

Peer Review

Review of: "L-Type Calcium Channel Blockers, Extrapyramidal Symptoms, and Delirium: A Systematic Review of Case Reports"

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The study presented by Venkata Vamshi Krishna Dondapati and collaborators investigates the potential central effects, such as extrapyramidal symptoms (EPS), of several calcium channel blockers (CCBs).

Positive comments:

- The abstract is clear and efficiently summarizes the methodology used and the findings.
- The introduction is concise and clear.
- The methodology is well-structured, and the PRISMA approach clearly shows no bias in selecting studies.
- The results are well described, and the PRISMA flowchart helps follow the rationale for the study selection and brings clarity to the selection criteria. Table 1 also helps categorize the patients. Tables 2 and 3 correctly summarize the patients and cases analyzed.
- The discussion is well-structured and navigates well across the state of the art and the collected results from the study.
- The limitations subsection is a plus.

Suggested improvements:

- I would try to rephrase the conclusions in the abstract since the use of delirium, EPS, and psychosis may look interchangeable to some readers, but they are not.
- I may not have found it, but it was not mentioned if patients historically suffered from any central disorder.

- Patients in all studies had multiple medications that could overestimate the effect of CCBs.
- The amount of data is reasonably low, but this does not mean that the study could not benefit from a statistical analysis.
- Although Table 2, entry 5 (Kaur U. 2018) claims that amlodipine crosses the BBB, it is not clearly established that it does so. The same applies to any other case regarding amlodipine. Amlodipine is considered a low-penetrant drug, and repeated exposure studies have not been performed in order to assess its long-term BBB penetration characteristics. One may assume that peripheral actions of amlodipine might lead to central effects, but without further investigations, the most plausible mechanism for a drug to act on the brain is to cross the BBB. On the other hand, it is well known that alterations of the BBB occur as part of the healthy aging process. These alterations may drive traditionally considered non-penetrant drugs to act on the brain and cause some of the symptoms described in the cases analyzed in this study. I would suggest the authors comment on that.
- The limitations section has clearly stated the fact that the analyzed studies are very old but could also benefit from a brief discussion about the advancement of treatments over the years.

In general, the article is well-structured, organized, and concise. The study may benefit from a statistical analysis of the collected data. Moreover, it might be worth trying to analyze the possible influence of other medications and the whole history of patients.

This work may serve as a reference for physicians to take into consideration the possible central side effects of some CCBs in the elderly population, although more investigations and studies are needed to reach consistent and strong evidence and conclusions.

Declarations

Potential competing interests: No potential competing interests to declare.