

The Efficacy of Antipsychotics in the treatment of Physical Aggressive behavior in Patients with Dementia in Nursing Homes

Nawzad S¹, Wiekpe Cahn¹ and Abdullah-Koolmees H*²

¹UMC Utrecht, Netherlands

²Division Laboratories, Pharmacy and Biomedical Genetics, UMC Utrecht, Netherlands

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***Corresponding author:** Abdullah-Koolmees H, Division Laboratories, Pharmacy and Biomedical Genetics, UMC Utrecht, Netherlands

Abstract

Patients with dementia often suffer from behavioral changes. A common behavioral change is acute physical aggressive behavior which is the most distressing change. This can lead to harm, which is especially problematic in nursing homes. Despite the serious safety concerns, antipsychotics are often prescribed to combat this problem. This article is aimed to review the evidence of the efficacy of utilizing antipsychotics in acutely treating physical aggressive behavior in patients with dementia in nursing homes. Therefore, a systematic literature search was performed. The results included a meta-analysis confirmed statistically significant reduction in physical aggression when risperidone was compared to placebo. On the other hand, a randomized controlled trial showed no change in physical aggressive behavior between quetiapine and placebo. More research is needed to fully investigate the benefits on physical aggressive behavior and safety concerns of all the antipsychotics in patients with dementia in nursing homes. .

Keywords: Dementia, Antipsychotics; Neuropsychiatric symptoms; Aggressive behavior and Cohen-Mansfield Agitation Inventory (CMAI) scale

Introduction

Patients with dementia often suffer from behavioral changes, referred to as neuropsychiatric symptoms (NPS) or behavioral and psychological symptoms of dementia (BPSD) [1]. Up to 90% of patients with dementia develop BPSD [2]. BPSD include uninhibited behavior, agitation, and aggression. BPSD are very distressing for patients. Acute physical aggression can even lead to self-harm and harm to others around them [3,4]. This is especially problematic in nursing homes and needs to be managed both diligently and expeditiously. Non-pharmacological interventions, which is first-line treatment, is not effective in managing these symptoms for every patient, their benefits are typically limited to milder severity of aggression. For many patients fail these interventions after initial success [4]. Therefore, a wide variety of pharmacotherapies are often prescribed off-label to combat this problem. There are currently no 'USA Food and Drug Administration' (FDA)-approved medications indicated for the treatment of aggression in patients with dementia. The European union, however, has only approved the antipsychotic risperidone for the treatment of persistent aggression in patients with moderate to severe Alzheimer's dementia [5]. Thus, there are no medications on

the market indicated to treat acute aggression in this patient population. Nevertheless, antipsychotics are often used for this indication. The FDA issued warnings in 2003 and 2005 regarding the use of antipsychotics in patients with dementia [2]. Post-marketing surveillance demonstrated serious adverse events associated with the use of antipsychotics, including increased mortality. Evidence from clinical trials demonstrated a 1.5 to 1.8-fold increased mortality [6,7]. Despite these safety concerns, antipsychotics are still being widely prescribed off-label. Recently, Zuidema et al. [4] published a practice guideline regarding the prescribing of antipsychotics to patients with dementia in nursing homes. This guideline is intended to further aid clinicians in the treatment process. However, it is not evidence-based. This article aims to review the evidence of the efficacy of utilizing antipsychotics in the acute treatment of non-psychotic-induced dementia-related physical aggressive behavior in patients with dementia in nursing homes.

Objective

To investigate the efficacy of antipsychotics in acutely treating physical aggressive behavior in patients with dementia in nursing homes.

