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Escitalopram versus risperidone for the treatment of behavioral and psychotic symptoms associated with Alzheimer's disease: a randomized double-blind pilot study

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ABSTRACT

Background: Antipsychotics are frequently used to treat psychosis, aggression and agitation in patients with Alzheimer's disease (AD), but safety warnings abound. Escitalopram was investigated since citalopram has demonstrated some effectiveness in AD. We compared escitalopram and risperidone for psychotic symptoms and agitation associated with AD.

Methods: Inpatients with AD, who had been hospitalized because of behavioral symptoms, were recruited to a six-week randomized, double-blind, controlled trial. Participants (n = 40) were randomized to once daily risperidone 1 mg or escitalopram 10 mg.

Results: The NPI total score improved in both groups. Onset was earlier in the risperidone-treated group, but improvement did not significantly differ between groups by study end. Completion rates differed for escitalopram (75%) and risperidone (55%), mainly due to adverse events. There were no adverse events in the escitalopram group, while in the risperidone group two patients suffered severe extrapyramidal symptoms and four patients suffered acute physical illness necessitating transfer to general hospital.

Conclusion: Escitalopram and risperidone did not differ in efficacy in reducing psychotic symptoms and agitation in patients with AD. Completion rates were higher for escitalopram-treated patients. Replication in larger trials with ambulatory patients is needed.

Key words: Alzheimer's disease, psychosis, escitalopram, risperidone

Introduction

Behavioral and psychological symptoms of dementia (BPSD), such as agitation, violence or psychosis, are among the most distressing manifestations of dementia. The management of these symptoms includes the identification of treatable physical and environmental precipitants, support and psycho-education for caregivers and psychosocial intervention. Nevertheless, pharmacotherapy is frequently used, especially in institutional settings (Schneider *et al.*, 2006).

The widespread use of second-generation antipsychotics (SGAs) in elderly patients with dementia over the past decade has led to the accumulation of randomized clinical trial results that suggest an increased mortality compared with placebo. The Food and Drug Administration therefore instituted a black-box warning for all SGAs concerning an increased risk of death in elderly patients with dementia and a similar warning was subsequently added to the labels of first-generation antipsychotics (Food and Drug Administration, 2005). However, physicians have very limited options in treating dementia-related psychosis and behavioral symptoms. Despite the risks associated with antipsychotic drugs, there is insufficient evidence to suggest that other psychotropics represent a safe and well-tolerated, let alone more effective treatment choice for psychosis or agitation in dementia. It is recommended that physicians carefully determine the cause of psychosis and behavioral symptoms in dementia and discuss treatment options, including behavioral treatment strategies, with patients and families.

The role of serotonin in aggression in general and in aggression and psychosis in AD has been demonstrated, so there is a scientific rationale for evaluating serotonergic compounds (Sweet *et al.*,

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2001). There is some evidence to suggest that citalopram may be an option in treating patients suffering from psychosis or agitation in dementia. In two published randomized controlled trials, citalopram was more efficacious than placebo and as efficacious as, but better tolerated, than perphenazine or risperidone in patients with dementia hospitalized for the treatment of agitation or psychosis (Pollock *et al.*, 2002; 2007). The rationale for studying escitalopram for this indication is the clinical response reported in geriatric patients treated with escitalopram (Gorwood *et al.*, 2007), who had better treatment persistence and fewer hospitalizations than patients treated with citalopram (Wu *et al.*, 2008). Furthermore, animal studies support the role of the allosteric modulation of the 5-HT transporter in the regulation of the recovery of 5-HT neuronal activity and long-lasting hippocampal cellular plasticity induced by escitalopram and not by citalopram (Mnie-Filali *et al.*, 2007). Thus, an evaluation of the efficacy and tolerability of escitalopram for the treatment of BPSD is warranted.

Methods

This six-week, double-blind, randomized, fixed-dose study included 40 patients from a psychiatric inpatient setting in Israel (Abarbanel Mental Health Center) from April 2008 to April 2010. The study was approved by the local Institutional Review Board. Written informed consent was obtained from the patients or their legally authorized representatives. The trial registration is available at clinicaltrials.gov Identifier: NCT 01119638.

Under double-blind conditions patients were randomly equally (1:1) to receive treatment with risperidone or escitalopram over six weeks. Study medication was given for oral administration, supplied as tablets of identical appearance. Doses were adjusted according to the protocol as follows: (a) risperidone 0.5 mg once daily for the first week and then 1 mg once daily till study completion; (b) escitalopram 5 mg once daily for the first week and then 10 mg once daily until study completion.

Patients fulfilled criteria for dementia of the Alzheimer's type (according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition). In addition, patients had to have a Mini-Mental State Examination (MMSE) score between 5 and 24 (Folstein *et al.*, 1975). To be eligible, patients had to be admitted to our psychiatric center (psychogeriatric ward) because of signs and symptoms of psychosis, aggression or agitation that were severe enough to warrant hospitalization. Eligible patients had to have suffered from delusions, hallucinations, aggression or agitation, which developed after the onset of dementia and which were severe enough to disrupt their functioning and, in the opinion of the study physicians, to justify treatment with antipsychotic drugs. Signs and symptoms of psychosis, aggression or agitation had to have occurred nearly daily during the week prior to enrollment. Patients were hospitalized for the duration of the study.

