Title: Prophylaxis pharmacotherapy to prevent the onset of post traumatic brain injury depression: a systematic review

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Fiona J Clay [1,2,3]

- Fiona.clay@unimelb.edu.au; Department of Psychiatry, University of Melbourne, Melbourne, Australia; 03 8344 6862

Amelia J Hicks [4!]

- Amelia.hicks@monash.edu; Monash-Epworth Rehabilitation Research Centre, Ground Floor, 185-187 Hoddle St, Richmond, 3121, Victoria, Australia; 03 9426 8923

Hadar Zaman [5!]

- HZaman4@bradford.ac.uk; Bradford School of Pharmacy & Medical Sciences, Faculty of Life Sciences, University of Bradford, Bradford, BD7 1DP, United Kingdom; +44 (0) 1274 234741

Jennie Ponsford [4]

- jennie.ponsford@monash.edu; Monash-Epworth Rehabilitation Research Centre, Ground Floor, 185-187 Hoddle St, Richmond, 3121, Victoria, Australia; 03 9426 8923

Rachel Batty [1]

- rachel.ann.batty@gmail.com; Professorial Psychiatry Unit, Albert Road Clinic, 31 Albert Road, Department of Psychiatry, University of Melbourne, Melbourne, Australia; 03 8344 6862

Luke A Perry [1]

- lukeaperry@gmail.com; Professorial Psychiatry Unit, Albert Road Clinic, 31 Albert Road, Department of Psychiatry, University of Melbourne, Melbourne, Australia; 03 8344 6862

Malcolm Hopwood [1,3]

- mhopwood@unimelb.edu.au; Professorial Psychiatry Unit, Albert Road Clinic, 31 Albert Road, Department of Psychiatry, University of Melbourne, Melbourne, Australia; 03 8344 6862

Note: ! Amelia Hicks and Hadar Zaman are joint second authors

Affiliations:

1. Department of Psychiatry, University of Melbourne, Melbourne, Australia

2. Department of Forensic Medicine, Monash University, Southbank, Australia

3. Professorial Psychiatry Unit Albert Road Clinic, Department of Psychiatry, University of Melbourne, Melbourne, Australia

4. Monash-Epworth Rehabilitation Research Centre, Monash Institute of Cognitive and Clinical Neurosciences, School of Psychological Sciences, Monash University, Melbourne, Australia

5. Bradford School of Pharmacy & Medical Sciences, Faculty of Life Sciences, University of Bradford, Bradford, United Kingdom

Corresponding Author: Dr Fiona J. Clay, Fiona.clay@unimelb.edu.au

Abstract

Background: Depression is a common psychiatric problem following traumatic brain injury (TBI) with reported prevalence rates of 30-77% in the first year post-TBI. Given the negative influence of post-TBI depression on cognition, interpersonal, social, physical and occupational functioning; early initiation of pharmacotherapy to prevent post-TBI depression has been considered. This systematic review will synthesize the available evidence from published studies on the effectiveness and harms of pharmacotherapy for the secondary prevention of post-TBI depression.

Method: Studies published prior to October 2018 were eligible for inclusion. Six databases were searched, with additional searching of key additional documents. Studies meeting inclusion criteria were evaluated for methodological quality.

Results: Six articles addressing five studies met inclusion criteria. Study designs included three randomized controlled trials (RCT), two retrospective cohorts and one case-control. Prophylactic pharmacotherapy included antidepressants, beta-blockers and statins. In one RCT, the number-needed-to-treat with sertraline to prevent one case of depression post-TBI at 24 weeks was 5.9 (95%CI: 3.1-71.1). In a second RCT affected by significant attrition, sertraline had no effect. Prescribing beta-blockers prior to TBI reduced the depression risk regardless of the specific brain trauma. TBI patients with pre-existing hyperlipidemia not treated with statins had an increased depression risk compared to those without hyperlipidemia.

Conclusion: Overall this systematic review yielded mixed evidence of prophylactic efficacy and insufficient evidence of harm. In the absence of tolerability data, existing data are insufficient to recommend sertraline prophylaxis. Optimal timing and treatment duration with identification of patients most likely to benefit from prophylaxis require further consideration. Dedicated prospective studies assessing the effects of beta-blockers and statins on post-TBI depression are required.

Keywords

Prophylaxis; depression; traumatic brain injury; pharmacotherapy

INTRODUCTION

Depression is one of the most common and disabling psychiatric complications that occurs following traumatic brain injury (TBI) [1,2] with studies reporting between 30% and 77% of individuals with TBI develop depression in the first twelve months post injury depending on the study design, irrespective of severity. [2-4] Rates of depression in persons with TBI are up to 7.9 times higher than rates reported in the general population.[5] Depressive symptoms may include; sadness, irritability; fatigue; sleep disturbances; detachment from social activities, difficulties with concentration and memory difficulties. [6,7]

Development of depressive symptoms post-TBI is associated with adverse outcomes that hamper recovery including increased reporting of post-concussive symptoms [8], poorer cognitive functioning [9], greater physical disability, impaired participation in activities of daily living, poor adherence with treatment plans [10], increased health service utilization, higher healthcare costs as well as poorer psychosocial outcomes. [11-13] Depression can undermine the survivor's capacity for social independence, employment, education and community integration [14,15]. Close relationships are at risk of breaking down and adding to the psychological burden felt by the survivor and their carers.[16] Emotional disturbances along with neurobehavioural difficulties impair quality of life the most for TBI survivors [17,18]. Long term disability is considerable and the risk of suicide is 2.7-4.1 times greater in those with TBI and depression than the general population. [19-20] This highlights the need to address depression post-TBI.

There is substantial heterogeneity associated with TBI and while not all patients with TBI develop depression, studies have shown that some survivors become depressed early, others become depressed in the post-acute stage and others have sub-threshold depressive symptoms that can lead to later depression. [21] Contributory factors to the onset and course of post-TBI depression include the extent of social support and post-acute services, preinjury mental health disorders, injury related changes and posttraumatic adaptive issues. Gender, age and level of education are important in some studies but not in others. [2] Once depression becomes established it likely becomes more difficult to treat and many individuals post-TBI require medications over extended periods for depression. [21,22]

Given the high prevalence of depression post-TBI, consideration of a preventative approach may be an option and indeed a desirable goal for clinicians, patients and carers. Secondary prevention aims to reduce the impact of a disease or injury that has already occurred. In the case of TBI, this is done by treating the TBI and associated symptoms like depression as early as possible to halt or reduce the likelihood of symptoms becoming chronic while at the same time implementing programs to return individuals to optimal health and function to prevent long-term problems.

Currently, the management of depressive symptoms post-TBI involves a multimodal and multidisciplinary approach incorporating social, psychotherapeutic and medical interventions [23,24]. Despite their potential for a lesser tolerability burden in this vulnerable population, unfortunately neither psychotherapeutic nor social interventions have an adequate evidence base to routinely support their use at this time. [25] The aim of pharmacotherapy is to provide targeted treatment for emotional disturbances on an individualized basis while managing the adverse effects of medications. A preventative approach to depression post-TBI would require supportive data indicating efficacy in prevention that is clinically meaningful in size. Further, preventative interventions would require a highly favourable risk benefit balance as some patients will inevitably be exposed to an intervention they do not need. This may appear less of a concern with a low risk intervention such as planned social interaction or even specific psychotherapeutic activity to facilitate adjustment. The utilisation of antidepressants is associated with more significant risks and would thus require significant evidence of benefit as well as clear information on those risks before clinicians and patients could feel comfortable proceeding.

