

Calcium channel blockers for bipolar disorder:
a systematic review and meta-analysis
(Protocol)

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Background

Bipolar disorder is a chronic, recurrent affective disorder in which there are mood swings between elevation and depression that are not caused by medication or physical comorbidities (Phillips and Kupfer 2013). The lifetime prevalence rate for bipolar disorder is approximately 1% in the general public; intriguingly, prevalence rates of bipolar disorder remain relatively constant between countries despite more widely varying rates of major depression (Merikangas 2011). Whilst the aetiopathogenesis of bipolar disorder has not been fully elucidated, there is clearly a strong genetic component (Craddock and Sklar 2013). Mood episodes normally start in the third decade of life and so bipolar disorder causes severe social distress; indeed, it accounted for more than 12 million Disability-Adjusted Life Years globally in 2010 alone (Murray 2012). Needless to say, such disability poses significant economic costs (Gonzalez-Pinto, Dardennes et al. 2010).

Pharmacological treatment options are of great importance in bipolar disorder (Geddes and Miklowitz 2013). Treatment is invariably long term and often lifelong. Lithium remains a first line mood stabiliser in the preventative treatment of bipolar mood episodes (Geddes and Miklowitz 2013). However, approximately one third of patients do not respond adequately to lithium therapy. Various second generation antipsychotics and anticonvulsants were often trialled but with varying, not to say limited, efficacy (Geddes and Miklowitz 2013). There is therefore a pressing need for adjunctive and alternative agents - possibly with new and different mechanisms of action - to be developed for the treatment of bipolar disorder.

Calcium channel blockers may be a novel class of agents to be used in bipolar disorder. Calcium currents recorded in different cell types have varying physiological and pharmacological properties, and 'L-type' calcium currents found throughout the cardiovascular system are specifically inhibited by calcium channel blockers belonging to the dihydropyridine, phenylalkylamine and benzothiazepine drug classes (Catterall, Perez-Reyes et al. 2005). Molecular biology has revealed that the 'L-type' calcium currents are mediated by four voltage gated calcium channels, termed

CaV1.1-Cav1.4, and that calcium channel blockers belonging to these drug classes act at three separate, but allosterically coupled, receptor sites on the alpha-1 subunits of these channels (Catterall 2000, Dolphin 2009). Thus, calcium channel blockers belonging to these drug classes have long been used in the treatment of hypertension and other cardiovascular disorders (Chen 2010). However, there is also a theoretical basis for why 'L-type' calcium channel blockers of the dihydropyridine, phenylalkylamine and benzothiazepine classes might be efficacious in bipolar disorder. Of the four voltage gated calcium channels (CaV1.1-CaV1.4) comprising the 'L-type' calcium currents that are specifically inhibited by these drugs, CaV1.2 and CaV1.3 are also expressed in neurones (Calin-Jageman and Lee 2008, Zuccotti, Clementi et al. 2011) where they may play a role in neurotransmitter release, synaptic plasticity and action potential generation (Streissnig 2006) (Quiroz, Gray et al. 2008). Mitochondria play an important role in sequestering and releasing intracellular calcium (Quiroz, Gray et al. 2008) and magnetic resonance studies have shown dysfunctional mitochondrial physiology in patients with bipolar disorder (Stork and Renshaw 2005, Kato 2008).

Mood altering therapies have also been shown to interact with intracellular calcium physiology. In vitro studies have shown that antidepressants inhibit L-type calcium currents in rodent neurones (Choi 1992) whilst inositol-1,4,5-triphosphate receptors, which play a crucial role in the release of calcium from intracellular stores (Foskett, White et al. 2007), have reduced expression in rat brains following electroconvulsive therapy (ECT) (Kim 2001), are indirectly inhibited by lithium in vitro (Schlecker, Boehmerle et al. 2006) and produce an antidepressant phenotype in mice following pharmacologic or protein knockdown (Galeotti, Vivoli et al. 2008). Further evidence suggesting a role for voltage gated calcium channels in the aetiopathogenesis of bipolar disorder comes from genome-wide association studies (GWAS) which have consistently reported the association of a common single nucleotide polymorphism (SNP) variation on the alpha1C subunit of the 'L-type' voltage gated calcium channel gene, CACNA1C (which encodes channel CaV1.2), with bipolar disorder (Ferreira, O'Donovan et al. 2008, Sklar, Smoller et al. 2008).

