ABSTRACT

Primary Objective: Development of depression after TBI is linked to poorer outcomes. The aim of this manuscript is to review evidence for the effectiveness of current treatments.

Research Design: Two meta-analyses were undertaken to examine the effectiveness of both pharmacological and non-pharmacological interventions for depression after mild –TBI

Method and Procedures: PubMed, Medline, PsychInfo, Web of Science, and Digital Dissertations were searched and 13 studies located. Meta Analyst Beta 3.13 was used to conduct analyses of pre versus post effects then to examine treatment group versus control group effects.

Main Outcomes and Results: Studies using a pre-post design produced an overall effect size of 1.89 (95% CI 1.20-2.58, p<.001), suggesting that treatments were effective, however the overall effect for controlled trials was 0.46 (95%CI -0.44-1.36, p<.001), which favoured the control rather than treatment groups.

Conclusions: This study highlights the need for additional large well controlled trials of effective treatments for depression post-TBI.

Keywords: Depression; Treatment; Meta-analysis; Mild brain injury; TBI; antidepressants; CBT

INTRODUCTION

Traumatic brain injury (TBI) is one of the most common causes of death and disability worldwide (Corrigan, Selassie et al. 2010). The majority (up to 90%) of TBIs are mild (Langlois, Keglar et al. 2003; Langlois, Rutland-Brown et al. 2006), and while most cases recover fully within three months (Rohling, Binder et al. 2011), a significant proportion report on-going difficulties. Depression is the most commonly reported psychiatric consequence of TBI, with reports suggesting that up to 60% of patients with TBI develop depression within 12 months of injury, even following a mild injury (Busch 1998; Hibbard, Uysal et al. 1998; Fann, Uomoto et al. 2000; Robinson and Jorge 2005; Hoge 2008). The etiological factors that underlie the development of depression after TBI remain unclear (Ownsworth 1998), although neurochemical changes and psychosocial reaction to injury have both been implicated (Grant 1987). There is a general consensus that a complex interaction of neurological, psychological and social factors contribute to the development of post-TBI depression (Williams and Evans 2003).

Development of depression post-TBI has been linked to poorer post-injury outcomes, including increased post-concussive symptoms and cognitive deficits (Rapoport, Kiss et al. 2006), as well as poorer psychosocial and functional outcomes (Rapoport, McCullagh et al. 2003; Jorge, Robinson et al. 2004). Given this, treatment of depression post-TBI is clearly needed.

Commonly used psychological and pharmacological treatments for major depressive disorder have been used to treat depression post-TBI but the effectiveness of these interventions is equivocal (Alderfer, Arciniegas et al. 2005; Chew and Zafonte 2009). The Neurobehavioural Guidelines Working Group (Warden, Gordon et al. 2006) suggest the use of amitriptyline, desipramine and sertraline, even though they note a lack of evidence to support any specific recommendations. A more recent systematic review (Fann, Hart et al.

2009) concluded that serotonergic antidepressants and cognitive behavioural interventions appeared to be the most promising interventions for depression following TBI, however they also noted that the studies they reviewed were difficult to compare due to study samples differing in TBI severity and acuity, intervention type, length of treatment and use of various outcome measures. In an attempt to obtain a clearer picture of the most efficacious treatment for depression following TBI, the current meta-analysis focuses on those with mild TBI, as they are the largest patient group. Studies evaluating both pharmacological and non-pharmacological interventions were incorporated to allow direct comparisons across different treatment types.

METHOD

Search Criteria

Criteria used to identify studies for inclusion in this systematic review were: (1) investigated a treatment intervention (pharmacological or non-pharmacological); (2) depression and/or depressive symptoms included as an outcome measure; (3) in an adult human population that included persons with mild TBI; (4) was produced after 1980; and (5) written or available in English. The start point of 1980 was selected in order to be consistent with the WHO collaborating task force on mild TBI (Carroll 2004), who provide a best-evidence synthesis of the literature including epidemiology, diagnosis, prognosis, treatment and economic costs. All study designs and types (e.g., review papers and meta-analyses) were included in the search, allowing studies cited in previous reviews to be identified and incorporated into the present study. For the purposes of this study, mild TBI was defined as Loss of consciousness $\leq$ 30 minutes and/or Post traumatic amnesia < 24 hours (Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine 1993).

Search Strategy

Data bases searched included; PubMed, Medline, PsychInfo, and Web of Science. To ensure best coverage of the literature the Digital Dissertations database was also searched, as were the reference lists of all relevant papers, including previous reviews (Gualtien 1999; Comper, Bisschop et al. 2005; Fann, Hart et al. 2009), to check for any new studies that had not already been identified. Citations to key articles were also identified through searching the Web of Science and checked for any studies not already identified. The specific search terms used were "depression or mood or affective or major depression or depressive disorder" and "brain injury or head injury or brain damage or concussion" and "mild or concussion or post concussive or postconcussive or minor". A flowchart summarising study selection is shown in Figure 1.

Criteria for Inclusion

The search terms used were broad and intended to identify all papers relevant to depression following mild TBI in adults. Abstracts for all 292 studies identified were reviewed for suitability. Initially, studies focusing on children or animals were excluded. Studies could involve any treatment modality (i.e., pharmacological, psychological, educational, exercise, electroconvulsive therapy (ECT), music therapy, etc.); but were required to include the assessment of depression both pre- and post-treatment. In order to be included, studies of brain injury more broadly were required to provide separate data by TBI severity (i.e., data for depression in those with mild TBI). For those studies with samples not exclusive to TBI, results from the TBI subsample needed to be reported separately.

In studies of "mild to moderate" TBI, the inclusion/exclusion criteria for each study were reviewed to determine how the groups were defined. In one such case, reported inclusion criteria were consistent with mild TBI (i.e., loss of consciousness ≤ 30 minutes; post traumatic amnesia < 24 hours)(Baker-Price 2003); and this study was therefore included.

In two further cases, the study authors were contacted and it was confirmed that all participants met these criteria (Rapoport 2005; Rapoport 2008). Where both mild and moderate TBI were included but separate data were not presented, study authors were contacted to obtain separate data for those with mild TBI (Rapoport 2008; Ashman 2009; Lanctot 2010; Topolovec-Vranic 2010).

Using these criteria, abstracts were reviewed by two reviewers (SB-C and NJS). Discrepancies were resolved by consensus. Studies not meeting criteria were excluded from further review. After reviewing the 183 abstracts in depth, 33 potential papers were obtained in full for more detailed review. Of these, 7 met inclusion criteria. A further 19 of the 26 studies that did not obviously meet criteria for inclusion had the potential to contribute data to the analyses and the authors were contacted (see Figure 1). A total of 13 studies were included in the analysis.

Insert Figure 1 around here.

Descriptive information of the studies included in the analyses is presented in Table 1. For each study, this includes the diagnostic criteria for depression, number of participants, timing of assessment, the outcome measure(s), the study design and type of intervention, and the mean and SD of the outcome measures pre and post treatment.

Insert Table 1 around here

Meta-analyses

Given the studies used different outcome measures, effect sizes (Cohen's *d*) were calculated for change from baseline scores for the treatment groups (Borenstein, Hedges et al. 2009). In order to calculate the effect size the standard deviations of the change scores were needed, in addition to the correlations between the pre and post-intervention scores. For studies where this information was unavailable, the standard deviations of the change scores were calculated from the square root of the pooled variance from the pre and post score standard

deviations (Borenstein, Hedges et al. 2009). For the correlations between the pre and post scores, we reviewed the literature to locate appropriate estimates of the correlation coefficients for each outcome measure, however, we were unable to find studies using a similar participant group within a comparable timeframe. Therefore, we followed recommendations from the Cochrane Handbook and used an estimated correlation of .5 (Follman, Elliot et al. 1992; Higgins, Deeks et al. 2011). As this may not be an accurate estimation of the pre-post test score correlations, the overall analyses were also conducted using low (.3) and high (.8) correlations, which revealed no large differences between effects sizes, suggesting that using the an estimated correlation of .5 would not bias the results of the analyses. A larger positive effect size indicated a greater decrease in depressive symptomatology.

