Journal of Clinical Epidemiology 101 (2018) 17–27

Journal of Clinical Epidemiology

REVIEW ARTICLE

Efficacy of antipsychotics in dementia depended on the definition of patients and outcomes: a meta-epidemiological study

C.H.W. Smeets[a,b], S.U. Zuidema[a], T.A. Hulshof[a], M. Smalbrugge[c], D.L. Gerritsen[b], R.T.C.M. Koopmans[b,d], H.J. Luijendijk[a,*]

[a]*Department of General Practice and Elderly Care Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*
[b]*Department of Primary and Community Care, Radboud University Medical Center, Radboud University Medical Center Alzheimer Center, Nijmegen, The Netherlands*
[c]*Department of General Practice and Elderly Care Medicine/EMGO + Institute for Health and Care Research, VU Medical Center, Amsterdam, The Netherlands*
[d]*Joachim en Anna, Center for Specialized Geriatric Care, Nijmegen, The Netherlands*

Accepted 14 May 2018; Published online 18 May 2018

Abstract

Objectives: Postulating that efficacy of antipsychotics for agitation and psychosis in dementia is best estimated in trials among patients with these symptoms and with symptom-specific outcomes, we investigated whether clinically broader definitions affected the pooled efficacy.

Study Design and Setting: Trials were searched in multiple databases and categorized according to patient population (agitated, psychotic, and mixed) and outcome scale (agitation, psychosis, and generic). Standardized mean differences with 95% confidence intervals were calculated for conventional and atypical antipsychotics separately.

Results: Thirty trials met our inclusion criteria. Conventional antipsychotics might have a small effect in agitated patients on agitation scales (−0.44, −0.88, 0.01) and in psychotic patients on psychosis scales (−0.31, −0.61, −0.02). There was no effect on generic scales. Efficacy of atypical antipsychotics was not established in agitated patients on agitation scales (−0.15, −0.43, 0.13) and in psychotic patients on psychosis scales (−0.11, −0.20, −0.03) but was small in mixed patients on agitation scales (−0.29, −0.40, −0.18).

Conclusion: Pooled efficacy of antipsychotics for agitation and psychosis in dementia is biased when based on trials that included patients without these target symptoms or on results measured with generic scales. This finding is important for reviewers and guideline developers who select trials for reviews.

Keywords: Dementia; Antipsychotics; Meta-analysis; Bias; Agitation; Psychosis

1. Introduction

Systematic reviews and guidelines are key information sources for clinicians who wish to practice evidence-based medicine. To ensure the validity of review results, reviewers usually adhere to internationally accepted methods, such as those described in the Cochrane Handbook and GRADE recommendations [1,2]. Both methods advise to define the research question in terms of the patients, intervention of interest, comparison intervention and outcome (PICO) a priori [3]. Subsequently, only those trials that meet this PICO should be included in the review.

While the definition of the intervention of interest and the comparison intervention seem straightforward, the patient population and outcome may deserve more attention. The Cochrane Handbook and GRADE recommendations emphasize that they need to be determined meticulously. Patients should be defined ''sufficiently broad'' but ''sufficiently narrow'' to include the most important characteristics [1]. If efficacy is pooled across different patient populations in which it cannot be expected to be similar, there is a risk that results of a review are not meaningful

Funding: This research was financially supported by grants from the Dutch Medicines Evaluation Board (CBG) and the Dutch Association of Elderly Care Physicians (Verenso).

Conflicts of interest: None.

* Corresponding author. Department of General Practice and Elderly Care Medicine, University of Groningen, University Medical Center Groningen, Postbus 196, Groningen 9700 AD, The Netherlands. Tel.: +31 50 361 6720; fax: +31 50 363 2964.

E-mail address: h.j.luijendijk@umcg.nl (H.J. Luijendijk).

https://doi.org/10.1016/j.jclinepi.2018.05.004
0895-4356/

What is New?

Key findings

- Pooled efficacy of antipsychotics for agitation and psychosis in dementia is biased when trials that enrolled patients with a broader definition of neuropsychiatric symptoms are included and when broader outcome scales are interpreted.