Notwithstanding a large theoretical basis for a putative role of calcium channel blockers in the treatment of bipolar disorder, the efficacy of the 'L-type' calcium channel blockers in the treatment of bipolar disorder has not been conclusively demonstrated in high quality, controlled clinical trials. The majority of positive studies have supported the efficacy of verapamil as either monotherapy or add-on therapy in the treatment of acute mania but were hindered by small sample sizes or lacked one or more features such as being controlled, randomised or blinded (Dubovsky 1986); (Mallinger 2008). A systematic review on this question found only one randomised, controlled trial which met their inclusion criteria (Yildiz, Vieta et al. 2011). Similar quality case series or open studies have supported the efficacy of nimodipine and nifedipine in mania (Snedkova et al. 1996, Yingling et al. 2002), diltiazem in reducing relapse of both mania and depression (Silverstone 2000) and isradipine as add-on therapy in the treatment of bipolar depression (Ostacher, Iosifescu et al. 2014). Calcium channel blockers are associated with several side effects including dizziness, headaches, flushing, palpitations, peripheral oedema, cardiac conduction disturbances, nausea, constipation, fatigue, rashes and reflex tachycardia (Russell et al. 1988, Dustan et al. 1989). In view of the conflicting evidence and the lack of a clear cut summary, the aim of this systematic review is to investigate efficacy and tolerability of calcium channel blockers in bipolar disorder. This is especially important considering potential drug interactions between lithium and verapamil (Chandragiri, Pasol et al. 1998) and the increased cardiovascular risk in the bipolar disorder population (Fiedorowicz, Jancic et al. 2014).

Objectives

1. To assess the efficacy of calcium channel blockers in:
 - a) attenuating acute manic/mixed episodes
 - b) attenuating depressive episodes
 - c) preventing relapse of mood episodes.

2. To assess the acceptability of calcium channel blockers in comparison with placebo or active treatment, in terms of dropout rate.
3. To assess the adverse effects of calcium channel blockers in comparison with placebo or active treatment.

Methods

Types of studies

All double-blind, randomised controlled trials will be included to assess efficacy and acceptability. For consideration of adverse effects, nonrandomised evidence will also be summarised. For trials that have a crossover design, only results from the first period prior to crossover will be considered. Cluster randomised trials will be excluded.

Types of participants

Patients of any age, of both sexes, of any ethnicity, based in any clinical setting, with a primary diagnosis of bipolar disorder will be included. Only studies adopting any standardised diagnostic criteria from the International Classification of Diseases (ICD) or the Diagnostic and Statistical Manual of Mental Disorders (DSM) to define patients suffering from bipolar disorder will be included. We will exclude studies which define bipolar disorder as scoring above a certain cut-off on a screening questionnaire.

We do not propose to introduce age restrictions as there appears to be relatively little literature into the use of calcium channel blockers in treating bipolar disorder and we feel that an inclusive approach will yield a more clinically valuable review. All subtypes of bipolar disorder (rapid cycling, type I, type II, not otherwise specified) will be included. No restrictions on clinician setting (e.g. primary or secondary care) will be applied. Patients will be excluded who have a concurrent primary diagnosis of an Axis I disorder or a serious concomitant medical illness.

Types of intervention

Experimental intervention

Calcium channel blocker therapy in any preparation, dose, frequency, route of delivery or delivery setting will be included. Trials in which calcium channel blocker therapy is 'added-on' to pre-existing treatments (e.g. lithium) will be included if the pre-existing treatments are evenly distributed in both the experimental and comparator intervention arms of the study. A sensitivity analysis will then be performed to investigate if co-treatment is responsible for altering the efficacy of calcium channel blockers in treating bipolar disorder.

This review will only consider 'L-type' calcium channel blockers of the dihydropyridine, phenylalkylamine or benzothiazepine classes, which include the following:

- 1) Dihydropyridines: amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, cilnidipine, clevidipine, efonidipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nocardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, pranidipine, ryodipine, trimetazidine
- 2) Phenylalkylamines: anipamil, devapamil, falipamil, gallopamil, tiapamil, verapamil
- 3) Benzothiazepines: clentiazem, diltiazem

Drugs not listed here which are found to be dihydropyridine, phenylalkylamine or benzothiazepine calcium channel blockers will also be considered. Trials which allow rescue medications (e.g. short-term use of hypnotics) will be included as long as these medications are equally distributed among the randomised intervention and comparator arms.