The studies located for the meta-analysis used pre-post designs either with or without a control group. The first analyses focused on the pre-post effects, and a second analysis focused on studies comparing treatment and control groups. For the second analysis, standardised mean group differences, with a correction for overestimation (Hedges' g) were used to evaluate the efficacy of the treatments (Hedges 1981). For this analysis, positive treatment effects were represented by a smaller (or negative) effect size and larger positive effect sizes favoured the control group. Meta Analyst Beta 3.13 (Wallace 2009) for windows was used to conduct the analyses. Overall effect sizes were estimated using random effects models, as there were substantial differences between the studies (e.g., diagnostic criteria, length of treatment it was unlikely that the studies would share a common effect size (Borenstein, Hedges et al. 2009).

The I^2 value was used as an indication of the heterogeneity of the effect sizes. This value reflects the proportion of the variance accounted for in the effect sizes by between study variance however it is not dependent on the location or spread of the true effects

(Borenstein, Hedges et al. 2009). I^2 can have a value between 0-100 and it has been suggested that values of 25%, 50% and 75% can be considered as low, moderate or high (Higgins, Thompson et al. 2003). A low value suggests that the variance is due to random error, whereas a high I^2 suggests that the variance is not random and may be attributable to factors such as treatment effect. Publication bias was assessed by inspection of funnel plots. Asymmetrical plots indicate the possibility of publication bias.

RESULTS

Study characteristics

As can be seen in Table 1, we located five studies whose treatment effect was determined using a control group for comparison (Saran 1985; Dinan 1992; Leonard 2002; Lee, Kim et al. 2005; Ashman, Cantor et al. 2009), while eight studies were pre- post comparisons without a control group (Baker-Price and Persinger 1996; Fann, Uomoto et al. 2001; Horsfield 2002; Baker-Price and Persinger 2003; Kanetani, Kimura et al. 2003; Rapoport, Chan et al. 2008; Lanctot, Rapoport et al. 2010; Topolovec-Vranic, Cullen et al. 2010). Across the studies there was variability in how presence of depression was identified, however, use of Diagnostic and Statistical Manual (DSM) criteria was the most commonly reported (n = 7). While the modal treatment length was 6 weeks (mean = 8.15 weeks), this ranged from 4 weeks to 8 months. This was included as a covariate in the analyses.

Treatments described also varied considerably, including a range of antidepressant medications, brain stimulation, psychotherapeutic interventions (individual, group, and computer mediated), and educational interventions. The most common measure of depressive outcomes was the Hamilton Depression Rating Scale (HAM-D), followed by the Beck Depression Inventory (BDI). To allow greater consistency HAM-D scores were used where available.

Pre to Post Treatment Effects

The initial analyses focused on pre to post treatment effects. Table 2 presents the treatment effect, standard error, and weightings (i.e., inverse weightings according to the variance) for each pre to post comparison. These are presented as a forest plot in Figure 2, along with the overall effect size, which is the mean effect size across the studies. For each study the effect size (the symbol size is proportional to study size and variance) with 95% confidence intervals is presented. All studies demonstrated positive effects with Cohen's *d* from 0.5 to 5.2 with an overall effect size of 1.89 (95% CI 1.20-2.58, p<.001).

Insert Table 2 and Figure 2 around here.

As can be seen in Figure 2, when examining the pharmacological treatments, the greatest positive effect was found for the selective serotonin reuptake inhibitor (SSRI) sertraline (Fann, Uomoto et al. 2001). Two similar sized trials of sertraline (Lee, Kim et al. 2005; Ashman, Cantor et al. 2009) also produced much smaller but positive effects. The reason for the varied effects sizes is unclear as all three studies had similar inclusion criteria for depression, used the HAM-D as their pre and post measure, and two of the three (one showing a large effect and the other showing a small effect) had dosage up to 200mg/week (Ashman, Cantor et al. 2009) while the third had a maximum dose of 100 mg/week (Lee, Kim et al. 2005). Furthermore, weeks of treatment provided in the study with the high positive effect (7 weeks) was midway between that of the remaining studies (4 and 10 weeks). Methylphenidate (Lee, Kim et al. 2005) was the only other pharmacological treatment to have an effect size greater than the pooled estimate. Citalopram (Rapoport, Chan et al. 2008; Lanctot, Rapoport et al. 2010), milnacipran (Kanetani, Kimura et al. 2003) and fluoxetine (Horsfield 2002) produced effect sizes close to the pooled estimate. Both studies examining amitriptyline (Saran 1985; Dinan 1992) produced effects lower than the pooled estimate. Within the non-pharmacological interventions, only intermittent burst-firing weak

magnetic field stimulation (Baker-Price and Persinger 2003) produced effects greater than the pooled estimate, although the confidence intervals were large. All other interventions produced effects sizes below the pooled estimate.

The studies were highly heterogeneous (I^2 = 71.1%; Tau squared = 1.20; $p < .001$), and when additional analyses were conducted, the pooled effect sizes for the pharmacological studies were found to be higher (d = 2.25, n = 10) than for the non-pharmacological studies (d = 0.97, n = 5). Another notable difference across the studies related to length of treatment, however a plot of effect size versus weeks of treatment revealed no significant relationship (slope = 0.09, $p > .05$).

Figure 3 presents a funnel plot of the intervention effect estimates from individual studies against a measure of each study's precision. It is typical when using funnel plots that the effect estimates from small studies scatter more widely at the bottom of a funnel plot, with the spread narrowing among larger studies. This expected distribution was not revealed in Figure 3, possibly as a reflection of the heterogeneity of the study interventions. Inspection of the funnel plot suggest that the study of sertraline, with the largest effect size (Fann, Uomoto et al. 2001) is an outlier as the other larger studies are more closely clustered together.

Insert Figure 3 around here

Alternatively, the plot may indicate bias, with larger studies (those with precision > 0.6) showing greater variability in effect than would be expected. Smaller and unpublished studies without statistically significant effects were included (identified through inclusion in of the Digital Dissertations database in the search), so there are no gaps at the bottom of the funnel plot, suggesting that the effect calculated in a meta-analysis will not overestimate the intervention effect (Egger, Smith et al. 1997; Villar, Piaggio et al. 1997).

Controlled Comparisons

Analyses of controlled studies were based on standardised means differences in the final outcome score between the control and active treatment groups (Hedges' *g*). Table 3 presents the treatment effect, standard error, confidence intervals, and weightings, for each treatment - control comparison. These studies are also summarised with the overall effect size and 95% confidence intervals in a Forest plot in Figure 4. The effect sizes ranged from –1.19 to 2.86 with an overall effect size of 0.46 (95% CI -0.44–1.36, p <.001). As can be seen in Figure 4 the overall effect across studies was in favour of the control group, with only 3 treatment-control comparisons producing effect sizes suggesting a positive effect of treatment. Consistent with pre-post comparisons, the findings suggest that amitriptyline is the least effective of the treatments trialled (Saran 1985; Dinan 1992), with mixed results for sertraline (Lee, Kim et al. 2005; Ashman, Cantor et al. 2009). The largest positive effect was found for methylphenidate (Lee, Kim et al. 2005), followed by sertraline (Lee, Kim et al. 2005) and group format CBT (Leonard 2002). Of these only methylphenidate had confidence intervals which did not overlap with zero or the pooled effect.