Methods

A systematic literature search was performed on October 29th, 2018 in the following databases: Pubmed, Cochrane, and Embase. The targeted search was built with a ‘patient intervention comparison outcome’ (PICO)-model based on the following question: what is the efficacy of antipsychotics for the treatment of acute non-psychotic-induced aggressive behavior in patients with dementia in nursing homes? The population included patients in nursing homes with different forms of dementia and non-psychotic-induced acute aggressive behavior. The intervention was comparing antipsychotic to placebo. The outcome was efficacy such as a change in manifestation of aggressive behavior or a change in the frequency of aggressive behavior. Therefore, the search included the synonyms of dementia, aggressive behavior, and antipsychotics found in MESH/Emtree terms, supplementary concept title, and abstract. The labels languages (English), species (humans), and text availability (full text) were also added to the search criteria (see Appendix 1 for exact search terms). All search results were first manually checked based on relevance by reading the title and the abstract. Article types other than observational studies or randomized clinical trials (RCTs) that compared antipsychotics with placebo or meta-analysis investigating the efficacy of antipsychotic drugs were excluded considering RCTs and meta-analysis of RCTs as the ‘best evidence’ in the study hierarchy of therapeutic trials [8]. Additionally, articles were excluded if patients with other disease states were included (e.g., schizophrenia, Parkinson’s disease, psychosis, and bipolar

disease), utilized interventions other than antipsychotics (e.g. antidepressants), and contained outcomes other than efficacy (e.g. results with only safety data). These remaining articles were screened by the first author on November 4th by inclusion criteria and outcome results. Articles that included patients without the diagnosis of dementia according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) in nursing homes or articles that did not specifically address acute aggressive behavior and had no separate data on aggressive behavior were also excluded.

Results

Overall, the initial search yielded 248 articles. Only 104 articles remained after excluding article types other than observational studies or RCTs that compared antipsychotics with placebo or meta-analysis. After reading the titles and abstracts, 35 articles remained based on the patient’s disease states, utilized interventions, and outcomes. These articles were further full text screened based on their inclusion criteria (i.e. patients with dementia in nursing homes) and reported outcomes (i.e. data on physical aggressive behavior), narrowing the search results down to five articles (Appendix 2). In total, only five articles evaluated acute non-psychotic-induced aggressive behavior in patients with dementia that were residing in nursing homes and being treated with antipsychotics. One of these articles was a meta-analysis [9] that contained three RCTs [10-12], which were already a part of the final search results and were therefore excluded.

Table S1: Summary of Trial Design of the study conducted by Meehan et al. [15].

Objective	Patient selection	Trial design	Efficacy assessment
To investigate the efficacy of intramuscular injection of olanzapine in the treatment of agitation associated with dementia.	Patients (age > 55y) were hospitalized or nursing home residents. They had diagnoses of probable or possible AD, vascular dementia or both (mixed dementia) according to DSM-IV or NINCDS/ADRDA and documented clinical symptoms of agitation.	A randomized, multicenter, double-blind, placebo-controlled parallel study. Study Period began with initiation of preliminary evaluations for the first injection and continued for 24 h.	Change in CMAI physical-aggression score from the first dose to 2 h, and 24 h post first injection.

Abbreviations: AD: Alzheimer’s disease, BPSD: behavioral and psychological symptoms of dementia CMAI: Cohen-Mansfield agitation inventory. DSM-IV: Diagnostic and Statistical Manual of Mental Disorders IV, NINCDS/ADRDA: National Institute of Neurological and Communicative Disorders and Stroke/the Alzheimer’s Disease and Related Disorders Association.

Table S2: Results of the total Cohen-Mansfield agitation inventory (CMAI) score.

Intervention, mean dose	Intervention		Placebo		Overall p-value
	N	Mean (SD)	N	Mean (SD)	
Olanzapine, 2.5 mg IM	71	-3.8 (2.9) * and -2.8 (3.2) **	67	-2.8 (3.4) * and -2.2 (3.6) **	>0.05
Olanzapine, 5 mg IM	66	-4.0 (3.9) * and -3.4 (3.9) **			<0.05* and >0.05**

Abbreviations: IM: Intramuscular Injection, SD: standard deviation. * Mean Change from Baseline at 2 Hours Post First Intramuscular Injection. ** Mean Change from Baseline at 24 Hours Post First Intramuscular Injection.