Previous studies have examined the efficacy of prophylactic treatment with antidepressant medications in other impaired cohorts at elevated risk of depression including persons undergoing open heart surgery,[26] those receiving anti-viral treatment for chronic hepatitis C,[27] and individuals being treated for stroke, [28] head and neck cancer,[29] and acute coronary syndrome. [30] Overall findings support the use of medication for secondary prevention of depression. The findings of the systematic review on stroke are particularly

relevant to the TBI population. Eight studies were included; pooled analyses indicated reduced odds of post stroke depression associated with pharmacologic treatment (odds ratio: 0.34, 95% CI 0.22-0.53). Given the debilitating nature of depression and the major impacts it can have on functioning and quality of life, consideration of the safety and effectiveness of prophylactic pharmacotherapy to reduce the risk of depression in an "at risk" population cohort is warranted.

As far as we can determine, prophylactic pharmacological management to reduce the risk of depression post-TBI has not been considered in clinical guidelines for TBI. Prior systematic reviews and meta-analyses of the pharmacological management of symptomatic depression post-TBI report that pharmacotherapy post-TBI may be associated with a reduction in depressive symptoms; [23,31,32] no systematic reviews could be found that have identified and synthesized the evidence for prophylactic pharmacological management of depression post-TBI.

This review forms part of a larger project to synthesize the evidence for the pharmacological management of neurobehavioural symptoms post-TBI as a prelude to the development of a clinical guideline for the pharmacological management of neurobehavioural symptoms following TBI. While the prophylactic use of pharmacotherapy as maintenance treatment following an initial depressive episode is common,[33,34] this is not the focus of this review.

The objective of this systematic review is to identify and synthesize the current evidence on the effectiveness and harms of prophylactic pharmacological treatment for the secondary prevention of depressive symptoms post-TBI.

MATERIALS and METHODS

Inclusion and exclusion criteria

Articles were selected for inclusion in the systematic review according to the following criteria.

Types of Participants

This systematic review includes studies of individuals who have sustained a TBI and were asymptomatic for depression at the time of study recruitment. For a study to be included in the review, depressive symptoms could be determined either by self-report or using a standardized diagnostic interview or validated assessment tool (e.g. Diagnostic and Statistical Manual of Mental Disorders criteria (DSM) or MINI International Neuropsychiatric Interview).

Traumatic brain injury is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force. Participants must have definite medical evidence of TBI. For the purpose of this review, this means that TBI had been documented in medical records or other health-medical reports sighted by the research team associated with the published article. These records had to provide unequivocal evidence of injury. Examples of unequivocal evidence include findings from brain imaging, Glasgow Coma Scale (GCS) score, post traumatic amnesia (PTA), loss of consciousness. Any reported period of PTA and reporting of GCS score (3-15) was taken to indicate the presence of TBI. As risk of depression increases over time post-TBI, only individuals in the early stages of recovery with a clinical assessment that they do not currently meet the criteria for a depressive disorder were included. As there is no universal time frame for 'early recovery', for the purpose of the review, early recovery was defined as within eight weeks post-injury.

This review included:

- Studies including persons 16 years and over, both males and females, who had sustained a TBI of any severity.
- Studies where >= 80% of the baseline population are 16 years and older.

- Studies were included regardless of injury mechanism with both penetrating and non-penetrating injuries included.
- Studies of acquired brain injury populations if data for TBI participants are reported separately.

This review excluded:

- Studies including self-reported TBI in the absence of other medical evidence regarding the head injury.
- Studies relying on self-report of depressive symptoms in the absence of a standardized diagnostic interview, validated scale or DSM criteria.
- Studies reporting on clusters of individuals rather than individuals themselves e.g. clinic attendees, families, people living in a defined geographical area.

Types of Intervention(s)

The focus of this review was on pharmacotherapeutic interventions. No restriction on dose, duration, frequency, timing of delivery, or combination of drug therapy was made. Pharmacotherapy had to be prescribed by a health provider. Studies of mixed interventions (e.g., pharmacotherapy and psychological therapy) were included only if the data for the pharmacological intervention was reported separately. Studies of complementary medicines and over the counter medicine were excluded unless these were part of the intervention, as a co-intervention to pharmacotherapy.

Types of Comparator(s)

This review included studies that compared the pharmacological intervention with all types of comparators. There were no restrictions on the type of comparator; placebo (dummy or active), supportive, standard care or a non- pharmacological intervention. Studies comparing drugs within a pharmacological class were eligible for inclusion.

Types of Outcomes

The primary outcomes of interest for the review were:

- Prescription of antidepressant therapy in the first 12 months post-TBI
- Incidence of new onset depressive disorder in the first 12 months post-TBI
- Time to onset of a depressive disorder

The secondary outcomes of interest were:

- Harms including adverse effects resulting from pharmacotherapy and study dropouts.
    - Adverse effects general and specific (qualitatively documented or documented using Medical Dictionary for Regulatory Activities (MEDRA), WHO Adverse Reaction Terminology (WHO-ART) or other classification systems) associated with pharmacotherapy. The need for medication to manage adverse effects as reported.
    - Study dropout: Loss to follow-up and leaving the study early due to adverse events, inefficacy of treatment, death, any reason

Types of studies

This review considered the following study types

- Randomised controlled trials; Controlled non-randomised clinical trials; Quasi-randomised controlled trials including, for example but not limited to controlled before and after studies, interrupted time series with a control group, interrupted time series without a parallel concurrent control group; analytical observational studies (including cohort and case–control studies) and single arm studies.

The following study types were excluded: editorials and opinion pieces, qualitative research, case reports, single case experimental designs, methodological papers, secondary studies including narrative reviews, systematic reviews and meta-analyses.

Search Strategy

The literature search was limited to the English language and human subjects. No date restriction was applied to the search for literature. This review was not registered on Prospero.

Published and unpublished studies were identified using a seven step approach. Initially, the Cochrane Library and Pubmed were searched to identify key words used in titles and abstracts and in the search strategies of relevant published systematic reviews. Second, a more extensive search of international electronic bibliographic databases was undertaken to further identify articles. The following databases were searched with no date limitation: MEDLINE, OVID SP interface; Pubmed excluding MEDLINE; CINAHL: Cumulative Index to Nursing and Allied Health Literature; EMBASE: Excerpta Medica Database excluding MEDLINE, OVID SP interface; PsycINFO, OVID SP interface; Cochrane Library: CENTRAL.

An information specialist with extensive experience in conducting systematic reviews developed and executed the search strategy for each database. Third, we conducted backwards citation searching of all reference lists of retrieved articles were reviewed to identify research articles not located through other search strategies. Fourth, electronic searching of the following online journals: Brain Injury, Neuropsychology, Journal of Neurotrauma and Journal of Head Trauma Rehabilitation were carried out. Fifth, the clinical trial registries: International Clinical Trials Registry Platform Search Portal and ClinicalTrials.gov were searched to identify ongoing studies. Sixth, we searched Research Gate and the international drug regulators Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to identify unpublished studies. We also consulted international experts in the study of TBI for relevant citations. Finally, to ensure as complete a search as possible, we supplemented a formal database searches by seeking additional citations from Google Scholar.

Search terms were mapped to Medical Subject Headings (MeSH) terms or subject headings and linked together using Boolean operators. The search strategies for the other databases was based on the PubMed strategy and modified in accordance with the specific requirements for the other databases.

This systematic review is part of a large project that will review and update the current evidence on a range of neurobehavioural symptoms as the first stage in the development of a clinical guideline on pharmacotherapy for the management of neurobehavioural symptoms in adults post-TBI in Australia. The

search strategy was developed based on the PICO (Population, Intervention, Comparator, Outcome) elements of relevance to this review (P=TBI, I=pharmacotherapy). The full search strategy for Ovid Medline is provided in Appendix 1.

