Galantamine Versus Risperidone Treatment of Neuropsychiatric Symptoms in Patients with Probable Dementia: An Open Randomized Trial

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Objective: *To examine the effects of galantamine and risperidone on neuropsychiatric symptoms in dementia (NPSD) and global function.* **Methods:** *Using a randomized, controlled and open-blind, one-center trial at an in- and outpatient clinic at a university hospital, we studied 100 adults with probable dementia and NPSD. Participants received galantamine (N = 50, target dose 24 mg) or risperidone (N = 50, target dose 1.5 mg) for 12 weeks. The primary outcome was effects on NPSD assessed by the Neuropsychiatric Inventory (NPI). Secondary measures included the Mini-Mental State Examination (MMSE), Clinical Dementia Rating, Clinical Global Impression, and Simpson Angus scales. All tests were performed before and after treatment.* **Results:** *Outcome measures were analyzed using analysis of covariance. Ninety-one patients (67% women, mean age 79 ± 7.5 years) with initial NPI score of 51.0 (± 25.8) and MMSE of 20.1 (± 4.6) completed the trial. Both galantamine and risperidone treatments resulted in improved NPSD symptoms and were equally effective in treating several NPI domains. However, risperidone showed a significant treatment advantage in the NPI domains irritation and agitation, F(1, 97) = 5.2, p = 0.02. Galantamine treatment also ameliorated cognitive functions where MMSE scores increased 2.8 points compared with baseline (95% confidence interval: 1.96−3.52). No treatment-related severe side effects occurred.* **Conclusions:** *These results support that galantamine, with its benign safety profile, can be used as first-line treatment of NPSD symptoms, unless symptoms of irritation and agitation are prominent, where risperidone is more efficient.* (Am J Geriatr Psychiatry 2014; 22:341−348)

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INTRODUCTION

The anticipated incidence of dementia is expected to rise to over 116 million worldwide in 2050.[1] Behavioral and psychological symptoms in dementia comprise depression, verbal and physical aggressive behaviors, and psychotic symptoms.[2] Newer terminology present them as neuropsychiatric symptoms in dementia (NPSD).[3] Affective symptoms can precede cognitive symptoms and create increased emotional burden for both patient and caregiver.[4] The increased support needed for activity of daily living functions often lead to earlier admittance to residential care, thereby increasing societal costs.[5–7]

To treat NPSD, these symptoms must be properly diagnosed and understood from the context of the patients' actual life situation. Guidelines suggest nonpharmacologic treatments as first-line therapy.[8,9] Antipsychotic drugs still have an indication for treatment of aggressive behavior[8–10] in Sweden but not in the United States.[11,12] However, antipsychotics can have severe side effects (i.e., extrapyramidal symptoms and anticholinergic effects). Instead of treating elderly patients with sedating conventional antipsychotics or drugs with anticholinergic activity, "atypical" antipsychotic drugs with fewer side effects are currently used.[3,13–15] In Sweden, the only antipsychotic drug with the indication for treatment of NPSD is risperidone. However, research indicates that both conventional and atypical antipsychotic drugs show increased risks for cerebrovascular and cardiovascular incidents.[3,16] Thus, there is a need for drugs with more benign safety profiles for treatment of NPSD.

Effects of acetylcholinesterase inhibitors (AChEI) on cognition have been studied in several randomized controlled trials in mild, moderate, and severe stages of Alzheimer disease (AD) indicating reduced NPSD symptoms.[17,18] Holmes et al.[19] showed that donepezil used in patients with mild to moderate AD using assessment of NPSDs as primary outcome had positive effects as compared with placebo. In contrast, Howard et al.,[20] when analyzing moderate to severe AD patients with agitation, showed that donepezil was not more effective than placebo. None of these studies has compared antipsychotics with AChEIs.

Our open randomized controlled study, based on a 12-week trial, examined the effects on the primary outcome measure of NPSD. Secondary measures evaluated the cognitive and global functions used in traditional clinical trials, comparing an AChEI (galantamine) to the antipsychotic drug risperidone in 100 patients with probable dementia.

METHODS

Participants

This study was conducted between January 2003 and September 2005 in which 100 patients were enrolled consecutively from a one-center memory clinic. All patients were living at home in the community, were referred from general practitioners, and were admitted due to NPSD and probable dementia clinically. Patients underwent a diagnostic set-up and were admitted to a geropsychiatric ward after being randomized to galantamine or risperidone for 12 weeks. Inclusion criteria required that patients had NPSD symptoms (with a score $\geq$ 10 using the Neuropsychiatric Inventory [NPI][21,22] and symptoms present for a minimum of 2 weeks before inclusion) and probable dementia or mild cognitive impairment according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.[23] Patients were excluded if they had a diagnosis of schizophrenia or other psychiatric disorders, a history of seizures, active peptic ulcer, clinically significant hepatic renal or metabolic disturbances, or did not have a significant caregiver.

One hundred forty-five patients were screened, and 100 were included and randomized (Fig. 1). Included patients were diagnosed with AD (34%), mixed AD (27%), vascular dementia (VaD, 18%), frontal lobe dementia (3%), Parkinson dementia (2%), unspecified dementia (4%) and mild cognitive impairment (12%).

The study was conducted according to good clinical practice and ethical principles of the Declaration of Helsinki. Both patient and caregiver gave written informed consent before entering the study. The regional Ethics Committee of Karolinska Institutet, Stockholm Sweden, approved the study.

Procedures

This study was designed as a 12-week open, randomized, blind-rated trial with parallel groups to