Insert Table 3 and Figure 4 around here

As suggested by the lack of overlap between the confidence intervals, the studies were highly heterogeneous (I^2 = 86.7%; Tau squared = 1.255; p < .001). Given the relatively small number of studies included in the meta-analysis it was difficult to investigate this further, however there was no significant relationship between treatment effect and length of treatment (slope =.16).

Figure 5 presents a funnel plot of the intervention effect estimates from individual studies against a measure of each study's precision. In Figure 5, the effect estimates from small studies scatter more widely at the bottom of the funnel plot, with the spread narrowing among larger studies suggesting there is not a bias in the studies (Egger, Smith et al. 1997).

Insert Figure 5 around here

DISCUSSION

These analyses were undertaken in an attempt to obtain a clearer picture of the most efficacious treatment for depression following mild TBI. Studies using pre-post designs and controlled trials evaluating both pharmacological and non-pharmacological interventions were incorporated to increase the number of available studies and allow direct comparisons across different treatment types. The overall effect size for the pre-post analysis indicated that depression symptoms decreased following treatment. This suggests that there may be effective treatments for depression post- mild TBI, with pharmacological treatments showing greater efficacy than other treatment approaches. In contrast, the overall effect size for the controlled trials (0.46) suggests that active treatment is no more beneficial than placebo. The only treatment showing an effect greater than zero was methylphenidate (Lee, Kim et al. 2005), whilst treatment with amitriptyline was less effective that placebo (Saran 1985; Dinan 1992). Other studies have indicated that methylphenidate was effective in improving attention post-TBI particularly processing speed and sustained attention (Chew and Zafonte 2009) which may mediate the improvement in depression symptoms, however its widespread use following TBI tends to be limited due to its potential to lower seizure thresholds.

The effectiveness of sertraline differed across the studies included in this meta-analysis. One study with a pre-post design (Fann, Uomoto et al. 2001) found a large positive effect, however the effects were less favourable in the controlled trials with one study suggesting that sertraline was less effective than placebo (Ashman, Cantor et al. 2009) and the other showed the effect to be no greater than zero (Lee, Kim et al. 2005) The most obvious difference between these studies is that Fann et al., (2001) used a pre-post design and only evaluated the effect of the placebo treatment over 1 week rather than a period equivalent to active treatment. Furthermore, there were differences in time since injury across the three

studies from approximately 1 month post- injury (Lee, Kim et al. 2005), 3-24 months post injury (Fann, Uomoto et al. 2001) and 17 years (on average) post-injury (Ashman, Cantor et al. 2009). In both controlled trials, however, the placebo group also showed a significant improvement over the treatment period, suggesting that the other factors (e.g., contact with clinic staff) rather than the active treatment may be responsible for the improvement in symptoms.

In contrast to the findings of the current study, a meta-analysis examining the efficacy of antidepressant in treating depression in neurological disorders (including TBI, stroke, Parkinson's), found that after 6-8 weeks treatment the odds of remission were twice that of a control group, however the authors acknowledge that there were too few studies to investigate the neurological disorders separately (Price, Rayner et al. 2011). This suggests that depression following mild TBI may require a somewhat different treatment approach.

The non-pharmacological treatments included in the meta-analysis appeared to show limited efficacy in treating depression post-TBI, this is somewhat surprising as two earlier studies found CBT improved emotional functioning post-TBI (Tiersky, Anselmi et al. 2005; Bradbury, Christensen et al. 2008). However, unlike the study incorporated into the meta-analysis, in both of these studies, the CBT was modified depending on the participants cognitive functioning and a diagnosis of depression was not required for inclusion in the study.

Overall the findings from the current meta-analysis suggest there are limited effective treatments for depression after mild TBI. However, the paucity of studies examining the efficacy of depression treatment post mild TBI has undoubtedly affected the quality and robustness of the current meta-analysis. In addition to the lack of high quality trials, the studies included in the meta-analysis also showed a high degree of heterogeneity, which is largely unsurprising given the differences in inclusion criteria, depression diagnostic criteria,

time since injury, length of treatment and different outcome measures. Future studies examining treatments of depression in this population are encouraged to state clearly what criteria are used in defining mild TBI, and to use the HAM-D as one of their outcome measures in order to allow comparison to the existing literature. Though difficult to establish, it is suggested that some standardization of pre- to post- measurement interval established. The most common interval found in this review was 6 weeks, though this ranged up to 3 months. As can be seen in Table 1, some authors conducted outcomes measurement at regular intervals. Thus, it is suggested that authors consider inclusion of an assessment at 6-weeks, even if this is in addition to other measurement time frames. In searching the literature it was not surprising, given the small samples, that many authors combined TBI severity groupings. While small sample size may require combining these groups to determine treatment effects it is suggested that studies which include individuals with both mild and moderate TBI present their data (means and standard deviations) separately for these groups in order that comparisons to the literature can be made.

The strengths of the current study are that it is the first meta-analysis to our knowledge that focuses on treatment of depression after mild TBI. In addition, it highlights the importance of controlled trials, as focusing solely on the studies using a pre-post design would suggest that treatments of depression post mild TBI are effective. Addressing depression post-TBI is important as there is an accumulation of evidence which suggests it is linked to poorer outcomes across a range of areas, including cognitive, psychosocial and functional outcomes (Jorge, Robinson et al. 2004; Alderfer, Arciniegas et al. 2005; Rapoport, Kiss et al. 2006). Thus, there is a clear need for large randomised controlled trials of treatment for depression after mild TBI. Overall, the findings from the current meta-analysis support the conclusions of previous reviews, that is, there is insufficient evidence to

recommend a particular type of treatment for depression after mild TBI (Warden, Gordon et al. 2006; Chew and Zafonte 2009; Fann, Hart et al. 2009).

