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Research report

The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis

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ABSTRACT

Background: Neuropsychiatric symptoms (NPS) are being increasingly recognized as common serious problems in Alzheimer's disease (AD). However, published data on the prevalence of NPS in persons with AD are conflicting. This meta-analysis aimed to estimate the prevalence of NPS in persons with AD.
Methods: Studies published from 1964 to September 30, 2014, were identified from PubMed and Embase database, reference lists and conference abstracts. We calculated prevalence rates and conducted meta-regression analysis with random-effects model, according to study characteristics, population demographics or condition information.
Results: We identified 48 eligible articles, which provided data for 12 NPS reported in Neuropsychiatric Inventory (NPI). The most frequent NPS was apathy, with an overall prevalence of 49% (95% CI 41–57%), followed by depression, aggression, anxiety and sleep disorder, the pooled prevalence estimates of which were 42% (95% CI 37–46%), 40% (95% CI 33–46%), 39% (95% CI 32–46%) and 39% (95% CI 30–47%), respectively. The less prevalent NPS were irritability (36%, 31–41%), appetite disorder (34%, 27–41%), aberrant motor behavior (32%, 25–38%), delusion (31%, 27–35%), disinhibition (17%, 12–21%) and hallucination (16%, 13–18%). Least common was euphoria, with an overall prevalence of 7% (95% CI 5–9%).
Limitations: Several aspects, such as the quality of included studies were not always optimal and there was significant heterogeneity of prevalence estimate across studies.
Conclusions: NPS were observed to be highly prevalent in AD patients. Disease duration, age, education level, population origin and the severity of cognitive impairment had influence on the prevalence of some NPS.

1. Introduction

Neuropsychiatric symptoms (NPS) are being increasingly recognized as core features of Alzheimer's disease (AD) and related dementias (Petrovic et al., 2007). In this article, we choose 12 neuropsychiatric symptoms reported in Neuropsychiatric Inventory (NPI) to study. It was demonstrated that NPS could be identified as different neuropsychiatric sub-syndromes in diverse studies (Aalten et al., 2007; Cheng et al., 2012). Aalten and colleagues reported the largest European database (EADC), identifying four different NPS sub-syndromes: hyperactivity (aggression, disinhibition, irritability, aberrant motor behavior and euphoria), psychosis (delusion, hallucination and sleep disorder), affective (depression and anxiety,) and apathy (apathy and appetite disorder) (Aalten et al., 2007). More than 80% demented patients exhibit at least one neuropsychiatric symptom, since the onset of cognitive impairment (Lyketsos et al., 2002). However, they are often under-recognized and improperly managed in persons with AD (Chow et al., 2002).

The occurrence of NPS in AD can accelerate disease progression and early institutionalization, and interfere with treatment effects and prognosis (Lyketsos et al., 2002; Steffens et al., 2005).

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Therefore, early and precise recognition of NPS in AD has become urgent as it can be effectively prevented and intervened (Wang et al., 2015). In addition, reliable data on the prevalence of NPS is essential to inform patients and caregivers, ascertain the overall burden of AD, and explore underlying mechanism. Published data on the prevalence rates of NPS in AD patients varied widely. These conflicting results may be attributed to heterogeneity in the study setting, population demographics, evaluation methods or the severity of cognitive impairment (Fuh, 2006; Mega et al., 1996; Teri et al., 1988). A systematic review and meta-analysis could help explain the variability in the existing literature and through pooling, produce more precise estimates of NPS prevalence in AD. The purpose of this systematic review was to investigate the prevalence of NPS in AD.

2. Methods

2.1. Search strategy

We followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria for systematic review and meta-analysis (Stroup et al., 2000). The search was executed in PubMed (1964–2014) and Embase (1981–2014) database, and references were exported and managed using EndNote X6. The key words used were: delusion OR hallucination OR apathy OR indifference OR depression OR aggression OR agitation OR anxiety OR euphoria OR elation OR disinhibition OR irritability OR aberrant motor behavior OR sleep disorder OR appetite disorder OR neuropsychiatric symptoms OR behavioral and psychological symptoms of dementia (BPSD) AND Alzheimer disease. The reference lists of suitable retrieved articles and proceedings from the past 3 years of relevant conferences were manually searched for additional studies. The final search was carried out on September 30, 2014.