Study Selection

Following the search, all identified citations were collated, uploaded into Endnote X8 and duplicates removed. Titles and abstracts were screened by pairs of independent reviewers (FC/LP and AH/RB) for assessment against the inclusion and exclusion criteria for the review. Disagreements were resolved through consensus.

Studies that potentially met the inclusion criteria at the title/abstract stage were retrieved in full and independently assessed against the inclusion criteria by two review team members (FC/LP and AH/RB). Disagreements over eligibility were resolved through discussion with a third reviewer (MH).

Reporting of the review adhered to the PRISMA guidelines. The results of the search are presented in a PRISMA flow diagram (Figure 1). Full text studies that did not meet the inclusion criteria and reasons for exclusion are provided in the PRISMA diagram.

Quality Assessment

Methodological quality was reported using the Cochrane Risk of Bias and Joanna Briggs Institute (JBI) cohort and case control critical appraisal instruments. Independent critical appraisal was conducted by two reviewers (FC/HZ); disagreements were resolved through discussion with a third reviewer (MH). No studies were excluded based on methodological quality; however the results were taken into account when drawing conclusions about the study findings.

The Cochrane Risk of Bias for clinical trials [41] assesses risk of bias across seven domains: sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias. The JBI

critical appraisal tools assess methodological quality of case control studies and cohort studies using 10 item and 11 item tools respectively. The questions that comprise each tool are included in Appendix 2.

Data Extraction

Where available, we extracted data from each of the included studies on design, analysis and results. The data were extracted using a customized data extraction tool piloted on two articles that do not form part of the review. Minor changes were made following the pilot testing.

After full review, the following data were extracted as they appeared in the original publication: country where study was carried out and setting, study design, baseline sample size, main inclusion and exclusion criteria, outcomes, outcome measures and timing of measurement, participant demographics and baseline characteristics, type of analysis, statistical procedures, study completion rates, compliance rates and extent of missing data, main results, treatment harms and adverse events. The following data were collected where available for the study population, depression diagnosis and pharmacotherapy intervention; TBI study population (nature of injury, injury severity, assessment scales, other injuries, time post-injury); depression diagnosis - assessment scales, severity, other symptoms, timing of onset, diagnostic criteria; pharmacotherapy intervention/exposure and control conditions if used including drug name and drug class, treatment dose, frequency and duration.

RESULTS

Literature search

The identification of literature and the screening process was completed for the broader study encompassing a range of neurobehavioural symptoms post-TBI, with selection of studies specifically related to prophylactic treatment to reduce the risk of depressive symptoms made after the screening was completed. The initial literature search identified 9468 articles from bibliographic databases and 445 from additional search sources. Following the search, all identified citations were uploaded into Endnote and 2030 duplicates removed, leaving 7883 to be screened for inclusion. After screening of title and abstract, a further 7572 articles were removed leaving 311 articles to be reviewed as full-text in order to determine whether they met study inclusion criteria. After full review, 239 further articles were excluded leaving 72 articles to be screened. Of these, 66 articles were deemed to not meet the inclusion criteria for this review with three articles eligible for this review. The percentage agreement between the two independent authors who completed the full-text screen was 83.3%. The search was rerun in November 2017 and identified a further three articles bringing the total number of articles eligible for inclusion in this review to six. These six articles reported on five unique studies. The literature search was rerun in October 2018 with no additional articles identified. The screening process and reasons for exclusion at full-text stage are documented in Figure 1.

Six articles representing five unique studies are included in the evidence tables on prophylaxis for the prevention of depression post-TBI. Three studies were randomized controlled trials (RCTs), two studies were retrospective cohorts based on trauma registry participants and the final study was a case control study using the Taiwan National Health Insurance Database. Two of the RCTs reported on the same study. Of the five unique studies included in this review, two were conducted in the USA [35,36], two in Sweden [37,38] and one in Taiwan [39].

Sertraline was the pharmacotherapy evaluated in the three randomized controlled trials [35,36]. Two retrospective cohort studies examined the impact of beta-blockers given prior to sustaining a TBI [37,38] and

the final study examined the risk of new onset depression in TBI patients with hyperlipidemia who were treated with statin medications [39].

The Jorge et al, [36] and Novack et al, [35] sertraline studies at baseline included a total of 195 individuals; the studies of beta-blockers included 148 matched pairs; and the sample for the statin medication study involved 3792 individuals. Consistent with the TBI population, there were more males than females in all of the included studies. For four of the five unique studies, the hospital was the setting. Only one study considered treatment harms [36]. Outcomes were measured up to 12 months except for one study by Ahl that measured outcomes to five years.

Sertraline studies

The sertraline RCT studies are outlined in Table 1. The Jorge, 2016 RCT investigated the efficacy of sertraline versus placebo in preventing depressive episodes following TBI [36]. Patients were randomised to either sertraline 100mg daily or placebo for 24 weeks or until the development of a mood disorder. The main outcome measure was time to onset of depressive disorders. The number needed to treat for sertraline versus placebo to prevent depression at 24 weeks was 5.9 (95%CI, 3.1-71.1; $\chi^2 = 4.6$; $P = .03$) in other words, for every 5.9 post-TBI individuals administered sertraline, one would avoid being subsequently diagnosed with a depressive disorder. While these outcomes are not the focus of this review, the authors noted that there was no difference in psychological scale scores (Apathy Evaluation Scale, Disability Rating Scale, Mania Rating Scale, Hamilton Anxiety and Depression Rating Scales, Clinician Administered PTSD Scale, Modified Overt Aggression Scale, Alcohol Use Disorders Identification Test) between the sertraline and placebo group at 24 weeks [36]. The authors recognised the limitations of this study, in particular the small sample size and the follow-up period being restricted to six months.

The Novack et al, 2009 RCT examined the effectiveness of sertraline administered in the first three months after moderate to severe TBI in reducing the incidence of depression [35]. Patients were given either sertraline 50mg once daily or placebo for three months. The primary outcome was the development of depressive symptoms and this was measured using the Hamilton Depression Rating Scale

and the Neurobehavioural Functioning Inventory- Depression Scale. During the 90 day intervention there was no cases of depression identified in the sertraline group whereas in the placebo group three cases were detected (χ^2 =3.03, p=0.08). For the remainder of the 1-year follow-up period, four cases (8.2%) of depression were identified in the treatment group, and seven in the placebo group (14%) (χ^2=0.133, p=0.72)[35]. The results do not support the early prescription of sertraline post-TBI to prevent depressive symptoms. Limitations of this study were the high dropout rate of 19/49 participants in the treatment group, 10/50 in the placebo group, small sample size and the low dose of sertraline used in the study[35].

The Banos et al, 2010 study was based on the same group of patients utilizing the same method and exposure of interventions between the groups as described for the Novack study [40]. The aim of this study was to assess whether sertraline improved cognition and behavioural outcomes. Outcome measures included the Neurobehavioural Functioning Inventory (NFI), Working Memory Index, Trail Making Test, Wechsler Memory Scale and Symbol-Digit Modalities Test. With the exception of the NFI, these outcomes are not the focus of this review. The reporting of results for the NFI depression subscale differ between the Novack and Banos studies. Due to the lack of information provided it is not possible to determine whether one was based on an intent to treat analysis and the other represented the efficacy subset. The study concluded that sertraline did not appear to prevent development of cognitive and behavioural problems post-TBI [40].