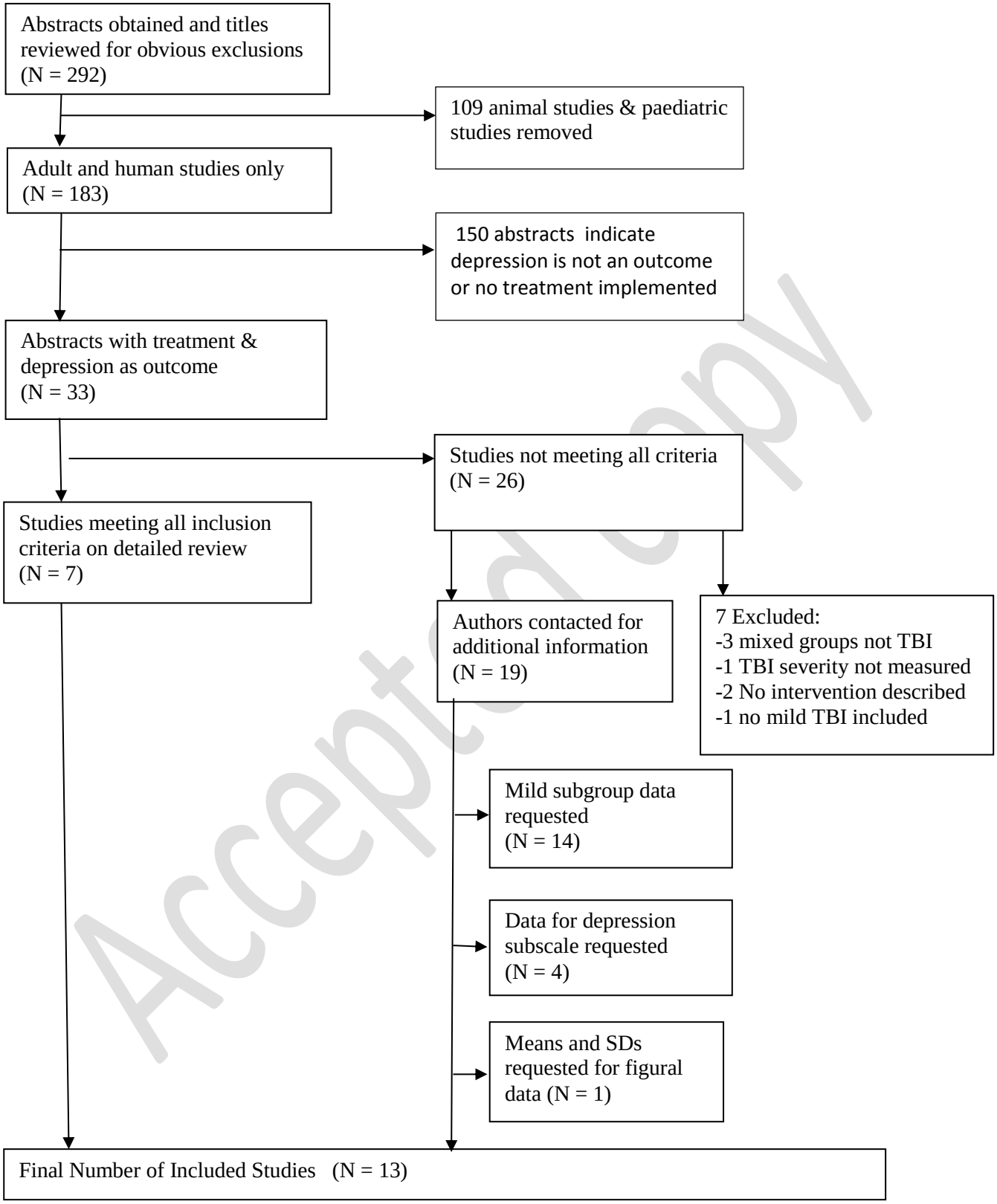

Figure 1. Overview of study review and selection.

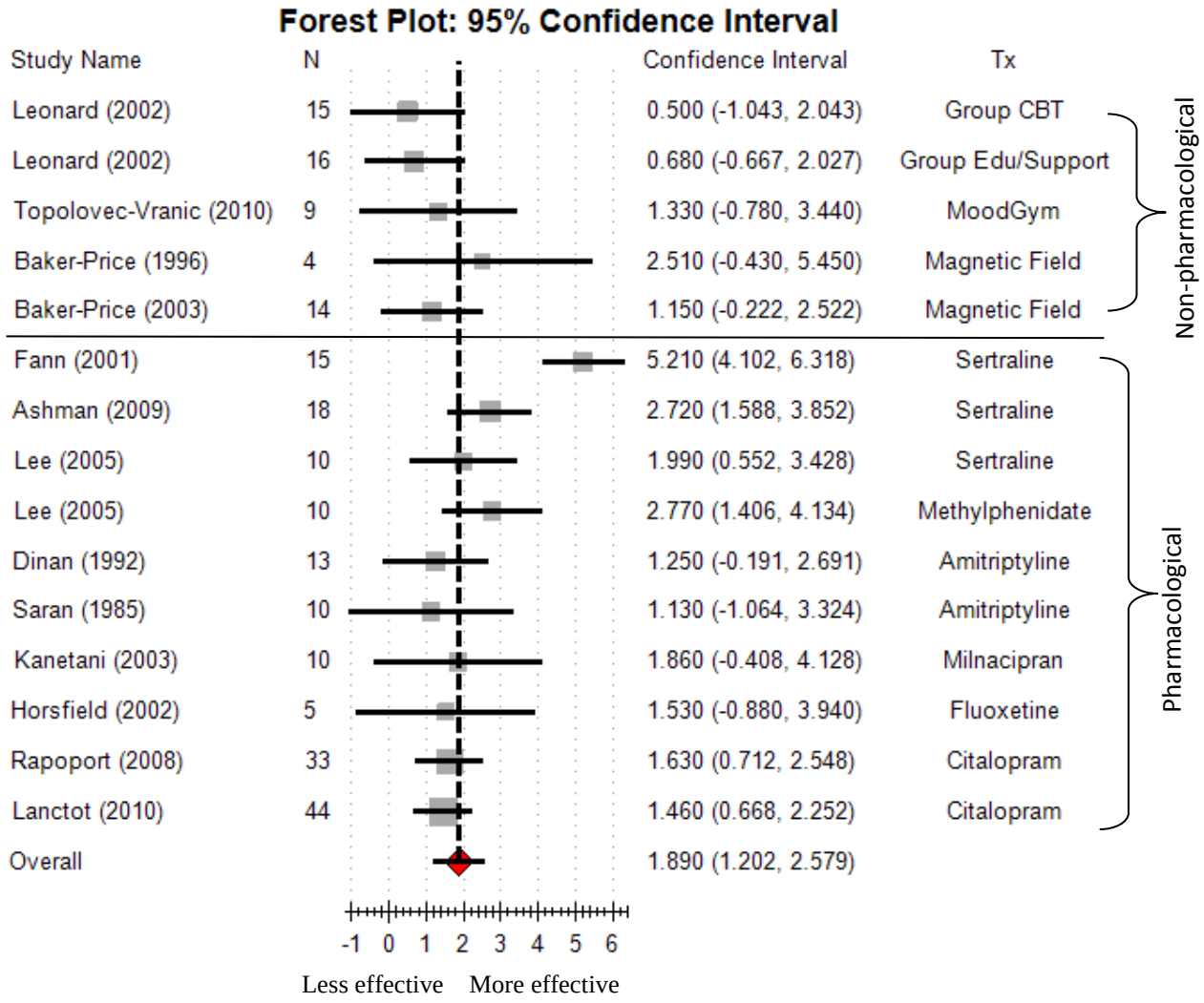

Figure 2. Forest plot showing effects for pre to post treatment comparisons for each pharmacological and non-pharmacological treatment examined across the studies (N=226).

