International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Psychiatric adverse events of calcium channel blockers – protocol for a systematic review and meta-analysis

INPLASY202480075
doi: 10.37766/inplasy2024.8.0075
Received: 15 August 2024
Published: 15 August 2024

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - R. Kreutz reports modest honoraria for consultancy, lectures, and support for research from Bayer Pharma AG, CinCor Pharma, Merck, Menarini Group, ProMed, PolPharma, Servier, and Tecnimede Group outside the submitted work. The other authors report no conflicts.

INPLASY registration number: INPLASY202480075

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 August 2024 and was last updated on 15 August 2024.

INTRODUCTION

Review question / Objective Calcium channel blockers (CCBs) are well-established in the treatment of cardiovascular disorders, primarily for their effects on the heart and blood vessels. However, the role of calcium channels extends beyond the cardiovascular system, with significant expression in brain tissue. This raises an important question: do CCBs influence brain functions, particularly mental health?
This systematic review and meta-analysis aims to investigate the occurrence of different types of psychiatric adverse events (PAEs) and the rates of withdrawal due to PAEs during CCB therapy in double-blind randomized controlled trials (RCTs). Specifically, the review seeks to determine which PAEs are common during therapy with CCBs and whether CCBs differ from placebo or active comparators in the frequency of PAEs / rates of withdrawal for PAE.
Given the limited and often conflicting evidence regarding the mental health effects of CCBs, this study is exploratory in nature.

Rationale This study is a follow-up to our previously published study on psychiatric adverse events during beta-blocker therapy. While exploratory, it closely follows the design of the previous beta-blocker project to maintain consistency and allow for direct comparison of findings. Any minor deviations in study design are explicitly justified, with clear rationales provided.

Condition being studied Psychiatric adverse events (PAE) and related symptoms such as depression, anorexia, insomnia, and anxiety in patients receiving calcium channel blockers. All cardiovascular or non-cardiovascular indications of

calcium channel blockers are allowed regardless of therapeutic efficacy, except for use in children, psychiatric patients, or healthy subjects.

METHODS

Search strategy Electronic searches for English or German articles were performed in PubMed, Embase, and Web of Science, spanning from their respective inception to August 1st, 2024. The search algorithm is shown below. References from relevant studies were scanned for additional literature. Unpublished data on PAE were sought by consulting through clinicaltrials.gov and the Food and Drug Administration (FDA) drug approval packages for all CCBs. Finally, in case of missing or incomplete adverse event reports in otherwise eligible recent studies, data was requested from the corresponding authors.

For database search we use the following algorithm:

(Verapamil OR Nifedipine OR Diltiazem OR ("Calcium channel blocker") OR ("Calcium antagonist") OR Amlodipine OR Nimodipine OR Nicardipine OR Nitrendipine OR Isradipine OR Felodipine OR ("Calcium channel antagonist") OR Gallopamil OR Nisoldipine OR Lacidipine OR Levamlodipine OR Aranidipine OR Pranidipine OR Barnidipine OR Clevidipine OR Efonidipine OR Fendiline OR Azelnidipine OR Cilnidipine OR Manidipine OR Lercanidipine OR Nilvadipine OR Benidipine) AND (random* OR (double AND (blind OR dummy) OR placebo)).

Participant or population The population for this systematic review includes human adolescent or adult patients who have been treated with calcium channel blockers (CCBs) for non-psychiatric conditions, where CCB monotherapy is used, allowing for back-up, background, and rescue medication. Exclusion criteria comprise pediatric populations, psychiatric populations, healthy subjects, and non-human populations.

Intervention The intervention under review is the use of systemic calcium channel blockers as monotherapy for a minimum duration of 14 days. Trials that do not include a CCB monotherapy treatment arm, those involving only CCB combination therapy, or those where CCBs are used solely as background medication will be excluded.

Comparator The comparator for this review includes any pharmacological treatment, with no further restrictions, including placebo and any active treatments.

Study designs to be included The study design for inclusion consists of double-blind randomized controlled trials (RCTs) with a parallel-arm design, featuring at least one CCB monotherapy treatment arm. Excluded study types include single-blind or open-label studies, cross-over studies, and non-interventional studies.

Eligibility criteria In addition to the specified criteria for population, intervention, comparator, and study design (see above), studies must report at least one psychiatric adverse event (PAE) with the frequency specified to be included. Studies that do not report PAEs or that report PAEs without specifying the frequency will be excluded.

Information sources The information sources for this systematic review include searches conducted in PubMed (MEDLINE), Embase, Web of Science, ClinicalTrials.gov, and FDA drug approval packages. Additional studies were identified by reviewing the references of articles found in the primary search. If data or information was missing in otherwise eligible recent studies, we contacted the authors for further information.

Main outcome(s) The main outcome of interest is the occurrence of psychiatric adverse events (PAEs) during calcium channel blocker therapy, as reported in the included studies. For the meta-analysis, odds ratios were calculated for each symptom reported in five or more comparable double-blind, parallel-arm RCTs. Separate analyses were conducted for different classes of calcium channel blockers. The adverse event “edema” serves as a positive control. In our previous study on beta-blockers, “fatigue” was used as a positive control but this symptom is not usually associated with CCBs. Measures of effect are odds ratios with 95% confidence intervals. Odds ratios are preferred over other statistical measures, such as absolute and relative risk or risk ratios, due to several advantages when analyzing adverse event data. One key advantage is their ability to handle situations where the event of interest is rare, providing a more reliable approximation of risk in cases with low event rates. Additionally, in meta-analyses, odds ratios offer consistency across studies with different baseline risks, remaining relatively constant despite variations in baseline risk, which facilitates the combination of results from diverse studies.

