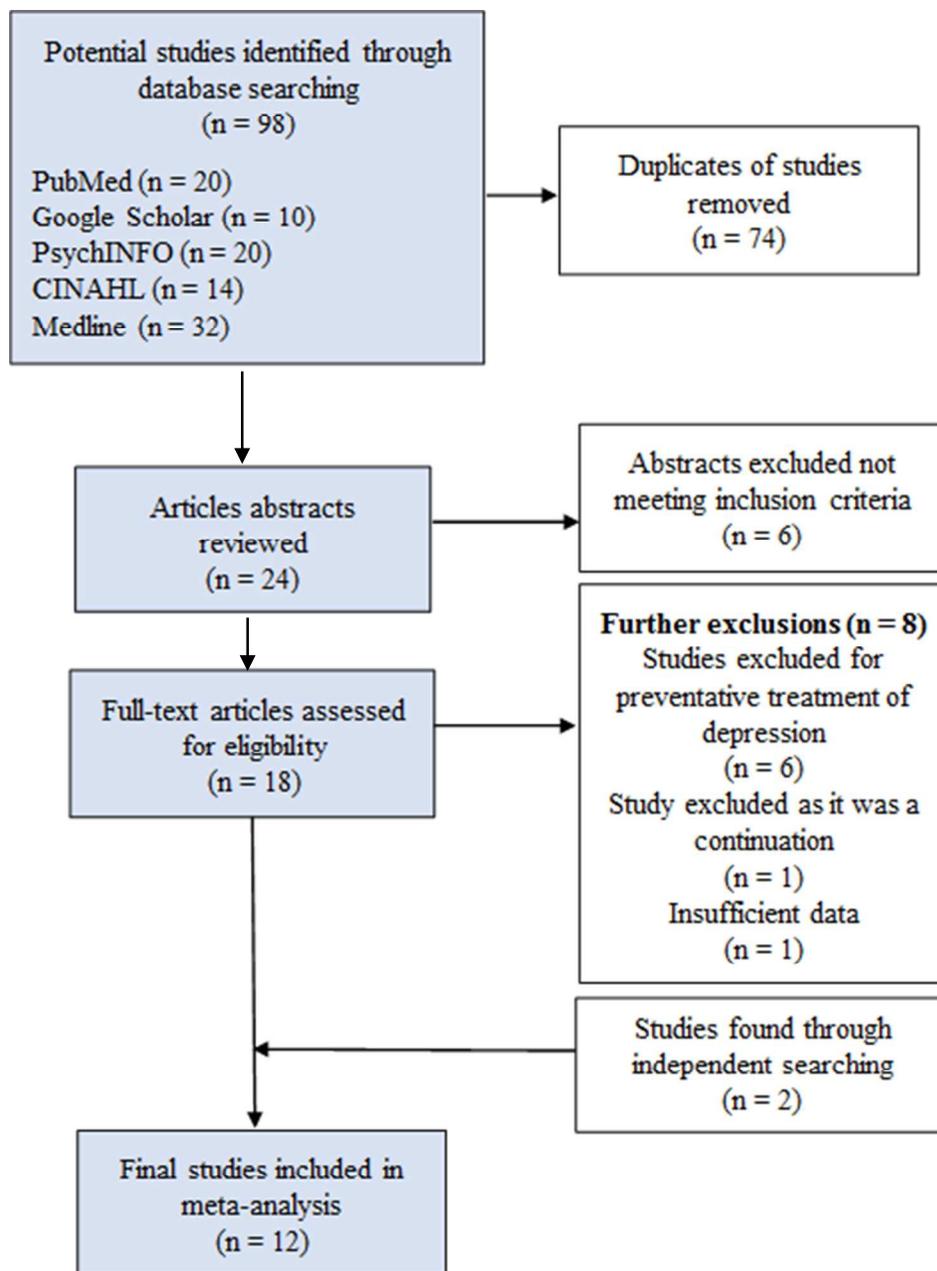


Figure 1: Flow chart overview of the study selection and exclusion process.

Study	n	Effect Size	SE	Lower CI (95%)	Upper CI (95%)	Weight	Treatment
Fann et al. (2017)	62	0.019	0.239	-0.45	0.488	1.345	Sertraline
Ansari et al. (2014)	80	-1.145	0.171	-1.480	-0.809	1.407	Sertraline
Ashman et al. (2009)	41	-0.546	0.278	-1.090	-0.001	1.318	Sertraline
Fann et al. (2000)	15	-3.624	0.710	-5.016	-2.232	0.843	Sertraline
Lee et al. (2005)	30	-0.831	0.409	-1.633	-0.030	1.178	Sertraline
Lee et al. (2005)	30	-1.283	0.437	-2.140	-0.426	1.146	Methylphenidate
Zhang and Wang (2017)	33	-1.069	0.315	-1.686	-0.451	1.281	Methylphenidate
Rapoport et al (2008)	54	-0.883	0.160	-1.197	-0.569	1.414	Citalopram
Perino et al (2001)	20	-0.673	0.248	-1.158	-0.187	1.346	Citalopram ^(a)
Wroblewski et al. (1996)	8	-1.119	0.451	-2.003	-0.235	1.130	Desipramine
Dinan and Moyabed (1992)	26	1.151	0.463	0.415	1.886	1.216	Amitriptyline
Saran (1988)	20	1.843	0.526	0.935	2.751	1.116	Amitriptyline
Saran (1988)	20	2.477	0.093	1.446	3.509	1.043	Phenelzine
Kanetani et al. (2003)	10	-1.316	0.093	-1.498	-1.133	1.449	Milnacipran
Summary		-0.491	0.241	-0.963	-0.019		

Table 1: The total sample size (n), effect size (Cohen's d), standard error (SE), 95% confidence intervals (CI) and weight of each study with the mean effect size below.