What this adds to what was known?

- Efficacy of conventional antipsychotics for agitation and psychosis in dementia might have been underestimated in reviews among patients without these target symptoms.
- Efficacy of atypical antipsychotics on agitation might have been overestimated in reviews among patients without these target symptoms.

What is the implication and what should change now?

- Trial selection criteria in a review should reflect not just the disease but also the target symptom for the treatment of interest.

or even misleading [1,4]. With respect to defining the outcome, it is advised to focus on outcomes that are likely to be clinically relevant and to exclude those that are "trivial or meaningless" [1]. Pooled results based on irrelevant or intermediate outcomes might be deceptive and may be a reason to rate down the quality of evidence [1,4].

A problem with defining the patients and outcome appears to exist in reviews on the efficacy of antipsychotics for agitation and psychosis in dementia. Those reviews have included not only trials among patients with agitation or psychosis but also trials among patients with neuropsychiatric symptoms (NPSs) in general [5−8]. NPSs can consist not only of agitation and psychosis but also of depression, anxiety, night-time behavior, or appetite change. As a result, those reviews were based on patients who did not necessarily all have the target symptom agitation or psychosis. For example, they may have included also patients with only depression.

Furthermore, reviews on the efficacy of antipsychotics for agitation and psychosis in dementia have pooled results that were not exclusively based on agitation- and psychosis-specific outcome scales [5−8]. Results based on generic outcome scales such as the Neuropsychiatric Inventory (NPI) and behavioral pathology in Alzheimer's disease scale were included as well [9,10]. These scales cover not only agitation and psychosis but also other NPSs. Yet, a treatment effect established with a generic scale does not represent the effect on agitation or psychosis specifically and may reflect a change in any other symptom profile. Such a change could therefore be regarded as less important or indirect to start with.

Current guidelines are based on meta-analyses of trials among patients with any kind of NPSs and include treatment effects measured with generic outcome scales. These guidelines support the use of antipsychotic drugs for severe agitation and for psychosis in dementia [11−15]. Usually, they differentiate conventional and atypical antipsychotics for their pharmacological properties, presumed mechanisms of effect, and side effect profiles. Some guidelines recommend the atypical antipsychotic risperidone as a drug of first choice or alternatively the conventional antipsychotic haloperidol [11,13−15].

We postulate that the best estimate for efficacy of antipsychotics in patients with dementia and agitation, or psychosis, is assessed in patients with the target symptom (i.e., indication) and measured with a target-specific outcome scale. We investigated whether a broad definition of patients and outcome differs clinically from a target-specific definition, for the pooled efficacy of antipsychotics for agitation and psychosis in dementia.

The aim of this study was to assess the following:

- The efficacy of conventional and atypical antipsychotics measured in patients with dementia and agitation or psychosis and measured with agitation- or psychosis-specific outcome scales;
- The efficacy of antipsychotics in patients with dementia and any type of NPSs, measured with agitation- or psychosis-specific outcome scales; and
- The efficacy of antipsychotics in patients with dementia and agitation or psychosis, measured with generic outcome scales for NPSs.

2. Methods

2.1. Search

Two researchers (T.A.H. and H.J.L.) searched PubMed, Embase, CINAHL, and the Cochrane Library through August 2017 for reported trials. In addition, references of systematic reviews and meta-analyses were hand-searched for relevant trials. For unpublished trials, we searched 17 trial registration web sites and the databases of the Dutch Medicines Evaluation Board and the U.S. Food and Drug Administration. Search terms included individual generic drug names in the group N05A of the World Health Organization Anatomical Therapeutic Chemical classification, "dementia", and "trial" [16].

We screened title and abstracts of the hits, followed by the full-text review of potentially eligible studies. We included trials that met the following criteria according to two independent reviewers (C.H.W.S. and H.J.L.): (1) a randomized trial; (2) testing efficacy of oral antipsychotics against placebo; (3) in patients with Alzheimer's, vascular, and/or mixed dementia; and (4) who had agitation, psychosis, or NPSs in general. We used no restrictions with regard to duration, language, or publication date.