Additional outcome(s) An additional outcome of interest is the rate of withdrawals due to

psychiatric adverse events. The adverse event "edema" serves as a positive control. Measures of effect are expressed as odds ratios with 95% confidence intervals. See above for the rationale of choosing odds ratios.

Data management Titles and/or abstracts of studies retrieved using the search strategy, as well as those from additional sources (e.g., references), were independently screened by two review authors to identify studies that potentially meet the inclusion criteria outlined above. The full text of these potentially eligible studies was then retrieved and independently assessed for eligibility by two review team members (MAF and TGR). Any disagreements regarding the eligibility of particular studies were resolved through discussion. Data were extracted from the included studies using a standardized, pre-piloted form to ensure consistency in assessing study quality and synthesizing evidence. Extracted information included details such as study sponsorship, study setting, study population, participant demographics and baseline characteristics, details of the intervention (calcium channel blocker name and dosage), control conditions (placebo or other treatments), study methodology (e.g., intervention, blinding), and adverse events (including the occurrence of events and withdrawals due to events). Two review authors (MAF, TGR) independently extracted the data, with discrepancies identified and resolved through discussion. Missing data were requested from the authors of recent trials.

Quality assessment / Risk of bias analysis Risk of bias for studies qualifying for meta-analysis was assessed using the Cochrane Risk of Bias 2 tool (RoB 2). Two reviewers (MAF, YK) independently conducted the assessments, with any discrepancies resolved through discussion with a third reviewer (TGR). Additionally, a self-designed instrument was employed to assess the quality of the adverse event (AE) measurement. Publication bias was evaluated using visual inspection of funnel plots, provided that there are at least 10 contributing studies.

Strategy of data synthesis If the eligible studies were sufficiently homogeneous, specifically those involving the same calcium channel blocker class and comparator class, and if at least five studies reported frequencies of a particular adverse event (AE) or AEs leading to study dropout, a quantitative synthesis was conducted. Meta-analytical calculations were performed using Review Manager 5.4, with results expressed as odds ratios with 95% confidence intervals and p-values. A random-effects model was employed to account for variability among studies, and heterogeneity was assessed using I^2 statistics.

Subgroup analysis Subgroup analyses were conducted to explore possible sources of heterogeneity, largely mirroring those employed in our previous study on beta-blockers, with two exceptions noted at the end of this paragraph. For placebo-controlled trials, we explored the impact of lipophilicity (low/high), the indication for CCB therapy (hypertension, other cardiovascular diseases, other indications), and industry sponsorship (presence or absence). For active-controlled trials, subgroup analyses were performed based on industry sponsorship and study incentive (CCB as the target drug vs. CCB as the comparator drug). The following deviations were made compared to our previous study on beta blockers: (1) The impact of intrinsic sympathomimetic activity was not investigated, as this property does not apply to CCBs. (2) Lipophilicity was analyzed in two ways: based on published logP values and using a previously established classification of CCBs as either brain-penetrating or non-brain-penetrating.

Sensitivity analysis We conducted eight sensitivity analyses to assess the robustness of our findings, two of which are novel to this study (#7 and #8) and were not employed in our previous project on beta-blockers. These analyses include:
1. Selective Inclusion of Studies Using Structured Adverse Event Measurement: Only studies that measure the frequencies of adverse events (AEs) using a structured approach, such as a checklist or direct questioning, were included to ensure systematic assessment.
2. Excluding the Two Studies with the Highest Weight: This analysis was conducted to evaluate the impact of the most influential studies on the overall results.
3. Restricting the Analysis to Hypertensive Patients: This analysis determined if the results were consistent across the specific patient group of hypertensive individuals.
4. Excluding Studies with High or Unclear Risk of Bias: Studies identified as having a high or unclear risk of bias in at least one category according to the RoB 2 tool were excluded to ensure that the findings were not skewed by methodological concerns.
5. Excluding Studies with a Duration of Fewer Than Eight Weeks: This analysis assessed the impact of study length on the outcomes by excluding shorter studies.
6. Excluding Studies Involving Patients on Backup Medication: To ensure that the results were not

confounded by additional treatments, studies involving patients on backup medication were excluded.
7. Restriction to Studies on Cardiovascular Indications: This sensitivity analysis focused on isolating the effects of CCBs in cardiovascular conditions, as extracted studies included both cardiovascular and neurological conditions. Cardiovascular indications are where CCBs have established therapeutic efficacy, and improvements in cardiovascular health may indirectly benefit mental health. In contrast, neurological conditions like Alzheimer's and Parkinson's disease, which may involve higher vulnerability to drug-induced psychiatric symptoms due to neurodegeneration and a disturbed blood-brain barrier, were excluded. Given that CCBs are primarily relevant for cardiovascular conditions, a sensitivity analysis, rather than a subgroup analysis, was chosen to isolate this effect.
8. Restriction to Data from Published Studies: This sensitivity analysis ensured that only peer-reviewed data contributed to the results, enhancing the reliability of the findings.

Language restriction Only articles written in German or English were considered eligible.

Country(ies) involved This study was carried out at Berlin, Germany.

Other relevant information None

Keywords Calcium channel blockers; psychiatric adverse events; dihydropyridines, non-dihydropyridines.

Dissemination plans The results of this systematic review and meta-analysis will be published in a peer-reviewed journal. Following the publication of the main findings, MAF will utilize his contribution to this study to write an inaugural dissertation.

Contributions of each author

Author 1 - Marc-Alexander Fürtig - Co-conception of the study, literature and data search, data extraction and synthesis, quality and risk of bias assessment, data analysis, interpretation and visualization, draft of the manuscript.
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