2.2. Selection criteria

Published studies fulfilling the following inclusion criteria were included in the analysis: were original research; were cross-sectional or longitudinal design; were on patients with probable or possible AD consistent with the *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition* (DSM-IV) or the criteria of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA); reported a prevalence of NPS in AD or sufficient information to calculate an estimate; NPS were assessed by validated scale; sample size at least 50; published in English.

We also considered abstracts and unpublished studies, but excluded review articles, editorials, commentaries, hypothesis papers, letters without original data, meta-analyses and papers focused on young-onset AD (YOAD). Where there was more than one publication reported on the same population, we chose data from the most comprehensive report and, where equal, the most recent report. If there was disagreement between authors about the eligibility of studies or data extraction, the articles were discussed in further detail until consensus was reached.

2.3. Data extraction and quality assessment

After the initial assessment for eligibility, two reviewers extracted and reached agreement on data from included articles using a standardized template. From each selected study, we extracted the following data: study characteristics (author, publication year, sample size, setting), population demographics (percentage of female, age, education level, MMSE score), condition information (data sources, AD diagnostic criteria, method of NPS assessment) and reported prevalence or the information needed to calculate an estimate. If a publication involved longitudinal assessment, only the baseline prevalence was included.

The main quality criterion in the evaluation of the prevalence of NPS is using a validated and comprehensive instrument. In this study, only publications that had used Neuropsychiatric Inventory (NPI) or other general scales which assess more than one NPS domain were included in order to ensure high-quality assessment of NPS in the primary studies.

2.4. Statistical analysis

We computed the crude prevalence for each study. Pooled estimates of prevalence and 95% confidence interval (CI) were calculated using random-effects meta-analysis, more robust and appropriate when there was substantial heterogeneity in prevalence between studies. The prevalence of NPS and the total number of included patients for each study population were used as variables. Analyses of the heterogeneity of prevalence across studies were done with I^2 statistic ($I^2 \geq 75\%$ indicating high heterogeneity). Publication bias was investigated using the Egger's test, and where statistically significant bias was found, we used the trim and fill method to adjust for it (Duval and Tweedie, 2000; Egger et al., 1997).

Meta-regression was used to estimate the extent to which measured covariates (publication year, sample size, the method of NPS assessment, study setting, population origin, disease duration, the percentage of female, the mean MMSE score, mean age and mean education level of participants) could explain the observed heterogeneity in prevalence estimates across studies.

For all tests, $p < 0.05$ was deemed to be significant. Combined prevalence was calculated separately for every single NPS. All analyses were carried out using STATA statistical software package, version 12.0.

3. Results

3.1. Identification and description of studies

The literature search yielded a total of 20,424 citations: 13,388 from Embase and 7,036 from PubMed (a total of 16,384 after duplicates removed) (Fig. 1). After the initial screen, 412 studies met the criteria for full-text review, of which 370 were excluded (129 not original research, 85 not AD population, 96 no prevalence or

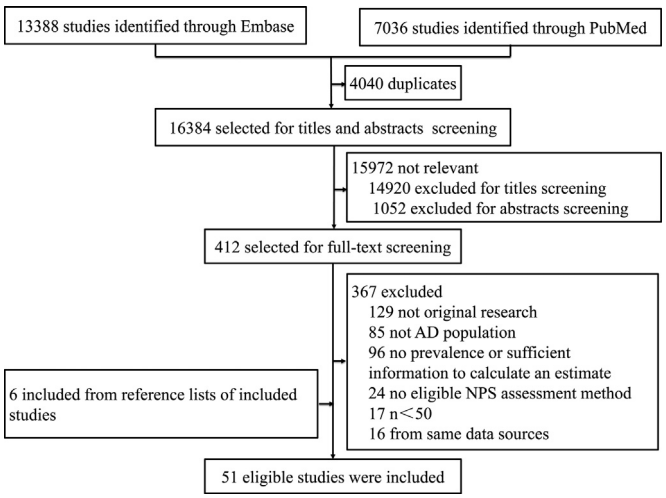

Fig. 1. Flowchart of studies included and excluded. AD=Alzheimer's Disease.