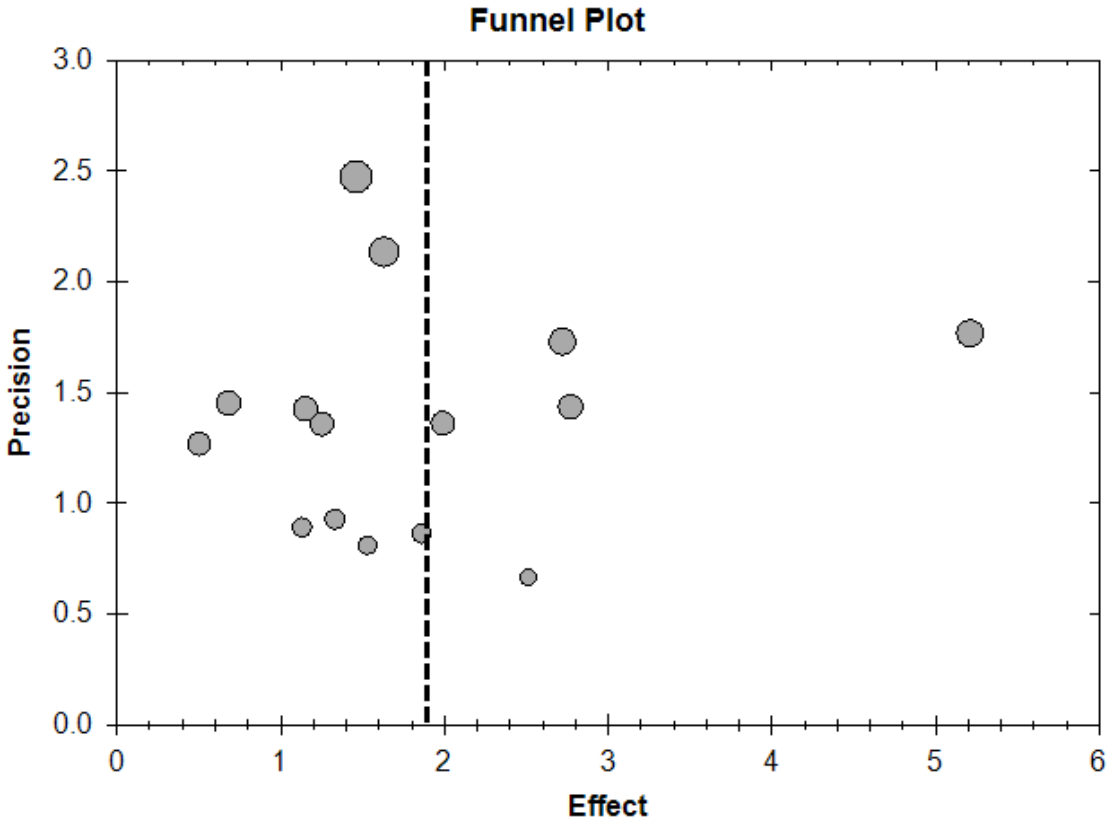

Figure 3. Funnel plot for studies included in pre- post- comparison analysis.

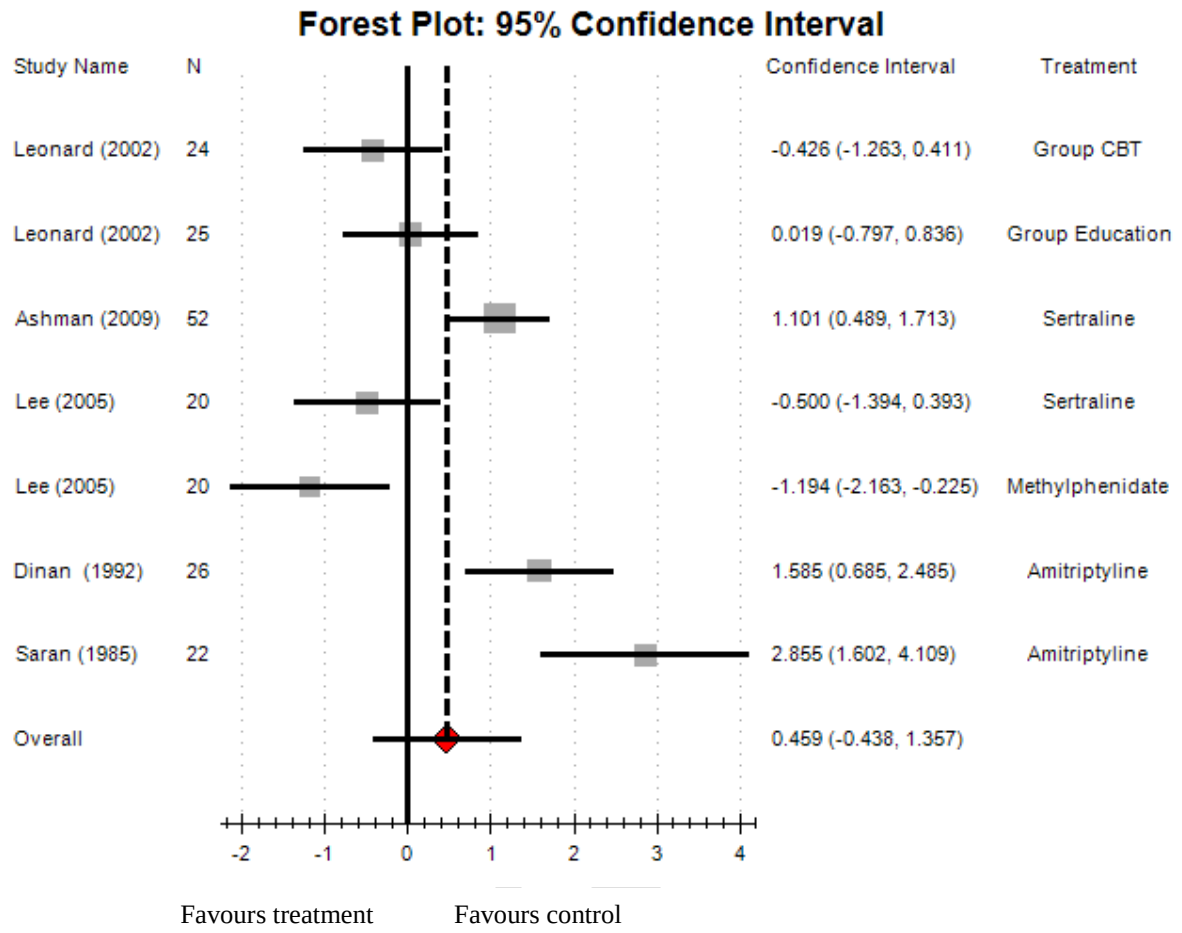

Figure 4. Forest plot showing effects (Hedges' *g*) for controlled comparisons for each pharmacological and non-pharmacological treatment examined across the studies (N=189).

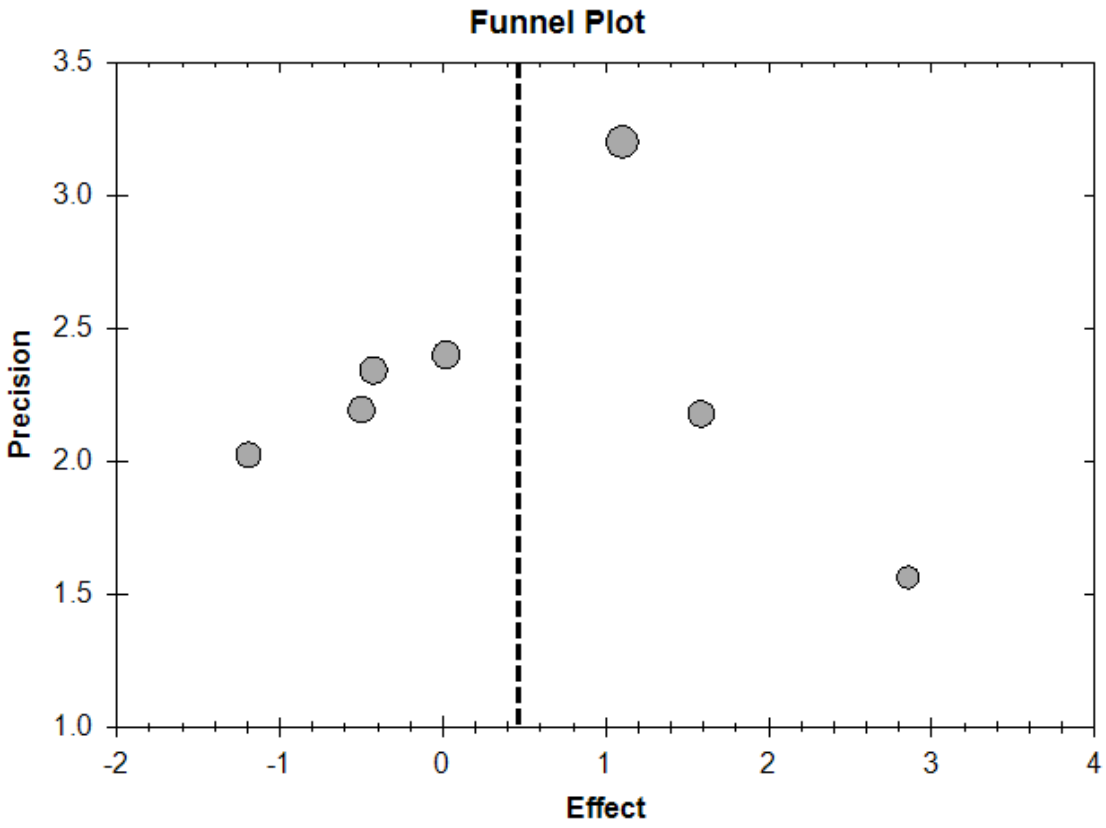

Figure 5. Funnel plot for studies included in controlled comparison analysis.