Ultimately, there was one RCT and one meta-analysis analyzed in this study [9,13] see Tables 1 & 2 for relevant trial design

and results. Their outcome, physical aggressive behavior, was assessed using the Cohen-Mansfield Agitation Inventory (CMAI)

scale. CMAI is a frequency rating scale containing 29-items to assess various aggressive and agitated behaviors reported as the CMAI total score. The CMAI score can also be divided into subscale scores, such as verbal or physical aggression subscale score. The outcome in the studies was reported as the observed mean change in CMAI physical-aggression subscale score from baseline to endpoint [9,14]. The pooled data of the meta-analysis of Deyn et al. [9] demonstrated a statistically significant reduction in physical aggression when comparing risperidone to placebo. However, Zhong et al. [13] demonstrated no difference in mean change (from baseline to evaluated points) in CMAI physical aggression subscale score between quetiapine and placebo. (Table 1 & 2)

Discussion

This systematic literature study shows that there is some evidence for the efficacy of risperidone in treating acute physical aggressive behavior in patients with dementia residing in nursing homes. However, quetiapine was not associated with statistically significant benefits, thus there is no evidence for the efficacy of quetiapine in treating acute physical aggressive behavior in patients with dementia in nursing homes. Other antipsychotics are not investigated to specifically treat non-psychosis-induced acute aggressive behavior in this specific patient population, namely patients with dementia residing in nursing homes. A double-blind study conducted by Meehan et al. [15] investigated the efficacy of rapid-acting intramuscular olanzapine in treating agitation associated with Alzheimer's disease and/or vascular dementia (Appendix 3). They concluded that olanzapine showed superiority to placebo on the CMAI score. A rapid acting intervention is precisely important in treating patient with acute physical aggressive behavior in nursing homes. However, this study did not report results on the psychical aggressive behavior subscale score separately and was therefore not included in this study. However, olanzapine may be promising to treat psychical aggressive behavior specifically in these patients who need acute treatment, although not all patients of this trial were nursing home residents. In addition, further research is needed to fully determine the efficacy of all the antipsychotic agents.

The strength of our study was the high level of evidence: results were obtained through a meta-analysis study and an RCT, all comparing antipsychotics to placebo. The meta-analysis conducted by De Deyn et al. [9] contained three RCTs, which were similar in design, patient characteristics, efficacy scale, intervention, and treatment duration. Therefore, pooling the data was justified and useful since a larger patient population allows more precise estimates of the effect size. Another strength was the specific research question and PICO. The population of this study was very specific: patients in nursing homes with different forms of dementia and non-psychotic-induced acute aggressive behavior. In order to investigate the efficacy of antipsychotics on change in manifestation of aggressive behavior or a change in the frequency of aggressive behavior, patients with psychosis

were excluded. Furthermore, the outcome was likewise specific, being the CMAI physical-aggression subscale score. Articles that did not specifically address acute aggressive behavior and had no separate data on aggressive behavior were also excluded.

One limitation of the De Deyn et al. [9] study was their patient population. Their study included patients with psychosis (approximately 60%), which was part of our exclusion criteria. However, they performed a subgroup analysis that showed significant improvement in aggressive behavior in patients that did not have psychosis. This ultimately indicates that risperidone may improve symptoms of aggression independent of its antipsychotic effect.

Currently, there is some evidence supporting the use of risperidone for treating acute physical aggressive behavior in patients with dementia residing in nursing homes. However, more research is needed on efficacy and safety. Thus, the recommendation for daily practice is to utilize risperidone when really necessary in this setting, despite its safety concerns, until we gain more insight into the safety and efficacy of utilizing these antipsychotics. The effect and safety should frequently be evaluated during treatment as antipsychotics can cause serious adverse events in elderly patients, including increased mortality [6,7].

Conclusion

The objective of this study was to evaluate the efficacy of antipsychotic agents compared to placebo in treating acute physical aggressive behavior in patients with dementia residing in nursing homes. Results of the meta-analysis of De Deyn et al. [9] confirmed that risperidone might be an effective treatment for reducing physical aggressive behavior in this patient population. On the other hand, the randomized controlled trial of Zhong et al. [13] showed no change in physical aggressive behavior between quetiapine and placebo. Currently, only risperidone is proven to be effective in one meta-analysis for this indication and patient population. In conclusion, more research is needed to fully investigate the benefits of all the antipsychotics in treating acute physical aggressive behavior in patients with dementia residing in nursing homes. In the interim, health care workers should prescribe antipsychotics reservedly and with extreme caution as a treatment for acute physical aggressive behavior in patients with dementia residing in nursing homes.

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