Beta-Blocker studies

The characteristics of the two beta-blocker retrospective cohort studies together with their findings are outlined in Table 2. Both of the Ahl et al studies [37-38] were retrospective cohorts that examined the effect of beta-blockers on depression post-TBI [37]. In the two retrospective cohort studies, 66% and 70% of the patients were on the lipophilic beta blocker metroprolol, twelve months prior to admission. Patient's naïve to beta blockers pre-injury were allocated to the non-beta blocker group together with a minority of

patients exposed to beta-blockers either in a single dose or a limited (non-continuous) number of times during their admission.

In the Ahl et al study published in World Surgery, the cohort comprised individuals with severe extra cranial injuries[37]. Propensity matching was used to create pairs of individuals who had been prescribed beta-blockers and compare their outcomes with individuals who did not receive beta-blockers. Individuals with and without pre-admission b-blockers were matched 1:1 by age, gender, Glasgow Coma Scale, Injury Severity Score and head Abbreviated Injury Scale. The primary outcome was the measurement of post-traumatic depression one year after TBI. Findings from the study were that trauma registry patients not on beta-blockade therapy had increased odds of depression (AOR 3.3, 95% CI 1.2–8.6, p = 0.02)[37]. The study concluded that patients on beta-blockers prior to sustaining their TBI had significantly reduced odds of developing depression up to one year after sustaining a severe TBI. The study did not record the different beta-blockers used [37].

The second study by Ahl and colleagues looked at the administration of beta-blockers prior to severe TBI on the development of depression. [38] The results from this study demonstrated that more patients who were not on beta-blockers prior to the TBI 33% (n=26/80) developed post traumatic depression, than patients who were taking beta-blockers 18% (n=14/80) (p=0.04). The study concluded that beta-blockers act prophylactically to lower the risk of post-traumatic depression in patients suffering from TBI.[38] The study had several limitations, notably the retrospective cohort study design and the inability to control the type of beta blockers used by patients. [38]

Statin study

The statin case-control study reported in Table 3 found that TBI patients with high cholesterol levels are at a greater risk of depression especially when their hyperlipidemia is not kept under control with statins.

The Wee et al study was a matched case control study with 3 years of follow-up examining the role of statin medications in the management of hyperlipidaemia and the risk of developing new-onset

depression post-TBI.[39] Using 8 years of Taiwan longitudinal health insurance data (1/2001-12/2008) - researchers followed 3792 patients with TBI with no history of depression. Of the participants, 1,264 showed signs of pre-existing hyperlipidemia and each of these participants were age and sex matched to two others without hyperlipidemia from the overall cohort. [39] During the final three years of follow-up, 4 percent of TBI patients with hyperlipidemia and 2.3 percent without hyperlipidemia exhibited signs of depression. After controlling for age, sex, income, statin use and the comorbidities of hypertension, cardiovascular disease or diabetes, TBI patients with hyperlipidemia were 61% more likely to develop depression [39].

The study established hyperlipidemia as an independent risk factor for a new depression diagnosis up to three years post-TBI. There was a 1.72 fold increased incidence of depression in TBI patients with hyperlipidaemia than without (p=0.0056). Furthermore, TBI patients with hyperlipidaemia not treated with statins experienced a 1.95 fold incidence risk ratio (p=0.0017) and higher risk of post-TBI new onset depression (HR=1.61; 95% CI, 1.03-2.53) compared to TBI patients without hyperlipidaemia (p=0.0378).[39] Together this suggests a critical role for statins in the development of new-onset depression [39].

Harms

Adverse events due to treatment were only reported in one study [36] where patients were prescribed sertraline. One patient in both groups experienced a serious adverse event (fractured hip) which was not associated with the study medication. Patients who received sertraline were at a higher risk of experiencing dry mouth (OR=7.2; 90% CI, 1.9-27.6; *p*= .01) and diarrhoea (OR= 2.3; 90% CI, 1.0-5.5; p = .10) compared to placebo [36].

Quality assessment

The quality assessment rating for each of the included studies is included in Table A. Methodological quality assessments were independently conducted by two reviewers (HZ,FC). Risk of bias for experimental studies was conducted using the criteria as recommended by Cochrane Effective Practice of

Care (EPOC) group [41]. RCTs were assessed for generation of allocation sequence, concealment of allocation, baseline outcome measurements, baseline characteristics, incomplete outcome data, blinding of outcome assessor, protection against contamination, selective outcome reporting and other risks of bias using the Cochrane Risk of Bias tool [41]. For retrospective cohort studies the Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies was used (see Appendix 2). The Kappa statistic for risk of bias ratings was not calculated.

The three intervention studies included in this review varied in terms of their risk of bias. The Jorge study was assessed as being at low risk of bias [36], whereas for the Novack and Banos studies it was difficult to reach conclusions regarding the risk of bias due to lack of data and information contained within the studies. The Novack and Banos study was affected by significant attrition with no explanation provided for the loss to follow-up [35,40]. The two retrospective cohort studies by Ahl and colleagues were judged to be at low risk of bias with most criteria in the critical appraisal of cohort studies being met[37,38]. However, both studies used a proxy indicator of depression based on prescription of antidepressants. The case-control study by Wee was judged as having a low risk of bias [39].

DISCUSSION

The focus of the current systematic review was to assess the effectiveness and tolerability of using prophylaxis medication to prevent the onset of depression post-TBI. The studies included in the review examined the effects of sertraline, beta-blockers and statins on the risk of new onset depression. Despite the use of different study designs, overall, the results provide some early support for a prophylactic secondary prevention approach.

Three articles focusing on two studies considered the effectiveness of sertraline. In the RCT by Jorge et al of the 94 patients in the study, the number needed to treat to prevent depression at 24 weeks post-TBI was 5.9 for sertraline treatment vs placebo (p=.03, 95% CI:3.1-71.1)[36]. In contrast, the RCT by Novack, Banos and colleagues did not find significant differences in rates of depressive symptoms between the treatment and placebo groups [35,40]. The Novack/Banos study was subject to significant attrition and there was no attempt to address the missing data in the analysis. Comparability between the two studies is limited due to the use of different dosages of sertraline (50mg/day, 100mg/day). The dose (50mg/day) of sertraline may have been suboptimal to impact serotonin levels. Moreover the lack of effect may be due to a smaller sample size than intended.

Sertraline belongs to a class of antidepressants called Selective Serotonin Reuptake Inhibitors (SSRIs) which prevent the uptake of serotonin by monoamine transporters in the presynaptic cleft thereby increasing the availability of serotonin in the synaptic cleft. [42] Serotonin is thought to impact mood, arousal and working memory and therefore SSRIs are seen as suitable pharmacotherapy for post-TBI neurocognitive and neuropsychiatric deficits. [42]

Despite the lack of current evidence to support the use of SSRIs in a post-TBI population, in non-TBI populations, SSRIs have been shown to significantly improve function and depressive symptoms suggesting that they are both effective and well tolerated.[43] As the use of SSRIs becomes more widespread in TBI patients, the risks associated with pharmacological treatment have become more

apparent [43]. SSRIs are associated with lowering the seizure threshold [42] and in patients with TBI, late onset seizures are a recognized problem. The extent to which SSRIs treatment exacerbate risk of seizures has yet to be quantified. Antidepressants with strong serotonin reuptake inhibition properties can increase the risk for intracranial hemorrhage particularly in the first months of administration. If anticoagulants are also prescribed, the impact may be greater. The risk of bleeding stems from inhibition of serotonin reuptake in platelets [44]. Other notable adverse effects of SSRIs include; serotonin syndrome, emergence of mania, hyponatraemia, impotence/sexual dysfunction, interactions with anticonvulsants and gastrointestinal effects [42-43]. In the RCT by Jorge et al, adverse events were recorded [36]. Notably, there was an increased odds of diarrhoea and dry mouth in the arm receiving sertraline. While the review by Jones et al noted that SSRIs appeared to be well tolerated post-TBI in the Jorge et al study, it does not discount the possibility of more serious side effects in a larger sample recruited from more than one location or country [45].

