Maturitas 85 (2016) 56–63

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review article

Adverse drug reactions in elderly patients with cognitive disorders: A systematic review

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ARTICLE INFO

Article history:
Received 23 September 2015
Received in revised form
21 December 2015
Accepted 22 December 2015

Keywords:
Adverse drug reaction
Elderly
Cognitive impairment

ABSTRACT

Elderly subjects with cognitive disorders are at particularly high risk of adverse drug reactions (ADRs). The objectives of our systematic review were to describe the prevalence of ADRs in elderly patients with cognitive disorders, the different types of ADRs and the medications suspected of involvement; to describe whether the ADRs were preventable or not, and to identify risk factors for occurrence of ADRs in this population. A bibliographic search was performed in the following databases: PubMed, Embase, Google Scholar, Opengrey and Scopus. The search included all publications up to and including 4th February 2015, with no specific start date specified. Studies concerning ADRs in elderly patients with cognitive disorders or dementia were included. Two senior authors identified eligible studies and extracted data independently. In total, 113 studies were identified by the bibliographic search, of which six full-text articles were retained and analyzed. Prevalence of ADRs ranged from 4.8 to 37%. The main ADRs reported were neurological and psychological disorders, gastro-intestinal disorders, dermatological and allergic disorders, falls, renal and urinary disorders, cardiovascular disorders, metabolic disorders and electrolyte imbalance, and hemorrhagic events. The medications most commonly suspected of involvement in the ADRs were drugs affecting the nervous system, cardiovascular drugs, anticoagulants, and painkillers. Medical prescriptions should take into account the presence of Alzheimer's disease and related syndromes. Compliance should systematically be evaluated, and cognitive disorders need to be better recognized. Therapeutic education of patients and/or their caregiver is key to management of elderly patients with cognitive disorders.

Contents

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http://dx.doi.org/10.1016/j.maturitas.2015.12.013
0378-5122/

1. Introduction

Elderly patients with cognitive disorders are at particularly high risk of adverse drug reactions (ADRs) [1]. Indeed, age was long considered as a risk factor for ADRs [2]. However, elderly subjects represent a heterogeneous population, and the ageing process differs significantly between individuals. Age in itself is not a risk factor for ADRs, but rather, many factors, such as increased gastric pH, reduced cardiac output, reduced glomerular filtration rate, malnutrition, or variations in the sensitivity of renal, vascular or cerebral receptors, are all associated with aging. These processes can lead to changes in the pharmacokinetics and pharmacodynamics of drugs, thus contributing to the occurrence of ADRs [3]. It has been reported that the effect of age on the occurrence of ADRs is no longer significant after adjustment for polypharmacy or comorbidities [4,5]. Indeed, elderly subjects often suffer from numerous comorbidities that require polypharmacy [6] or increased length of hospital stay [7].

Dementia is one such comorbid condition. Elderly subjects with dementia syndrome generally receive specific treatment for Alzheimer's disease (AD), but also drugs aimed at managing symptoms that arise as dementia progresses, such as psychotropic drugs. Reduced blood flow to the brain and changes in permeability of the blood–brain barrier may concur to increase the duration of exposition of the cerebral tissue to psychotropic drug. This could at least partially account for the increased sensitivity of elderly subjects to the effects of psychotropic drug [8]. Thereby, these medications can cause ADRs.

Drug prescription is based on guidelines derived from clinical trial that have not included elderly subject with multiple comorbidities, as elderly subject with dementia syndrome. Data regarding drug safety from clinical trials alone are insufficient. In addition, ADRs are often under-reported to pharmacovigilance systems. Therefore, data from real-life usage of drugs are vital to evaluate the true risk-benefit ratio of drugs before prescribing them.

We performed a systematic review of the literature to describe the prevalence of ADRs in elderly subjects with cognitive disorders, the different types of ADRs and the suspected drugs involved, the preventable nature of the ADRs, and risk factors for the occurrence of ADRs.

2. Methods

2.1. Search strategy

A bibliographic search was performed in the following databases: PubMed, Embase, Google Scholar, Opengrey and Scopus. The search included all publications up to and including 4th February 2015, with no specific start date specified. There was no language restriction. The references of articles retained for analysis were also searched to identify any additional publications. The search strategy, on the article title, was as follows: ((*dementia* OR *cognitive impairment* OR *cognitively impaired* OR *demented* OR *Alzheimer*) AND (*adverse drug reaction* OR *adverse drug reactions* OR *adverse drug event OR adverse drug events* OR *iatrogenic* OR *pharmacovigilance* OR *side effect*)).

2.2. Data extraction

After eliminating duplicates, two senior authors (MD, NO) independently reviewed the titles and abstracts of all articles (previously rendered anonymous). In case of disagreement about whether or not to include an article, the case was discussed until consensus was reached, and the opinion of a third author (TT) was requested where necessary. Agreement between the two senior authors was assessed using the Kappa coefficient. After agreement, the full text of all articles designated for inclusion was obtained. Two senior authors (MD, LK) checked to ensure all articles met the criteria for inclusion in this analysis, and then extracted independently the data. Extracted data were: study design, characteristic of the study population (number of subject included, age, MMSE score, dementia or cognitive impairment definition criterion, number of medication, and place where ADR were recorded). Extracted data regarding ADR were: definition, prevalence of ADR and serious ADR, type, drug suspected of involvement in ADR, percentage of preventable ADR and identified risk factors. Data were extracted using data extraction form for non-randomized studies of Cochrane. Extracted data were presented in Section 3 as percentage and 95% confidence intervals for qualitative variables, and as mean and standard deviation for quantitative variables.

2.3. Study selection criteria

Studies were eligible for inclusion if they presented all the following criteria:

- Interventional or observational studies (while literature reviews, case series, case reports, article commentaries, letters to the editor and book chapters were excluded),
- Elderly patients with cognitive disorders or dementia syndrome,
- A measure of the prevalence of ADR (studies that assess the prevalence of ADR of a specific drug were excluded).

2.4. Quality assessment

The quality of included studies was assessed independently by two researchers (MD, LK) using the Newcastle-Ottawa scale (NOS) for cohort studies [9] and a modified version of Newcastle-Ottawa scale for cross-sectional studies [10]. NOS consists of three parameters of quality: selection, comparability, and outcome assessment. NOS assigns a maximum of four points (five points for cross-sectional studies) for selection, two points for comparability and three points for outcome. NOS scores of $\geq$7 were considered as high quality studies and of 5–6 as moderate quality [11]. Disagreement was resolved by joint review of the manuscript to reach consensus and the opinion of a third researcher (TT) was requested where necessary.