Table 1 Characteristics of the studies included in the meta-analysis.

Reference	*Depression Criteria*	*Mild TBI Number*	*Timing of Assessment*	*Outcome*	*Design and Intervention*	*Mean (SD) Pre and Post Treatment by Group*	
Treatment Studies with Control Groups							
Leonard, 2002	No depression inclusion criteria	N = 40 mild TBI (15 GCBT, 16 GEST, 9 Wait list control)	**Pre** & post ; **3 month** follow-up	**BDI-II**	Pre-post randomised 3 arm study: Wait-list controls, 5-session Group Cognitive-Behaviour therapy, 5-session Group Education and Support.	GCBT GEST Wait	pre = 16.7 (10.45) post = 13.4 (8.17) pre = 20.5 (7.07) post = 16.9 (8.02) pre = 18.5 (5.83) post = 16.8 (6.45)
Ashman et al., 2009	Major depression diagnosis and HAM-D≥ 18	N = 18 mild TBI (N = 52 total)	**Pre** and **post** (pre + 10 weeks)	**HAM-D** BDI	Pre post study Sertraline 25mg initial dose increasing to therapeutic level (max 200mg) or placebo	Sertraline Placebo	pre = 32.5 (1.73) post = 21.0 (10.23) pre = 27.1 (7.60) post = 12.1 (6.49)
Lee et al., 2005	DSM-IV criteria Major Depressive episode	N = 30 mild TBI (10 each Methylphenidate, Sertraline & placebo)	**Pre** & **post** (pre + 4 weeks).	**HAM-D** BDI	Double-blind pre- post parallel groups. Methylphenidate 5mg/day increased until 20 mg/day. Sertraline 25mg/day increased until 100mg/day	Methylphenidate Sertraline Placebo	pre = 25.2 (4.1) post = 15.7 (5.6) pre = 27.6 (6.2) post = 20.0 (4.6) pre = 25.7 (4.7) post = 22.3 (4.2)
Saran, 1985	DSM-III Major Depression. Feighner (1972) criteria	N = 10 mild TBI N = 12 controls	**Pre** & **post** (pre + 4 weeks)	**HAM-D**	Pre post study. Amytriptyline 100mg/day which could be raised 25 mg/day every 2-3 days to maximum 300mg/day.	mTBI Control	pre = 34.0 post = 24.0 pre = 34.0 post = 10.0
Dinan, 1992	DSM-III Major depression HAM-D > 17	N = 13 mild TBI N = 13 matched functionally depressed controls.	**Pre** and **post** (pre + 1, 3, 4, and 6 weeks).	LSSAD **HAM-D**	Single blind matched control study. Amitriptyline 100 mg/daily, inc by 50mg/week to max 250 mg/day.	mTBI Control	pre = 25.0 (7.2) post = 18.8 (6.8) pre = 24.0 (~7.5) post = 10.0 (3.0)

Pre- Post- Comparisons without Control Groups						
Topolovec-Vranic et al., 2010	Score ≥12 on the PHQ-9	N = 9 mild. (N = 21 total)	**Pre** & **post** (pre + 6 weeks) & 12-month follow-up	**CES-D** PHQ-9	Pre-post study. MoodGYM- a free interactive internet based program. Weekly for 6 weeks	pre = 31.78 (11.42) post = 22.0 (9.43)
Baker-Price & Persinger, 1996	Persistent or frequent intermittent depression. Non-responder to medications.	N = 4 [b]	**Pre** and post (pre + 1, 2, 3, 4, and **5 weeks**).	**BDI** SCL-90R WPSC	Pre-post study Burst-fire magnetic field every 3 sec for 30 minutes weekly in temporoparietal areas for 5 weeks.	Weekly BDI scores: 1 = 33 (9); 2 = 27 (7); 3 = 20 (10); 4 = 21 (8); 5 = 17 (9)
Baker-Price, 2003	Chronic depression post-TBI not responding to antidepressants	N = 14 [b] mild-moderate but meet criteria for mild.	**Pre & post** (pre + 6 weeks) and 6-week follow-up	**BDI**	Pre-post design with 2 areas of brain treated. Burst-fire magnetic field once every 3 sec for 30 minutes once per week for in temporal or frontal areas for 6 weeks	pre = 19.7 (8.6) post = 14.1 (5.2) follow-up = 15.1 (7.6) (Area of treatment not related to size of effect)
Fann et al., 2001	DSM-III-R Major Depression HAM-D score >17	N = 15 mild TBI	**Baseline,** and at 1, 2, 4, 6, and **8 weeks** after Sertraline introduced.	**HAM-D**	Single-blind non-randomised. "Pre" measure taken then 1 week Placebo, then Sertraline 25mg (1 week); 25-50mg/day (week 2); 25-100 mg/day (week 3). 25-200 mg/day (weeks 4-8) dependent on tolerance/response.	pre = 25.0 (4.36) (pre placebo) post = 7.2 (5.30)
Kanetani et al., 2003	DSM-IV Major depressive episode or minor depression	N = 7 (GCS > 13) at time of injury. (10 in total)	**Pre**, 2, 4, and **6 weeks**	**HAM-D**	Open pre-post study. Milnacipran 30 mg/day twice daily, dose adjusted weekly to max dose range 30-150 mg.	pre = 31.83 (13.82) post= 14.17 (12.99)
Horsfield, 2002	Either "no or moderate depression".	N = 5 males with head injury (some with multiple, all	**Pre** & **post** (pre +8 months)	**HAM-D**	Open label pre-post study. Fluoxetine 20-60 mg/day for 8 months	pre = 18. 0 (7.07) post = 9.8 (8.07)

	Criteria not specified.	LOC < 2 hrs)				
Rapoport et al., 2008	Major Depression (SCID-IV)	N = 33 mild TBI	**Pre** and **Post** (**pre + 6** or 10 weeks)	**HAM-D**	Citalopram 20 mg/day initial dose to max 50 mg/day; 6 or 10 weeks	pre = 24.27 (6.15) post = 15.93 (8.35) follow-up = 12.63 (7.52)
Lanctot et al., 2010	DSM-IV (SCID)	N=44 mild TBI (N=90 total)	**Pre** and **Post** (pre+ 6 weeks)	**HAM-D**	Pre-post study Citalopram 20 mg/day; 6 weeks	pre = 24.05 (5.96) post = 16.64 (8.36)

BDI= Beck Depression Inventory; CES-D= Center for epidemiological studies-Depression Scale; HAM-D = Hamilton Depression Rating Scale; LSSAD = Leeds Scale for the Self-assessment of Anxiety and Depression; TBI = Traumatic brain injury; PHQ-9= Patient health questionnaire-9 item depression module; SCL-90R= Symptom Checklist 90-revised; WPSC=Wahler Physical Symptoms Checklist

[b] While this group is described as mild-moderate by the authors, their inclusion criteria (unconsciousness <20 minutes, memory loss < 24 hours) would fall within accepted definitions for mild TBI. **Bold** text indicates time frame of data used in analysis and outcome measure used for analyses.