Comparator intervention

Placebo or any other active pharmacological treatment (any preparation, dose, frequency, route of delivery or delivery setting).

Types of outcome measures

Primary outcomes

1. Efficacy of calcium channel blockers in the treatment of acute mood episodes in bipolar disorder, as follows:
 - (a) Hospital admission during the study period;
 - (b) Length of hospital admission;
 - (c) Time to cessation of additional treatment for manic/depressive symptoms;
 - (d) Changes on validated manic/depressive symptom rating scales from baseline;
 - (e) Changes on validated psychotic symptom rating scales from baseline;
 - (f) Response to treatment, defined as showing an improvement of at least 50% on any validated manic/depressive rating scale
2. Efficacy of calcium channel blockers in the long term treatment of bipolar disorder:
 - (a) Time to recurrence of any mood episodes;
 - (b) Number of recurrences of any mood episodes during the trial period.
 - (c) Number of recurrences of manic episodes during the trial period
 - (d) Number of recurrences of mixed episodes during the trial period
 - (e) Number of recurrences of depressive episodes during the trial period.

Recurrence will be defined either as (i) study withdrawal due to recurrence of any mood episode, (ii) admission to hospital (time to next admission and number of admissions during trial period), or (iii) institution of additional treatment for any mood episode and time to institution.

Secondary outcomes

2. Acceptability of calcium channel blocker treatment:
 - (a) Participants dropping out of the treatment during the study period

- (b) Participants dropping out of the treatment during the study period due to inefficacy
- (c) Participants dropping out of the treatment during the study period due to adverse events

3. Adverse events:

- (a) Participants experiencing at least one troublesome side effect of any nature
- (b) Participants experiencing each of the following specific side effects:

- Dizziness
- Headaches
- Flushing
- Palpitations
- Peripheral oedema
- Cardiac conduction disturbances
- Nausea
- Constipation
- Fatigue
- Rashes
- Reflex tachycardia

In order not to miss any relatively rare or unexpected yet important adverse events, in the data extraction phase we will collect all side effects data reported in the included studies and discuss ways to summarise them post hoc.

Search methods for identification of studies

Electronic searches

Appropriate terms for bipolar disorder (bipolar disorder or bipolar depression or manic depression) and calcium channel blockers (dihydropyridine, phenylalkylamine, benzothiazepine, amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, cilnidipine, clevidipine, efonidipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine,

nisoldipine, nitrendipine, pranidipine, ryodipine, trimetazidine, anipamil, devapamil, falipamil, gallopamil, tiapamil, verapamil, clentiazem, diltiazem) will be searched on the following electronic databases:

- The Cochrane Library
- MEDLINE
- EMBASE
- PsycINFO

International trial registries will be searched for unpublished research:

- clinicaltrials.gov
- The WHO registry for randomised controlled trials (<http://www.who.int/ictrp/en/>)

There will be no restrictions on date, language or publication status applied to the searches.

Searching other resources

Appropriate journals and conference proceedings relating to bipolar disorder will be hand-searched. Experts in this field will be asked if they know of any additional studies which meet the inclusion criteria of this systematic review. Reference lists of all included studies, relevant papers, previous systematic reviews and major textbooks of affective disorder written in English will be checked for published reports and citations of unpublished research.

Data collection and analysis

Selection of studies

Two review authors (JS, KS, PP, MJA) will independently check the titles and abstracts of all of the studies generated by the above search strategies to decide if they meet the inclusion criteria. All of the studies rated as possible candidates for inclusion by either of the two review authors will be added to the preliminary list, and their full text articles will be retrieved. The two authors will then assess all of the full text articles in this preliminary list to see if they still meet the inclusion criteria. If

the authors disagree, the final decision will be made by consensus with the involvement of another review author (AC or JG). Duplicate publications will be excluded.

Data extraction and management

Two review authors (JS, KS, PP, MJA) will independently extract data from the included studies. Any disagreement will be discussed, and decisions documented. If necessary, we will contact authors of studies for clarification and original data not included in published papers. The following data will be extracted from all studies meeting the inclusion criteria:

- Study characteristics (blinding, randomisation, sponsorship, crossover/parallel group design)
- Participant characteristics (age, sex, diagnosis, ethnicity, study setting, primary diagnosis according to DSM or ICD classification, comorbidity, illness severity, treatment history for the index episode)
- Intervention details (intervention arm treatment, comparator arm treatment, mean dosage, mean frequency of administration, drug preparation, route of administration, duration of therapy, co-intervention if any)
- Outcome measures of interest in terms of efficacy, tolerability and adverse events

Assessment of risk of bias in included studies

Two review authors (JS, KS, PP, MJA) will independently assess trial quality using the Cochrane risk of bias tool (Higgins 2011). The following factors will be assessed:

- sequence generation
- allocation concealment
- blinding
- incomplete outcome data
- selective reporting and other potential sources of bias.

