Treatment for depression after traumatic brain injury: a systematic review
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CRD summary
This review concluded that there was a paucity of randomised controlled trials for depression following traumatic brain injury. Serotonergic antidepressants and cognitive behavioural interventions appeared to have the best preliminary evidence for treating depression following traumatic brain injury. Although there were some methodological and reporting weaknesses, these conclusions appear to be appropriate.

Authors' objectives
To investigate interventions for depression following traumatic brain injury.

Searching
PubMed, CINAHL, PsycINFO, ProQuest and Web of Science databases and Google Scholar were searched for peer-reviewed studies published in English since 1980. Search terms were reported. A flow chart suggested some form of external review and recommendations for other studies not identified in the searches.

Study selection
Studies of any design that investigated depression (as a primary outcome) and depressive symptomology (as a secondary outcome) in an adult population that included those with traumatic brain injury were eligible for inclusion. Results from any traumatic brain injury subgroup had to be reported separately. Studies could include any treatment modality (pharmacological, psycho-therapeutic, rehabilitation-based, exercise, electroconvulsive therapy (ECT) or transcranial magnetic stimulation). Studies that did not report quantitative scores on a validated depression diagnostic or severity instrument both pre- and post-intervention were excluded.

Included studies investigated: effects of pharmacological interventions such as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs); other biological interventions (ECT, low-intensity magnetic field exposure, biofeedback and acupuncture); and psychotherapeutic and rehabilitation interventions. Treatment models varied and included cognitive-behavioural therapy (CBT) in groups or individually and sometimes other components (such as cognitive retraining and attention self-control techniques associated with mindfulness meditation) and other interdisciplinary and multidisciplinary techniques. Various outcomes were reported. Severity of depression varied between studies.

Two reviewers selected studies for inclusion. Discrepancies were resolved by consensus.

Assessment of study quality
No formal quality assessment was performed. The included studies were categorised by one reviewer (with consultation with another as needed) according to American Academy of Neurology criteria for classifying therapeutic studies. It appeared that studies were categorised from classes I to IV; no further information was reported, but the tables appeared to show that class I was the highest quality and class IV was lowest. Studies were further classified as: prospectively enrolled depressed patients; depressed patients retrospectively identified at baseline and results reported separately; pre-post scores on depression measure reported, but no selection for depressed patients as a subgroup.

Data extraction
Data were extracted independently by two reviewers. Differences were resolved by consensus.

Methods of synthesis
The studies were presented in a narrative synthesis according to the type of intervention.

Results of the review
Twenty-seven studies were included in the review (826 patients, range one to 145).

Pharmacological interventions (13 studies; 301 patients): One study was evidence class I, one was class II, two were
class III and nine were class IV. Eleven studies prospectively enrolled depressed patients and examined depression "caseness" post-intervention; two investigated pre- and post-intervention depression scores only. Ten were uncontrolled studies.

No significant difference was found in response rates or decrease in Hamilton rating scale for depression scores for sertraline compared with placebo (one study, evidence class I). Methodological limitations did not allow conclusions to be drawn about the efficacy of tricyclic antidepressants (one study; evidence class III).

Two class III and IV studies of patients treated with amitriptyline showed no improvements in patients with depression and minor traumatic brain injury compared to people with primary depression without traumatic brain injury. MAOI phenelzine was not efficacious in one class III study; MAO-A isoenzyme blocker was effective in one class IV study.

Evidence from seven studies of SSRIs suggested that these drugs were efficacious and well-tolerated in some people with traumatic brain injury. One study of dual action SNRI (milnacipran) suggested it may be efficacious.

Other biological interventions (six studies, 40 patients): One study was class II, one was class III and four were class IV. Three prospectively enrolled depressed patients, one identified patients retrospectively and two reported pre/post depression scores only. There were limited data to support the efficacy and tolerability of ECT, low-intensity magnetic field exposure, biofeedback and acupuncture for treating depression after traumatic brain injury; the authors stressed that the results of these studies were highly preliminary.

Psychotherapeutic and rehabilitation interventions (eight studies, 485 patients): One study was class I, two were class II, one was class III and the others were class IV. None of the studies was designed to evaluate treatments for depression specifically. Seven studies reported pre/post scores only; one study did not report this.

Three of four CBT-based studies (one class II, two class IV) reported positive effects of the treatment on mood. Two studies based on mindfulness-meditation: one (class II) reported no significant difference between treatment and controls; the other reported a marginally significant difference pre- to post-treatment (class IV).

Two studies were of intensive multifaceted treatments delivered by a rehabilitation team: one (class I) reported no significant difference on the proportions of patients that met the criteria for depression; the other (class IV) reported significant improvement in Brain Injury Community Rehabilitation Outcome-39 Scales.

Authors' conclusions
There was a paucity of randomised controlled trials for depression following traumatic brain injury. Serotonergic antidepressants and cognitive behavioural interventions appeared to have the best preliminary evidence for treating depression following traumatic brain injury.

CRD commentary
The research question was supported by clear inclusion criteria, which were broad for study design. Limiting searches to published English-language studies meant that language and publication bias were possible. Two reviewers were involved in the review processes, which reduced risks of reviewer error and bias. Study quality did not appear to be systematically assessed, although studies were categorised by design, whether the participants were selected prospectively or retrospectively and whether studies had a pre/post design. The reporting was unclear, although study quality often appeared to be limited or poor. A narrative synthesis appeared appropriate given the heterogeneity between studies; better-quality study designs were highlighted. Many of the included studies had small sample sizes.

Although there were some methodological and reporting weaknesses, the authors' conclusions appear to be appropriate.

Implications of the review for practice and research
Practice: The authors stated that it was advisable to start with low doses of medication with slow titration toward a therapeutic response. Depression measures that had been validated in the traumatic brain injury population should be used. There was evidence for use of sertraline (25 to 150mg/day) for depression after traumatic brain injury. There was limited evidence that citalopram (20 to 50mg) may be effective and well tolerated. SNRIs may be a reasonable option in the traumatic brain injury population with depression. There was evidence of possible reduced efficacy and higher risk
of side-effects that may limit the use of tricyclic antidepressants in this population. Moclobemide may be a viable second-line treatment for cognitively intact patients. ECT appeared viable for treatment-refractory patients, but cognitive side effects needed to be monitored. Magnetic stimulation, biofeedback and acupuncture remained experimental. There was insufficient evidence to support practice recommendations for any of the psychotherapeutic or rehabilitation interventions.

**Research:** The authors stated that large appropriately controlled pharmacological, psychosocial, alternative and multimodal prevention and treatment studies were needed; they made a number of research recommendations regarding the methodology of future research.

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