Table 2. Treatment effect (Cohen's *d*), standard error (SE), confidence intervals and weightings for each pre- to post- comparison.

Study Name	*Treatment Effect*	*SE*	*95% Confidence Interval*		*Weight*	*Treatment*
			Lower	*Upper*		
Leonard (2002)	0.50	0.79	-1.04	2.04	0.051	Group CBT
Leonard (2002)	0.68	0.69	-0.67	2.03	0.066	Group Education
Topolovec-Vranic (2010)	1.33	1.08	-0.78	3.44	0.027	MoodGym
Baker-Price (1996)	2.51	1.50	-0.43	5.45	0.014	Magnetic Field
Baker-Price (2003)	1.15	0.70	-0.22	2.52	0.064	Magnetic Field
Fann (2001)	5.21	0.57	4.10	6.32	0.098	Sertraline
Ashman (2009)	2.72	0.58	1.59	3.85	0.094	Sertraline
Lee (2005)	1.99	0.73	0.55	3.43	0.058	Sertraline
Lee (2005)	2.77	0.70	1.41	4.13	0.065	Methylphenidate
Dinan (1992)	1.25	0.74	-0.19	2.69	0.058	Amitriptyline
Saran (1985)	1.13	1.12	-1.06	3.32	0.025	Amitriptyline
Kanetani (2003)	1.86	1.16	-0.41	4.13	0.023	Milnacipran
Horsfield (2002)	1.53	1.23	-0.88	3.94	0.021	Fluoxetine
Rapoport (2008)	1.63	0.47	0.71	2.55	0.143	Citalopram
Lanctot (2010)	1.46	0.40	0.67	2.25	0.192	Citalopram

Table 3. Treatment effect (Hedges' *g*), standard error, confidence intervals, and weightings, for each treatment - control comparison.

Study	*Treatment Effect*	*SE*	*95% Confidence Interval*		*Weight*	*Treatment*
			Lower	*Upper*		
Leonard (2002)	-0.43	0.43	-1.26	0.41	0.15	Group CBT
Leonard (2002)	0.02	0.42	-0.80	0.84	0.15	Group Education
Ashman (2009)	1.10	0.31	0.49	1.71	0.27	Sertraline
Lee (2005)	-0.50	0.46	-1.39	0.39	0.13	Sertraline
Lee (2005)	-1.19	0.49	-2.16	-0.23	0.11	Methylphenidate
Dinan (1992)	1.59	0.46	0.69	2.49	0.13	Amitriptyline
Saran (1985)	2.86	0.64	1.60	4.11	0.07	Amitriptyline

CBT= cognitive behaviour therapy

References

Alderfer, B. S., D. B. Arciniegas, et al. (2005). "Treatment of depression following traumatic brain injury." Journal of Head Trauma Rehabilitation **20**(6): 544-562.

Ashman, T. A., J. B. Cantor, et al. (2009). "A Randomized Controlled Trial of Sertraline for the Treatment of Depression in Persons With Traumatic Brain Injury." Archives of Physical Medicine and Rehabilitation **90**(5): 733-740.

Ashman, T. A., Cantor, J. B., Gordon, W. A., Spielman, L., Flannagan, S., Ginsberg, A., Engmann, C., Egan, M., Ambrose, F., Greenwald, B. (2009). "A randomized controlled trial of sertraline for the treatment of depression in persons with traumatic braininjury." Archives of Physical and Medical Rehabilitation **90**: 733-740.

Baker-Price, L., & Persinger, M. (2003). "Intermittent burst-firing weak (1 micro tesla) magnetic fields reduce psychometric depression in patients who sustain closed head injuries: A replication and electroencephalographic validation." Perceptual and Motor Skills **96**: 965-974.

Baker-Price, L. A. and M. A. Persinger (1996). "Weak, but complex pulsed magnetic fields may reduce depression following traumatic brain injury." Perceptual and Motor Skills **85**(2): 491-498.

Baker-Price, L. A. and M. A. Persinger (2003). "Intermittent burst-firing weak (1 micro tesla) magnetic fields reduce psychometric depression in patients who sustain closed head injuries: A replication and electroencephalographic validation." Perceptual and Motor Skills **96**: 965-974.

Borenstein, M., L. V. Hedges, et al. (2009). Effect sizes based on means. Introduction to Meta-analysis. New Jersey, USA, Wiley**:** 53-65.

Borenstein, M., L. V. Hedges, et al. (2009). Identifying and quantifying heterogeneity. Introduction to Meta-analysis. New Jersey, USA, Wiley**:** 139-159.

Borenstein, M., L. V. Hedges, et al. (2009). Random-Effects Model. Introduction to Meta-analysis. New Jersey, USA, Wiley**:** 69-86.

Bradbury, C. L., B. K. Christensen, et al. (2008). "The Efficacy of Cognitive Behavior Therapy in the Treatment of Emotional Distress After Acquired Brain Injury." Archives of Physical Medicine and Rehabilitation **89**(12 SUPPL.): S61-S68.

Busch, C. R., Alpern, H. P. (1998). "Depression after mild traumatic brain injury: A review of current research." Neuropsychology Reviews **8**: 95-108.

Carroll, L. J., Cassidy, J. D., Peloso, P. M., Bog, J., van Holst, H., Holm, L., Paniak, C., Pepin, M. (2004). "Prognosis for mild traumatic brain injury: Results of the WHO collaborating centre task force on mild traumatic brain injury." Journal of Rehabilitation Medicine **Suppl 43**: 84-105.

Chew, E. and R. D. Zafonte (2009). "Pharmacological management of neurobehavioural disorders following traumatic brain injury - A state-of-the-art review." Journal of Rehabilitation Research and Development **46**(6): 851-878.

Comper, P., S. M. Bisschop, et al. (2005). "A systematic review of treatments for mild traumatic brain injury." Brain Injury **19**(11): 863-880.

Corrigan, J. D., A. W. Selassie, et al. (2010). "The epidemiology of traumatic brain injury." The Journal of Head Trauma Rehabilitation **25**(2): 72-80.

Dinan, T. G., Mobayed, M. (1992). "Treatment resistance of depression after head injury: a preliminary study of amitriptyline response." Acta Psychiatrica Scandinavica **85**: 292-294.

Egger, M., G. D. Smith, et al. (1997). "Bias in meta-analysis detected by a simple, graphical test." British Medical Journal **315**(7109): 629-634.

Fann, J. R., T. Hart, et al. (2009). "Treatment for depression after traumatic brain injury: a systematic review." Journal of Neurotrauma **26**(12): 2383-2402.

Fann, J. R., J. M. Uomoto, et al. (2000). "Sertraline in the treatment of major depression following mild traumatic brain injury." Journal of Neuropsychiatry and Clinical Neurosciences **12**(2): 226-232.

Fann, J. R., J. M. Uomoto, et al. (2001). "Cognitive improvement with treatment of depression following mild traumatic brain injury." Psychosomatics **42**(1): 48-54.

Feighner, J. P., Robins, E., Guze, S.B. (1972). "Diagnostic criteria for use in psychiatric research." Archives of General Psychiatry **26**: 57-63.

Follman, D., P. Elliot, et al. (1992). "Variance imputation for overviews of clinical trials with continuous response." Journal of Clinical Epidemiology **45**(7): 769-773.