The studies by Ahl and Wee used trauma registries [37-39] and administrative claims databases[39] to retrospectively examine the effectiveness of beta-blockers and statins on new onset depression post-TBI. It is important to emphasize that these patients were not prescribed beta-blockers or statins because they had a TBI and physicians were concerned about depression. The registry and health insurance databases were not set up to explicitly assess the relationship (if any) between these pharmacotherapies and new onset depression. In this regard, these studies[37-39] differ from the RCTs that focused on [39] prescription of sertraline. It is also one reason why there is no information on harms and adverse events in these studies. In terms of effectiveness of the pharmacotherapy and potential application as a prophylactic treatment, the lack of information on harms is a significant concern. While the three studies show promise with respect to the measured outcomes, before any consideration of the clinical use post-TBI of these pharmacotherapies, further studies in large well conducted randomized controlled trials involving post-TBI patients are needed to confirm the benefits and harms of beta-blockers and statins.

Beta Blockers

Beta blockers have varying impacts on glucose control, depression and lipid dysfunction. The mechanism of action of beta-blockers on behavioural disorders remains unclear but it is proposed they reduce hyperadrenergic activity.[46] In patients with TBI there can be an imbalance in the autonomic nervous system which leads to increased sympathetic activity termed as Paroxysmal Sympathetic Hyperactivity (PSH).[47] PSH is thought to be one potential mechanism of agitation post-TBI. Beta-blockers are hypothesized to protect against social anxiety and have been used to treat and reduce the intensity and frequency of neurobehavioral symptoms such as agitation or aggression in the subacute and chronic phases of TBI. [48]

The benefit and safety of beta-blockers post-TBI, as well as their differential effects and interactions are uncertain. There is a lack of research on the long-term effects on functional recovery and cognitive capacities are not well studied. Attention needs to be paid to the safety of beta-blockers in TBI. The one RCT study that did investigate clinically significant adverse effects of beta-blockers including hypotension, bradycardia, bronchospasm and congestive heart failure in TBI patients compared to placebo revealed no increase adverse events in the beta-blocker group [49].

A proxy outcome for depression –antidepressant therapy within one year post discharge was used in the two studies by Ahl and colleagues [37,38]. This may overestimate the odds of a depressive disorder diagnosis as beta-blockers are sometimes prescribed off label to manage an individual's physical reactions to a range of anxiety disorders including social anxiety disorder and performance anxiety.

Statins

The included study by Wee et al, 2016 found that TBI patients with preexisting hyperlipidemia that was not treated with statins had a greater risk of new-onset depression than TBI patients without hyperlipidemia.[39] Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors

that influence multiple mechanisms of acute and secondary neuronal injury. Although the beneficial effects of statins have been ascribed to their lipid lowering properties there is now evidence that statins have additional neuroprotective properties that may promote the timely resolution of the inflammatory response, preventing persistence of inflammation and resultant pathology post-TBI. [50] Statins have mixed effects as neuroprotection agents with some studies reporting beneficial effects of statins with respect to neuroprotection while other studies do not. [51,52] While the study by Wee provides support for an effect of statins post-TBI, the precise effect with respect to depression remains to be established.

Statins have been widely used and their adverse effect profile is well documented with few complications. However, statins can cause rhabdomyolysis [53], and it is not known whether patient's post-TBI, or those with hypoperfusion are more prone to this problem. Statins are also known to affect the coagulation and fibrinolytic systems, despite this a clinically significant effect on coagulopathy in TBI patients not having been reported. [54] Moreover, in 2012 the U.S Food and Administration issued a statement on cognitive impairment as a potential adverse effect of statins, with myopathy being the most well-characterized adverse sequalae. [55] The use of statins in a TBI population could present risks if abrupt discontinuation is required, for example because of an adverse event, as this may exacerbate neuroinflammation that is occurring because of the TBI. [56-57]

Practical concerns

Prescriptions drugs like sertraline are approved by regulators like the Therapeutic Good Administration (TGA) for a particular indication. Off-label prescribing happens when a drug is prescribed for an indication, route of administration or patient group that is not included in the approved product information document for that drug. It means that the regulator has not approved the indication, route of administration or patient group. The prescription of sertraline for the secondary prevention of depression in a person post-TBI is an example of off label prescribing

While there are no legal barriers to prescribing off-label, the prescriber must be able to defend their prescription for an indication not listed in the product information. The grounds for off-label prescribing are likely to be open to more scrutiny should a serious adverse event related to the medication occur.

One of the risks with using medicines off-label is that the quality of evidence to support such use may be lower than for approved indications. If the medicine is used for an off-label patient population such as those post-TBI, the risks and side effects may be unclear. Moreover, the extent to which patients will benefit from using the medicine might be unknown as the effectiveness of a medicine used for an off-label indication may not have been comprehensively assessed in clinical trials. In the case of the current review, only one of the studies on sertraline reported on the harms. The RCT was relatively small with recruitment being restricted to a single site in the USA.

For the patient, the cost of using medicines off-label may be prohibitive. Medicines prescribed off-label are not eligible to be subsidized on the Pharmaceutical Benefits Scheme in Australia, meaning the patient has to pay the full cost. In the case of sertraline, betablockers and statins which are now all off patent, the costs are not expensive. If prescribed medicines are subject to reimbursement from other sources, for example, insurance providers, off-label prescribing may have implications for reimbursement.

Clinical concerns

The clinical utilization of preventative antidepressant therapy in high risk situations such as post-TBI remains controversial. The majority of existing evidence on the use of antidepressants in the treatment of major depression in a general population lies in either acute episode treatment or prophylaxis in individuals with an established history of depression. This evidence alone cannot be taken to indicate antidepressants will be similarly efficacious in someone with no history of depression but significant risk factors for depression. It is also clear that not all or even perhaps the majority of individual's post-TBI will experience major depression. This suggests that most individuals given prophylactic interventions in this

case antidepressants will not require them. If this is the case, any intervention must have a very low risk of potential harm to justify its use. Finally, the clinical utility of these findings is affected by the variability across the six studies in the end outcome of depression.

Ethical concerns

It is appropriate to consider the application of the ethical principles of beneficence and nonmaleficence, to the prophylactic secondary prevention approach to reduce the risk of depression in individual's post-TBI including the possibility of prescribing to individuals who may never get depression. Physicians need to ensure that the individual risk of depression in patient's post-TBI is properly and progressively assessed and managed along the post-TBI continuum of care. The outcome of an assessment, together with shared decision making with the patient might result in prescribing pharmacotherapy. Alleviating the risk of depression post-TBI needs to be balanced with the equally important responsibility of not exposing individuals to unnecessary harms associated with medication.

The ethical principle of beneficence specifies that a physician must provide a net benefit to the patient. Given the lack of research on depression post-TBI; even with clinical experience, empathy and an open mind, it is not simple to estimate the benefits that a post-TBI patient will obtain from pharmacotherapy. The principle of nonmaleficence guides physicians to avoid or minimize harm or the risk of harm, the physician must consider the harms and risks of adverse effects associated with prescribing medication to the patient.

Strengths and Limitations

This systematic review has a number of limitations. Only a small number of studies were identified and given this meta-analysis was not appropriate. Moreover, the studies considered three different medications and there was insufficient detail available on the timing of the pharmacologic agent delivery. The studies of beta-blockers and statins didn't differentiate the drugs further, so we are not able to

attribute an effect to a particular drug. Given the retrospective nature of some of the studies, pharmacovigilance data on harms and adverse events was not available. Moreover, the findings from the statins and beta-blockers studies need to be interpreted with caution as a direct causal link cannot be established given that these studies were retrospective. It is possible that we have missed relevant peer reviewed articles. We think the likelihood of this is small given the involvement of an information specialist in the design of the search, the range of databases searched, reference lists consulted and search of Google scholar and grey literature.

