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Letter to the Editor

Lithium pharmacogenetics

To the Editor,

Pagani et al. (2019) have recently performed a systematic critical appraisal of the literature on genetic determinants of lithium response and tolerability. We commend the authors for their effort in summarizing the ponderous existing evidence on lithium pharmacogenetics/genomics, which has been the object of previous narrative reviews (Pisanu et al., 2016; Papiol et al., 2018). However, some methodological considerations should be made. The main concern for this systematic review consists in the lack of clarity about the specific inclusion and exclusion criteria applied for the selection of studies. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) diagram appears incomplete and incongruent in some parts compared to the criteria reported in the text. Illustrative of these incongruences is the statement made by the authors that articles were searched in Medline and Embase. However, the diagram reports only articles identified through Medline. Furthermore, the exclusion criteria applied at each stage of the systematic search should be described. The analytical pipeline is further confused by the extremely low number of articles included in the systematic review ($n = 37$) compared to the vast literature available in the field. This seems particularly inconsistent given that the process to include these 37 articles has not been described in sufficient detail. In addition, the authors state that 258 articles were identified as potentially eligible, but that only 55 were "retrieved". The latter term does not clarify whether the authors included these papers according to their *a priori* specific selection criteria, or if they simply included those papers they were able to access. A similar inconsistency is evident for the criteria applied to narrow this number down to 37 articles. We believe that these inaccuracies led to unexpected results. For instance, the synthesis of the literature on GWAS studies fails to quote the first GWAS performed in BD patients characterized for a response to long-term maintenance treatment with lithium (Squassina et al., 2011). The same applies to candidate gene studies. A great number of relevant papers published in the last twenty years were not included in the systematic review with no apparent reason, provided, again, that our interpretation of the scant selection criteria is correct. As a further note, and possibly a relevant limitation to mention, this systematic review did not address the literature about gene expression changes due to lithium treatment and/or their eventual correlation with a clinical response. Indeed, the analysis of lithium transcriptomic effects is a vast and rapidly growing field, as pointed out by other recent non-systematic reviews (Bellivier and Marie-Clair, 2018). Finally, while the article by Pagani and colleagues aims to assess the evidence on the role of genetic determinants in modulating the risk of side effects during lithium treatemnt, it failed to include studies exploring the role of genetic determinants in modulating lithium tolerability.

In conclusion, systematic reviews are powerful tools requiring accurate and transparent design of the protocol to permit reproducibility of findings. Given the potential implications for future research, we should remain vigilant about proper conduction of this relevant type of study.

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