^{a)} Study administered carbamazepine with citalopram.

Note:

Negative (-) effect size indicates reduction in depression scores.

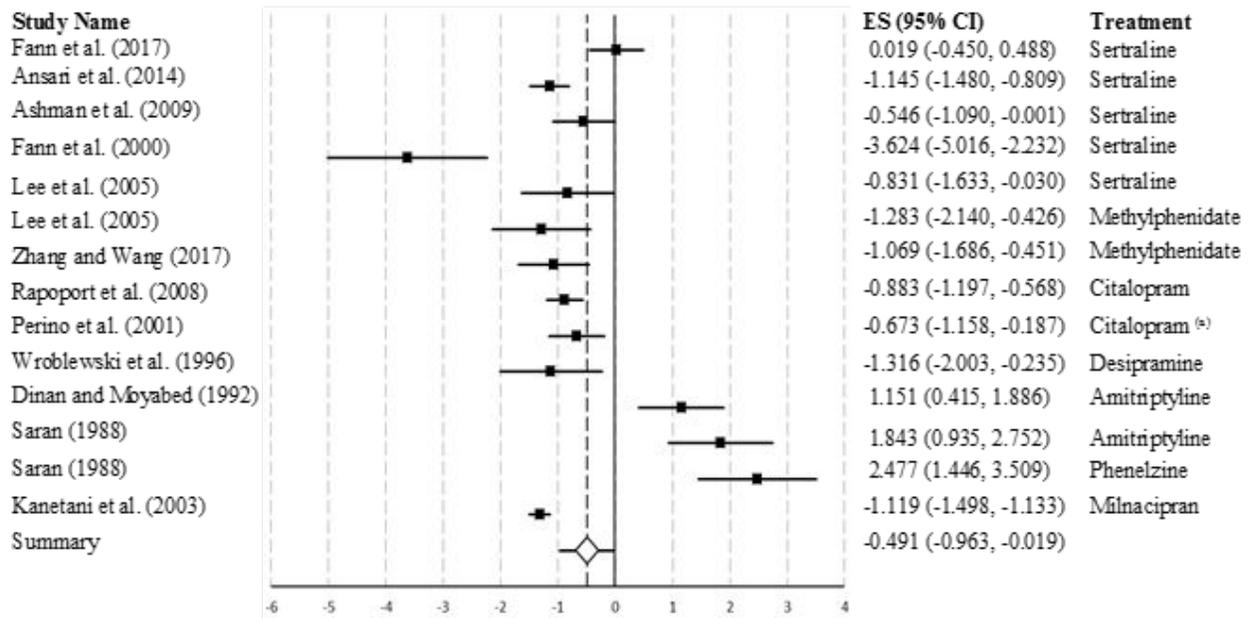


Figure 2: Forest plot of effect size (ES) and 95% confidence intervals (CI) of studies with the summary effect size displayed below.

^(a)Study administered carbamazepine with citalopram.

Note: Negative (-) effect size indicates reduction in depression scores.

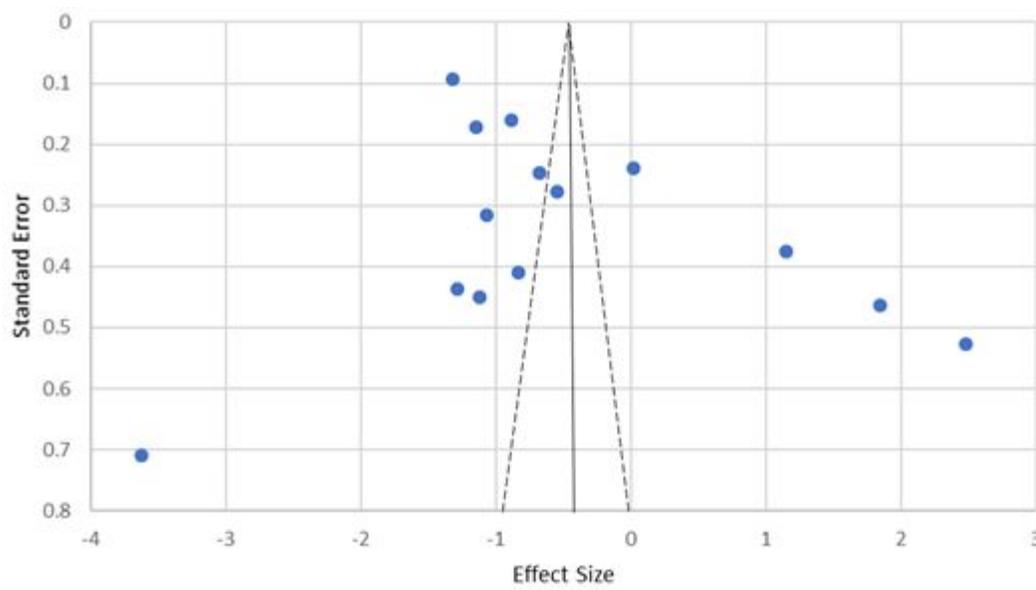


Figure 3: Funnel plot to assess publication bias. Summary effect size indicated by the straight line and dashed diagonal lines represent the 95 per cent confidence interval around the summary effect size.

Note: Negative (-) effect size indicates reduction in depression scores.