Notwithstanding this, the strengths of the review include the systematic identification of relevant studies using a specified search strategy developed by an information specialist that included a search of clinical trials sites and a critical appraisal of the reports quality. Moreover, no date restriction was applied, all studies were assessed for methodological quality and we followed the PRISMA reporting guidelines. [58] The review brings together five independent studies of prophylactic treatment to prevent the onset of post-TBI depression. By doing so it helps clinicians to better understand the clinical course of depression post-TBI and may offer guidance in the personalization of treatments in clinical practice.

CONCLUSION

This systematic review has identified and synthesized the evidence on the prophylactic use of medication to prevent the onset of depression post-TBI. The review included six articles reporting on five studies involving sertraline, beta-blockers and statins. Overall, the review identified mixed evidence of prophylactic efficacy for the three drug classes and insufficient evidence concerning harm. While we hope this review will serve to stimulate further study on pharmacologic prophylaxis in this population, concerns over the quality of evidence, cost of medications, off-label prescribing, lack of data on safety together with the clinical and ethical concerns over potentially prescribing medication to individual's post-TBI who may never get depression limit any recommendations for clinical practice. Moreover, given the range of severity for both depression and TBI, a prophylactic pharmacological intervention may not meet the needs of all patients at risk of developing depression post-TBI

In the age of genomics and personalized medicine, finding biomarkers to identify individuals at greater risk of depression may focus prophylactic secondary prevention to those who are most at risk of developing depression post TBI. Until then, further research in large post-TBI cohorts using a range of study designs that collect data on risks and harms is needed. A clear definition of depression, depression severity and reporting of the specific pharmacological drug including the dose, frequency and time to drug initiation would be informative.

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Author Disclosure Statement

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APPENDIX 1

MEDLINE search strategy

1. Exp Brain Hemorrhage, Traumatic/ OR Brain Injuries/ OR Brain Injury, Chronic/ OR Cerebral Hemorrhage, Traumatic/ OR Cerebrovascular Trauma/ OR Craniocerebral Trauma/ OR Diffuse Axonal Injury/ OR Exp Head Injuries, Closed/ OR Head Injuries, Penetrating/ OR Exp Intracranial Hemorrhage, Traumatic/ OR Exp Pneumocephalus/ OR (((Brain OR Cerebr$ OR Crani$ OR Crushing Skull OR Diffuse Axonal OR Head OR Hemisphere?) adj1 (Injur$ OR Trauma$)) OR ((Cerebr$ OR Crani$ OR Head) adj (Lesion? OR Wound?)) OR ((Posttraumatic OR Traumatic) adj Encephalopath$) OR (Traumatic adj (Brain OR Cerebr$)) OR Concuss$ OR DAI OR DAIs OR Pneumocephalus OR TBI OR TBIs).ti,ab.

2. "Anti-Anxiety Agents"/ OR "Anticonvulsants"/ OR "Antidepressive Agents"/ OR "Antipsychotic Agents"/ OR "Benzodiazepines"/ OR "Adrenergic Beta-Antagonists"/ OR Alprazolam/ OR Amitriptyline/ OR Amoxapine/ OR Aripiprazole/ OR Atenolol/ OR Atomoxetine Hydrochloride/ OR Benztropine/ OR Bromazepam/ OR Bupropion/ OR Buspirone/ OR Carbamazepine/ OR Chlordiazepoxide/ OR Chlorpromazine/ OR Citalopram/ OR Clomipramine/ OR Clonazepam/ OR Clopenthixol/ OR Clorazepate Dipotassium/ OR Clozapine/ OR Desipramine/ OR Desvenlafaxine Succinate/ OR Dextroamphetamine/ OR Diazepam/ OR Valproic Acid/ OR Domperidone/ OR Dothiepin/ OR Doxepin/ OR Droperidol/ OR Duloxetine Hydrochloride/ OR Estazolam/ OR Eszopiclone/ OR Flunitrazepam/ OR Fluoxetine/ OR Flupenthixol/ OR Fluphenazine/ OR Fluvoxamine/ OR Guanfacine/ OR Haloperidol/ OR Imipramine/ OR Isocarboxazid/ OR Methotrimeprazine/ OR Lithium/ OR Lithium Carbonate/ OR Lorazepam/ OR Loxapine/ OR Lurasidone Hydrochloride/ OR Methylphenidate/ OR Mianserin/ OR Midazolam/ OR Moclobemide/ OR Molindone/ OR Nitrazepam/ OR Nortriptyline/ OR Oxazepam/ OR Paliperidone Palmitate/ OR Paroxetine/ OR Phenelzine/ OR Phenobarbital/ OR Pindolol/ OR Prazepam/ OR Pregabalin/ OR Prochlorperazine/ OR Promazine/ OR Promethazine/ OR Propranolol/ OR Protriptyline/ OR Quetiapine Fumarate/ OR Remoxipride/ OR

Risperidone/ OR Selegiline/ OR Sertraline/ OR Sulpiride/ OR Temazepam/ OR Thioridazine/ OR Thiothixene/ OR Tranylcypromine/ OR Trazodone/ OR Triazolam/ OR Trifluoperazine/ OR Trimipramine/ OR Venlafaxine Hydrochloride/ OR Vigabatrin/ OR ((Adrenergic adj Beta adj2 (Antagonist OR Block$)) OR Anti Anxiety OR Anti Convuls$ OR Anti Depress$ OR Anti Epilep$ OR Anti Psychotic? OR Antianxiety OR Anticonvuls$ OR Antidepress$ OR Antiepilep$ OR Antipsychotic$ OR Anxiolytic$ OR Benzodiazepine$ OR (Beta adj Block$) OR (Beta adj1 Adrenergic adj2 Block$) OR Thymoanaleptic$ OR Thymoleptic$ OR Agomelatine OR "S 20098" OR S20098 OR Thymanax OR Valdoxan OR "AGO 178" OR AGO178 OR Alprazolam OR Alprazolan OR "Apo Alpraz" OR ApoAlpraz OR Cassadan OR "D 65MT" OR D65MT OR Xanax OR Tafil OR Trankimazin OR "Novo Alprazol" OR NovoAlprazol OR "Nu Alpraz" OR NuAlpraz OR Ralozam OR "U-31,889" OR "U31,889" OR Alprox OR Esparon OR Kalma OR Amisulpride OR Sultopride OR Barnetil OR "DAN 2163" OR Solian OR "LIN 1418" OR Amitriptyline OR Amineurin OR Amitrip OR Amitriptylin OR Amitrol OR Tryptine OR ApoAmitriptyline OR Damilen OR Domical OR Laroxyl OR Endep OR Lentizol OR Novoprotect OR Saroten OR Sarotex OR Syneudon OR Triptafen OR Tryptizol OR Tryptanol OR Elavil OR Anapsique OR Amoxapine OR Desmethylloxapine OR "CL 67,772" OR "CL67,772" OR Demolox OR Asendin OR Defanyl OR Asendis OR Aripiprazole OR Aripiprazol OR "OPC 14597" OR Abilify OR Asenapine OR Saphris OR " OR G 5222" OR Atenolol OR Tenormine OR Tenormin OR "ICI 66082" OR ICI66082 OR Atomoxetine OR Tomoxetine OR Strattera OR "LY 139603" OR Benztropine OR Benzatropine OR Bensylate OR PMSBenztropine OR Cogentin OR Cogentinol OR Methylbenztropine OR ApoBenztropine OR Brexpiprazole OR Bromazepam OR BromaLich OR "Bromaz 1A Pharma" OR Bromazanil OR "Bromazep von CT" OR Durazanil OR Lexotan OR Lexotanil OR Lexatin OR Lexomil OR "Ro 5-3350" OR "Ro 53350" OR Anxyrex OR Bupropion OR Amfebutamone OR Zyntabac OR Quomen OR Wellbutrin OR Zyban OR Buspirone OR "MJ 9022 1" OR MJ90221 OR Neurosine OR Busp OR Anxut OR Buspar OR Bespar OR Carbamazepine OR Tegretol OR Carbazepin OR Epitol OR Finlepsin OR Neurotol OR Amizepine OR Cariprazine OR "RGH 188" OR Chlordiazepoxide OR Methaminodiazepoxide OR Librium

