BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12461

Letter to the Editors

Critical assessment of the systematic review on hospitalization resulting from medicine related problems

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Medicine related problems resulting in hospitalizations constitute an important public health problem that should influence prevention strategies defined by healthcare decision makers. Systematic reviews are useful to provide evidence on the magnitude of this problem. Al Hamid *et al*. [1] are to be congratulated for the relevance of their research. However, several concerns arise that may hinder the conclusions of their study.

The authors applied two exclusion criteria that may limit the external validity of their study. Although they declared in the methods section that studies were eligible when having at least an abstract written in English, ultimately they excluded articles written in any other language. In addition, they only considered studies published after 2000 without providing any reasons for that time limit. We could identify 21 studies published before 2000 and 16 studies published in non-English languages, that could be included in this systematic review.

Apart from these limitations, this review does not fully comply with the Prisma statement [2] and AMSTAR instrument [3], which may also affect its internal validity and reliability. We could not replicate the studies selection process for two reasons. Al Hamid *et al*. [1] retrieved 1950 articles, including duplicated records, from 14 databases. However, using the strategy provided and limiting the search until May 2013, we could only retrieve 2146 articles in Pubmed. Additionally, Prisma recommends providing the reasons of exclusion at each stage of the eligibility process, while AMSTAR requires the full list of excluded papers, both of them not included in the article or in supplementary materials.

But even more important, the authors did not perform an appropriate quality assessment of the included studies, and consequently they could not issue any conclusions according to their quality. Loney *et al*. [4] developed an instrument to assess the quality of studies measuring prevalence of a health problem. As Al Hamid *et al*. [1] have not reported if the included studies used any sampling method, selection bias cannot be excluded, which is highly relevant in cross-sectional studies. Information regarding whether randomization existed or not, and the response rate are crucial to determine the representativeness of the results.

The Loney instrument [4] also allows the identification of information bias derived from poor quality outcome measurements. In Al Hamid *et al*.'s study [1] two concerns may arise regarding this topic. Information about causality assessment within the studies was lacking. Some studies used only pharmacists to establish the association between hospitalization and medicines, while others also included physicians. Even more important is the muddled use of the main outcome variable. Although in the introduction the authors stated that medicine related problems (MRPs) comprise adverse drug reactions (ADRs), adverse drug events (ADEs), and medication errors, they divided the results into ADRs, ADEs and MRPs. This inconsistency reinforces the existence of a conceptual chaos around terms used in patient safety related to medication [5]. The lack of commonly accepted definitions is a major limitation when attempting to determine the prevalence of an event.

Additionally, the authors recognized a large heterogeneity of results preventing them to perform meta-analysis, although they did not use a robust subgroup analysis to manage it. The study presents only two subgroup analyses: One was based on the outcomes assessed, despite the conceptual confusion around them, as previously mentioned. The other subgroup analysis was based on the orientation of included studies (retrospective *vs*. prospective). Notwithstanding the latter, prevalence obtained ranged from 0.76 to 54.5% in ADRs, from 1.99 to 30.4 % in

ADEs and from 1 to 72 % in MRPs, even ignoring the confidence intervals of these distributions. The authors associated the higher prevalence in prospective studies with 'closer contact with the patient'. Study orientation could be a confounder of the other underlying variable, the data collection method. Retrospective studies usually evaluate medical records or databases, whereas prospective studies may evaluate these two sources of information but also patient interviews, which provide an actual closer contact with the patient. In addition, other heterogeneity causes were not considered with appropriate subgroup analyses. For instance, reported patients' average age in the included studies ranged from 41.92 to 81.8 years, duration ranged from 0.24 to 120 months and sample sizes ranged from 48 to 6 830 067 patients. Moreover, one of the most important variables to segment the studies, the average number of medicines per patient, was ignored.

We could obtain data to perform meta-analyses from 19 out of the 45 studies included in Al Hamid *et al*. study [1]. Specially, out of the 21 studies reported as investigating ADRs related hospitalizations, 17 contained enough data to perform a meta-analysis. From the 21 studies we identified published before 2000, three could be included in a meta-analysis, resulting in a total of 20 studies. A subgroup analysis by age produces event rates of 13% in elderly studies, 7.5% in adult/elderly and 2.3% in unrestricted age studies. Another relevant sub-group analysis could be the data collection system, resulting in event rates of 11.7% when patient interview existed and 5.9% when interviews were not used.

As a result of not having performed a subgroup analysis considering the quality of included studies or their heterogeneous characteristics, central tendency measures of prevalence reported by Al Hamid *et al*. [1], like median, may be misleading. This limitation could be overcome by analyzing the sources of heterogeneity and carrying out meta-analyses by subgroups, considering normality adjustment and adequate statistical methods and models.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work. Specifically none of the authors has anything to disclose.

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RECEIVED
16 March 2014

ACCEPTED
6 May 2014

ACCEPTED ARTICLE PUBLISHED ONLINE
9 July 2014

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