Each item will be rated as high, low or unclear risk of bias, and a justification from the study report will be supplied to support the judgement as appropriate. If the authors disagree, the final decision will be made by consensus with a third review author.

Measures of treatment effect

Dichotomous data

For dichotomous, or event-like, data, the risk ratio (RR) will be calculated with its 95% confidence interval (CI). For statistically significant results, we will calculate the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH) as the inverse of the risk difference.

Continuous data

For continuous data, mean differences (MDs) or standardised mean differences (SMDs) will be calculated with 95% CIs. MDs will be used when the same scale is used to measure an outcome; SMDs will be employed when different scales are used to measure the same outcome.

Continuous data on clinical outcomes often are not normally distributed, and skewed data will be presented descriptively. If papers report a mean and a standard deviation (SD), as well as an absolute minimum possible value for the outcome, we will divide the mean by the SD. If this value is less than two, then we will conclude that some indication of skewness is present. If the value is less than one (i.e. the SD is bigger than the mean), then skewness will almost certainly be present. If papers do not report the skewness and simply report means, SDs and sample sizes, these numbers will be used. Because these data may not have been properly analysed and can be misleading, analyses will be conducted with and without these studies. If the data are log-transformed for analysis, and the geometric means reported, skewness will be reduced. This is the recommended method for analysis of skewed data (Higgins 2011).

Studies with multiple treatment groups

For a particular multi-arm study, the intervention groups of relevance to a systematic review are all those that could be included in a pair-wise comparison of intervention groups that, if investigated alone, would meet the criteria for inclusion of studies in the review. Each meta-analysis addresses only a single pair-wise comparison, so we will first consider whether a study of each possible pair-wise comparison of interventions in the study is eligible for the meta-analysis. Then, several possible

approaches to including a study with multiple intervention groups could be used in a particular meta-analysis (Higgins 2011).

For binary outcomes, we will combine all relevant experimental intervention groups of the study into a single experimental group, and combine all relevant control intervention groups into a single control group. For continuous outcomes, we will combine means and standard deviations using methods described in Chapter 7 of the Cochrane Handbook for Systematic Review of Interventions.

Dealing with missing data

Binary outcomes will be calculated on a strict intention-to-treat (ITT) basis: Dropouts will be included in this analysis. When data are missing and the method of “last observation carried forward” (LOCF) has been used to do an ITT analysis, then the LOCF data will be used. When standard deviations (SDs) are missing, we will present data descriptively. When SDs are not reported, we will ask authors to supply the data. When only the standard error (SE) or t-statistics or the P value is reported, we will calculate SDs in accordance with Altman (1996).

Assessment of heterogeneity

Heterogeneity between studies will be investigated by the I^2 statistic (Higgins 2003) (I^2 equal to or greater than 50% will be considered indicative of heterogeneity) and by visual inspection of the forest plots. Given that the value of I^2 depends on the sample size of the included studies, the magnitude and direction of effects and the strength of evidence for heterogeneity, we will use arbitrary threshold to perform a preliminary evaluation. If the I^2 value is below 50% but the direction and magnitude of treatment effects are suggestive of important heterogeneity, we will investigate the potential sources of heterogeneity.

Assessment of reporting biases

Data from included studies will be entered into a funnel plot (trial effect against trial variance) for investigation of small-study effects (Sterne 2000). We plan to use the tests for funnel plot asymmetry only if at least 10 studies are included in the meta-analysis (Higgins 2011). Funnel plot asymmetry may be noted for many possible reasons, so if evidence of small-study effects are

identified, all possible reasons for funnel plot asymmetry, including publication bias, will be investigated.

Subgroup and sensitivity analyses

No subgroup analysis will be undertaken. We will carry out only one sensitivity analysis, excluding trials in which calcium channel blockers were used as 'add-on' therapy to another treatment to determine if co-prescription may affect the efficacy of the calcium channel blocker.

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