OR Chlozepid OR Elenium OR Chlorpromazine OR Thorazine OR Aminazine OR Largactil OR Chlordelazine OR Contomin OR Fenactil OR Propaphenin OR Chlorazine OR Citalopram OR Cytalopram OR "Lu 10 171" OR Lu10171 OR Escitalopram OR Lexapro OR Clobazam OR "HR 376" OR Onfi OR "LM 2717" OR Frisium OR Urbanyl OR Clomipramine OR Chlomipramine OR Chlorimipramine OR Hydiphen OR Anafranil OR Clonazepam OR "Ro 5 4023" OR "Ro 54023" OR Antelepsin OR Rivotril OR Clopenthixol OR Zuclopenthixol OR Cisordinol OR Clorazepate OR Chlorazepate OR Tranxene OR Tranxilium OR "4306 CB" OR Clozapine OR Clozaril OR Leponex OR Desipramine OR Desmethylimipramine OR Demethylimipramine OR Norpramin OR Pertofrane OR Pertrofran OR Pertofran OR Petylyl OR Desvenlafaxine OR "O Desmethylvenlafaxine" OR "WY 45,233" OR "WY 45,233" OR "WY45,233" OR "WY 45233" OR WY45233 OR Pristiq OR Dextroamphetamine OR Dexamphetamine OR Dexamfetamine OR "Dextro Amphetamine" OR "D Amphetamine" OR Dexedrine OR DextroStat OR Oxydess OR Diazepam OR Diazemuls OR Faustan OR Valium OR Seduxen OR Sibazon OR Stesolid OR Apaurin OR Relanium OR "Valproic Acid" OR Divalproex OR "Propylisopropylacetic Acid" OR "2 Propylpentanoic Acid" OR Convulsofin OR Depakene OR Depakine OR Depakote OR Vupral OR Valproate OR Ergenyl OR "Dipropyl Acetate" OR Domperidone OR Domperidon OR Domidon OR Gastrocure OR Motilium OR Nauzelin OR Peridys OR "R 33,812" OR "R33,812" OR "R 33812" OR R33812 OR Dothiepin OR Dosulepin OR Prothiaden OR Doxepin OR Deptran OR Desidox OR Doneurin OR Doxepia OR Espadox OR Mareen OR Prudoxin OR Quitaxon OR Sinequan OR Sinquan OR Zonalon OR Xepin OR Aponal OR ApoDoxepin OR Droperidol OR Inapsine OR Dehidrobenzperidol OR Dehydrobenzperidol OR Droleptan OR Duloxetine OR "LY 248686" OR LY248686 OR "LY 227942" OR LY227942 OR Cymbalta OR Estazolam OR Tasedan OR ProSom OR "D 40TA" OR D40TA OR Nuctalon OR Eszopiclone OR Lunesta OR Estorra OR Flunitrazepam OR Fluridrazepam OR Flunibeta OR Flunimerck OR Fluninoc OR Rohypnol OR Rohipnol OR Narcozep OR "Flunizep von CT" OR "RO 5 4200" OR RO54200 OR Fluoxetine OR Fluoxetin OR "Lilly 110140" OR Lilly110140 OR Sarafem OR Prozac OR Flupenthixol OR Flupentixol OR Emergil OR Fluanxol OR

Fluphenazine OR Flufenazin OR Lyogen OR Prolixin OR Fluvoxamine OR Fluvoxadura OR Fluvoxamin OR Fluvoxamina OR Luvox OR Fevarin OR Floxyfral OR Dumirox OR Faverin OR Desiflu OR "DU 23000" OR DU23000 OR Guanfacine OR Tenex OR Lon798 OR "BS 100 141" OR BS100141 OR Estulic OR Haloperidol OR Haldol OR Iloperidone OR Zomaril OR Fanapt OR "HP 873" OR Imipramine OR Imizin OR Norchlorimipramine OR Imidobenzyle OR Tofranil OR Melipramine OR Pryleugan OR Janimine OR Isocarboxazid OR Lamotrigine OR Crisomet OR Lamictal OR Lamiktal OR "BW 430C" OR Labileno OR Methotrimeprazine OR Levomepromazine OR Levopromazine OR Levomeprazin OR Tisercin OR Tizercine OR Tizertsin OR Lithium OR Dilithium OR Lithane OR Lithobid OR Lithonate OR "CP-15,467 61" OR "CP15,46761" OR Micalith OR "NSC 16895" OR NSC16895 OR Priadel OR "Quilinorm Retard" OR Quilinormretard OR Eskalith OR Lithotabs OR Lorazepam OR Ativan OR Temesta OR "Orfidal Wyeth" OR Donix OR Duralozam OR Durazolam OR Idalprem OR Laubeel OR "Lorazep von CT" OR "Novo Lorazem" OR NovoLorazem OR "Nu Loraz" OR NuLoraz OR Sedicepan OR Sinestron OR Somagerol OR Tolid OR "WY 4036" OR WY4036 OR ApoLorazepam OR Loxapine OR Cloxazepine OR Oxilapine OR Loxitane OR Loxipine OR Loxapinsuccinate OR "CL 71,563" OR "CL71,563" OR Lurasidone OR "SM 13496" OR SM13496 OR "SM-13,496" OR "SM13,496" OR Latuda OR Methylphenidate OR Metadate OR Equasym OR Methylin OR Concerta OR Phenidylate OR Ritalin OR Ritaline OR Tsentedrin OR Centedrin OR Daytrana OR Mianserin OR Tolvon OR Lerivon OR Org GB 94 OR Midazolam OR Dormicum OR Versed OR "Ro 21 3981" OR "Ro 213981" OR Milnacipran OR Midalcipran OR Levomilnacipran OR Savella OR "F 2207" OR Ixel OR Mirtazapine OR "6 Azamianserin" OR Esmirtazapine OR Remeron OR Remergil OR Zispin OR Norset OR Rexer OR "Org 50081" OR " OR G 3770" OR Moclobemide OR Moclobamide OR Arima OR Aurorix OR Manerix OR Moclamine OR Aurorex OR Deprenorm OR Feraken OR Moclobemid OR Moclobeta OR Moclodura OR Moclonorm OR Rimoc OR "Ro 11 1163" OR Modafinil OR Benzhydrylsulfinylacetamide OR "CRL 40476" OR Vigil OR Provigil OR Sparlon OR Alertec OR Modiodal OR Molindone OR Moban OR Nefazodone OR Rulivan OR Serzone OR Dutonin OR Nefadar OR Menfazona OR Nitrazepam OR Nitrodiazepam OR "Dormo Puren"