Grant, I., Alves, W. (1987). Psychiatric and psychosocial disturbances in head injury. Neurobehavioural recovery from head injury. H. S. Levin, Grafman, J., Eisenberg, HM. New York, Oxford University Press.

Gualtien, C. T. (1999). The pharmacological treatment of mild brain injury. The evaluation and treatment of mild traumatic brain injury. N. R. V. R. J. Roberts. New York, Lawrence Erlbaum Associates, Inc.**:** 411-420.

Hedges, L. V. (1981). "Distribution theory for Glass's estimator of effect size and related estimators." Journal of Educational Statistics **6**: 107-128.

Hibbard, M. R., S. Uysal, et al. (1998). "Axis I psychopathology in individuals with traumatic brain injury." Journal of Head Trauma Rehabilitation **13**(4): 24-39.

Higgins, J. P. T., J. J. Deeks, et al. (2011). Chapter 16: Special topics in statistics. Cochrane Handbook for Systematic Reviews of Interventions J. P. T. Higgins and S. Green, The Cochrane Collboration. **5.1.0**.

Higgins, J. P. T., S. G. Thompson, et al. (2003). "Measuring inconsistency in meta-analyses." British Medical Journal **327**: 557-560.

Hoge, C. W., McGurk, D., Thomas, J. L., Cox, A. L., Engel, C. C., Castro, C. A. (2008). "Mild traumatic brain injury in U.S. soldiers returning from Iraq." New England Journal of Medicine **358**: 453-463.

Horsfield, S. A., Rosse, R. B., Tomasino, V., Schwartz, B. L., Mastropaolo, J., Deutsch, S. I. (2002). "Fluoxetine's effects on cognitive performance in patients with traimatic brain injury." International Journal of Psychiatry in Medicine **32**(4): 337-344.

Jorge, R., R. G. Robinson, et al. (2004). "Major depression following traumatic brain injury." Archives of General Psychiatry **61**(1): 42-50.

Kanetani, K., M. Kimura, et al. (2003). "Therapeutic effects of milnacipran (serotonin noradrenalin reuptake inhibitor) on depression following mild and moderate traumatic brain injury." Journal of Nippon Medical School **70**(4): 313-320.

Lanctot, K. L., M. J. Rapoport, et al. (2010). "Genetic predictors of response to treatment with citalopram in depression secondary to traumatic brain injury." Brain Injury **24**(7-8): 959-969.

Lanctot, K. L., Rapoport, M. J., Chan, F., Rajaram, R. D., Strauss, J., Sicard, T., McCullagh, S., Feinstein, A., Kiss, A., Kennedy, J. L., Bassett, A. S., Herrmann, N. (2010). "Genetic predictors of response to treatment with citalopram in depression secondary to traumatic brain injury." Brain Injury **24**(7-8): 959-969.

Langlois, J. A., S. R. Keglar, et al. (2003). "Traumatic brain injury-related hospital discharges. Results from a 14-state surveillance system, 1997." Mrobidity and Mortality Weekly Report **52**: 1-20.

Langlois, J. A., W. Rutland-Brown, et al. (2006). "The Epidemiology and Impact of Traumatic Brain Injury: A Brief Overview." The Journal of Head Trauma Rehabilitation **21**(5): 375-378.

Lee, H., S. W. Kim, et al. (2005). "Comparing effects of methylphenidate, sertraline and placebo on neuropsychiatric sequelae in patients with traumatic brain injury." Human Psychopharmacology **20**(2): 97-104.

Leonard, K. L. (2002). Cognitive-behavioural intervention in persistent postconcussion syndrome: A controlled treatment outcome study. PhD, The University of Texas.

Ownsworth, T. L., Oei, T. P. (1998). "Depression after traumatic brain injury:Conceptualisation and treatment considerations." Brain Injury **12**: 735-751.

Price, A., L. Rayner, et al. (2011). "Antidepressants for the treatment of depression in neurological disorders: A systematic review and meta-analysis of randomised controlled trials." Journal of Neurology, Neurosurgery and Psychiatry.

Rapoport, M. J., F. Chan, et al. (2008). "An open-label study of citalopram for major depression following traumatic brain injury." Journal of Psychopharmacology **22**(8): 860-864.

Rapoport, M. J., Chan, F., Lanctot, K., Herrmann, N., McCullagh, S., Feinstein, A. (2008). "An open-label study of citalopram for major edpression following traumatic brain injury." Journal of Psychopharmacology **22**(8): 860-864.

Rapoport, M. J., A. Kiss, et al. (2006). "The impact of major depression on outcome following mild-to-moderate traumatic brain injury in older adults." Journal of Affective Disorders **92**(2-3): 273-276.

Rapoport, M. J., S. McCullagh, et al. (2003). "The clinical significance of major depression following mild traumatic brain injury." Psychosomatics **44**(1): 31-37.

Rapoport, M. J., McCullagh, S., Shammi, P., Feinstein, A. (2005). "Cognitive impairment associated with major depression following mild and moderate traumatic brain injury." Journal of Neuropsychiatry & Clinical Neurosciences **17**(1): 61-65.

Robinson, R. G. and R. Jorge (2005). Mood Disorders. Textbook of Traumatic Brain Injury. J. M. Silver, T. W. McAllister and S. C. Yudofsky. Washington, DC, American Psychiatric Publishing Inc**:** 201-212.

Rohling, M. L., L. M. Binder, et al. (2011). "A meta-analysis of neuropsychological outcome after mild traumatic brain injury: Re-analyses and reconsiderations of Binder et al. (1997), Frencham et al. (2005), and Pertab et al. (2009)." The Clinical Neuropsychologist **25**(4): 608-623.

Saran, A. S. (1985). "Depression after minor closed head injury: Role of dexamethasone suppression test and antidepressants." Journal of Clinical Psychiatry **46**(8): 335-338.

Tiersky, L. A., V. Anselmi, et al. (2005). "A trial of neuropsychologic rehabilitation in mild-spectrum traumatic brain injury." Archives of Physical and Medical Rehabilitation **86**(8): 1565-1574.

Topolovec-Vranic, J., N. Cullen, et al. (2010). "Evaluation of an online cognitive behavioural therapy program by patients with traumatic brain injury and depression." Brain Injury **24**(5): 762-772.

Topolovec-Vranic, J., Cullen, N., Michalak, A., Ouchterlony, D., Bhalerao, S., Masanic, C., Cusimano, M. (2010). "Evaluation of an online cognitive behavioural therapy program by patients with traumatic brain injury and depression." Brain Injury **24**(5): 762-772.

Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (1993). "Definition of mild traumatic brain injury." Journal of Head Trauma Rehabilitation **8**(3): 86-87.

Villar, J., G. Piaggio, et al. (1997). "Factors affecting the comparability of meta-analyses and largest trials results in perinatology." Journal of Clinical Epidemiology **50**(9): 997-1002.

Wallace, B. C., Schmid, Christopher H., Lau, Joseph, Trikalinos, Thomas A. (2009). "Meta-analyst: software for meta-analysis of binary, continuous and diagnostic data." BMC Medical Research Methodology **9**(1): 80+.

Warden, D. L., B. Gordon, et al. (2006). "Guidelines for the pharmacologic treatment of neurobehavioural sequelae of traumatic brain injury." Journal of Neurotrauma **23**(10): 1468-1501.

Williams, W. H. and J. J. Evans (2003). "Brain injury and emotion: An overview to a special issue on biopsychosocial approaches in neurorehabilitation." Neuropsychological Rehabilitation **13**(1-2): 1-11.