OR Eatan OR Imadorm OR Imeson OR Mogadon OR Nitrazadon OR Nitrazep OR Novanox OR Radedorm OR Remnos OR Serenade OR Somnite OR Alodorm OR Dormalon OR Nortriptyline OR Desmethylamitriptylin OR Desitriptyline OR Aventyl OR Paxtibi OR Allegron OR Norfenazin OR Pamelor OR Nortrilen OR Olanzapine OR Zolafren OR "LY 170052" OR Zyprexa OR "LY 170053" OR Oxazepam OR Serax OR Tazepam OR Adumbran OR Oxcarbazepine OR Timox OR Trileptal OR "GP 47680" OR Paliperidone OR "9 OH Risperidone" OR "9 Hydroxy Risperidone" OR "9 Hydroxyrisperidone" OR Invega OR "R 76477" OR R76477 OR Paroxetine OR "BRL 29060" OR BRL29060 OR "FG 7051" OR FG7051 OR Seroxat OR Paxil OR Aropax OR Periciazine OR Propericiazine OR Pericyazine OR Neuleptil OR Neuleptyl OR Aolept OR Phenelzine OR "Beta Phenylethylhydrazine" OR "2 Phenethylhydrazine" OR Fenelzin OR Phenethylhydrazine OR Nardelzine OR Nardil OR Phenobarbital OR Phenobarbitone OR "Phenylethylbarbituric Acid" OR Phenemal OR Phenylbarbital OR Hysteps OR Luminal OR Gardenal OR Pindolol OR Prindolol OR Visken OR "LB 46" OR LB46 OR Prazepam OR Lysanxia OR Reapam OR Centrax OR Demetrin OR Pregabalin OR "3 Isobutyl GABA" OR Lyrica OR "CI 1008" OR CI1008 OR Prochlorperazine OR Compazine OR Promazine OR Sparine OR Sinophenin OR Protactyl OR Promethazine OR Prometazin OR Proazamine OR Rumergan OR Diprazin OR Phenergan OR Phenargan OR Phensedyl OR Pipolfen OR Pipolphen OR Promet OR Prothazin OR Pyrethia OR Remsed OR Atosil OR Diphergan OR Propranolol OR Propanolol OR Inderal OR Avlocardyl OR "AY 20694" OR AY20694 OR Rexigen OR Dexpropranolol OR Dociton OR Obsidan OR Obzidan OR Anaprilin OR Anapriline OR Betadren OR Protriptyline OR Vivactil OR Quetiapine OR "ICI 204,636" OR "ICI 204636" OR ICI204636 OR Seroquel OR Reboxetine OR Vestra OR Remoxipride OR "FLA 731" OR FLA731 OR Risperidone OR Risperdal OR Risperidal OR "R 64,766" OR "R64,766" OR "R 64766" OR R64766 OR Selegiline OR Selegyline OR "L Deprenyl" OR "E 250" OR E250 OR Eldepryl OR Emsam OR Zelapar OR Deprenil OR Deprenalin OR Yumex OR Jumex OR Humex OR Deprenyl OR Sertindole OR Serlect OR "Lu 23 174" OR Serdolect OR Sertraline OR Zoloft OR Altruline OR Lustral OR Aremis OR Besitran OR Sealdin OR Gladem OR Sulpiride OR Sulperide OR Arminol OR Deponerton OR Meresa OR

Desisulpid OR Digton OR Dogmatil OR Dolmatil OR Eglonyl OR Ekilid OR Guastil OR Lebopride OR Neogama OR Pontiride OR Psicocen OR Sulp OR Sulpitil OR Sulpivert OR Sulpor OR Synedil OR Tepavil OR Aiglonyl OR Temazepam OR Hydroxydiazepam OR Methyloxazepam OR Signopam OR Tenox OR "WY 3917" OR WY3917 OR Dasuen OR Euhypnos OR Levanxol OR "Norkotral Tema" OR Normison OR Nocturne OR Temtabs OR Normitab OR Nortem OR Planum OR "Pronervon T" OR Remestan OR Restoril OR "Ro 5 5345" OR Ro55345 OR "SaH 47 603" OR "SaH 47603" OR Temaze OR "Temazep von CT" OR Thioridazine OR ApoThioridazine OR Meleril OR Melleril OR Melleryl OR Mellaril OR Melleretten OR Melzine OR Thiozine OR Sonapax OR Thioridazineneurazpharm OR Aldazine OR Rideril OR Thiothixene OR Tiotixene OR Navane OR Topiramate OR USL255 OR "McN 4853" OR Topamax OR Epitomax OR Tranylcypromine OR "Trans 2 Phenylcyclopropylamine" OR Jatrosom OR Transamine OR Parnate OR Trazodone OR Tradozone OR "AF 1161" OR AF1161 OR Deprax OR Desyrel OR Molipaxin OR Trittico OR Thombran OR "Trazodon Hexal" OR "Trazodon Neuraxpharm" OR Trazon OR Triazolam OR "U 33,030" OR "U33,030" OR Halcion OR Trilam OR "Apo Triazo" OR Trifluoperazine OR Trifluoroperazine OR Trifluperazine OR Eskazine OR Flupazine OR Terfluzine OR Triftazin OR Stelazine OR Trimipramine OR Trimeprimine OR Herphonal OR Trimineurin OR NovoTripramine OR Rhotrimine OR Stangyl OR Surmontil OR Trimidura OR Trimineurin OR Trimipramin OR "Apo Trimip" OR ApoTrimip OR Eldoral OR Venlafaxine OR "Wy 45030" OR Wy45030 OR "Wy 45,030" OR "Wy45,030" OR Effexor OR Trevilor OR Vandral OR Efexor OR Dobupal OR Vigabatrin OR "Gamma Vinyl GABA" OR "Gamma Vinyl Gamma Aminobutyric Acid" OR Sabril OR Sabrilex OR Vortioxetine OR Brintellix OR "Lu AA21004" OR LuAA21004 OR Zaleplon OR "SKP 1041" OR Sonata OR Zelepion OR Starnoc OR "CL 284,846" OR "CL284,846" OR "CL 284846" OR "L 846" OR Ziprasidone OR Ziprazidone OR "CP 88,059" OR "CP 88059" OR Zolpidem OR Amsic OR Bikalm OR Dalparan OR "SL 80.0750" OR "SL 800750 23 N" OR Stilnoct OR Stilnox OR Zodormdura OR Zoldem OR Zolirin OR "Zolpi Lich" OR Zolpinox OR Zolpimist OR Ambien OR Zopiclone OR Zop OR Zopicalma OR Zopiclodura OR Zopiclon OR Zopitan OR Zorclone OR Imovane OR Ximovan OR Zimovane OR Limovan OR Optidorm OR Rhovane OR "RP 27 267" OR

Siaten OR Somnosan OR Zileze OR Zimoclone OR "Zopi Puren" OR Zopicalm OR Zotepine OR Zoleptil OR Nipolept OR Zuclopenthixol OR Zuclopentixol OR Clopixol OR Zuclopenthixole OR Acuphase).ti,ab.

3. (1 AND 2) NOT (Animals NOT (Humans NOT Animals)).sh.

Limit 3 to English

APPENDIX 2

Joanna Briggs Institute Critical appraisal checklists

Critical appraisal checklist for case control studies

1. Were the groups comparable other than presence of disease in cases or absence of disease in controls?
2. Were cases and controls matched appropriately?
3. Were the same criteria used for identification of cases and controls?
4. Was exposure measured in a standard, valid and reliable way?
5. Was exposure measured in the same way for cases and controls?
6. Were confounding factors identified?
7. Were strategies to deal with confounding factors stated?
8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?
9. Was the exposure period of interest long enough to be meaningful?
10. Was appropriate statistical analysis used?

Critical appraisal checklist for cohort studies

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?

4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?
10. Were strategies to address incomplete follow up utilized?
11. Was appropriate statistical analysis used?

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