Exclusion criteria were: (a) a diagnosis of a primary psychotic disorder (e.g. schizophrenia) or delirium; (b) psychosis, agitation or aggression that could be better accounted for by another medical condition; (c) alcohol or substance abuse; and (d) previous treatment with the drugs under study, or contraindications to the study drugs.

A board-certified psychiatrist on the psychogeriatric ward who was blinded to medication status performed the Neuropsychiatric Inventory (NPI) assessments at baseline and weekly for the duration of the study (Cummings *et al.*, 1994).

Patients who met the selection criteria were assigned to double-blind treatment according to a computer-generated randomization list. The details of the randomization series were unknown to investigators and were contained in a set of sealed opaque envelopes. Sequentially enrolled patients were assigned the lowest randomization number available in blocks of four. All investigators, trial personnel and patients were blinded to treatment assignment for the duration of the study.

Other drugs

Participants were permitted to continue cholinesterase inhibitors or memantine if they had been taking them for at least 12 weeks and at the same dose for at least 4 weeks prior to screening. Other psychotropics (except for clonazepam, used as a "hypnotic" only at bedtime) had to be discontinued prior to randomization.

Sample size

A sample size of 17 patients in each group would have 80% power to detect a difference of 5 points in the total NPI score (assuming that the common SD is 4 to 6) using a t-test with a two-sided p-value <0.05 for statistical significance. Thus, we enrolled 20 patients in each group, expecting a 15% drop-out rate. All adverse events (including any change in concurrent illnesses or new illnesses) either observed by the investigator or reported spontaneously by the patient were recorded.

Statistical analysis

Patients who were randomized and had received at least one dose of the study medication were included

Table 1. Patients' demographic and clinical characteristics

CHARACTERISTIC	ESCITALOPRAM (n = 20)	RISPERIDONE (n = 20)
Age (years)	76.6 (9.2)	80.1 (6.2)
Women % (n)	60 (12)	55 (11)
MMSE score at baseline	15.6 (5.3)	13.4 (3.7)
Disease duration (years)	2.3 (1.5)	1.6 (0.5)
NPI total score at baseline	21.3 (11.8)	17.4 (4.5)
NPI total score at Week 6 (study completion)	16.6 (9.1)	9.6 (5.3)
NPI score change (LOCF)	−4.7 (7.3)*	−7.7 (6.8)**

Values are means (SD).
*p = 0.028, **p = 0.004 differences between baseline and week 6 mean NPI scores.

in the intention-to-treat sample (ITT). The last observation-carried-forward (LOCF) method was used for imputing missing values. The primary outcome measure was the change from baseline in the Neuropsychiatric Inventory (NPI) total score (Cummings *et al.*, 1994). The primary efficacy analysis was an analysis of covariance (ANCOVA) of the change from baseline in NPI total score at Week 6 (ITT, LOCF), with treatment as the factor and the baseline NPI total score as a covariate. Variables are presented as mean and standard deviation (SD). All tests were two-tailed and $p < 0.05$ was considered statistically significant.

Results

Patients had a mean age of about 78 years and just over half were women. The mean MMSE score was about 14 and the mean NPI score was approximately 19 at baseline. The gender distribution, age and baseline MMSE scores of the 40 patients treated in this study did not differ significantly between the two treatment groups (Table 1). Two participants in each group continued existing treatment with a stable dose of a cholinesterase inhibitor. Two participants in the escitalopram group were on memantine during the study.

Overall, 67.5% (27/40) of the participants completed the 6-week trial; 75% (n = 16) in the escitalopram group and 55% (n = 11) in the risperidone group (Figure 1). Reasons for patient discontinuation were: two patients transferred to a nursing home and two patients withdrew consent (escitalopram); one patient was transferred to nursing home, two patients withdrew consent, two patients suffered from severe EPS and recurrent falls and four patients suffered from an acute physical illness necessitating transfer to a general hospital (myocardial infarction, pneumonia and two urosepsis) (risperidone). Thus, no adverse events were reported by escitalopram-treatment patients, and six risperidone-treated patients reported adverse events. The investigators considered the two EPs adverse events as due to the investigational medicine risperidone.

The mean NPI scores decreased significantly from baseline in both treatment groups over six weeks (escitalopram p = 0.02; risperidone p = 0.004). The treatment difference between groups in mean change from baseline was not statistically significant (p = 0.28), although the improvement was greater in the risperidone-treated group. In the escitalopram-treated group, the mean (SD) change from baseline to Week 6 of treatment was –4.7 (7.3). In the risperidone-treated group, the mean (SD) change from baseline to Week 6 of treatment was –7.7 (6.8).

Although not defined as an outcome measure we analyzed (post-hoc) the changes in the "delusions, hallucinations, agitation/aggression" cluster. The mean total score at baseline and at Week 6 (completion) for these three NPI items was 4.4 (SD = 1.8) reduced to 2.5 (SD = 1.7) with escitalopram and 4.7 (SD = 2.1) reduced to 1.8 (SD = 2.3) for risperidone.

Discussion

The major neuropsychiatric symptoms occurring as part of AD include aggression, disinhibition, agitation, restlessness, shouting, violence and other behavior likely to give rise to difficulties for the patient, caretakers and health-care professionals. It has been well established that aggression, agitation and psychosis occur in about 20% of people suffering from AD living in the community and in 40% to 60% of patients in care facilities (Margallo-Lana *et al.*, 2001). Importantly, 90% of patients suffering from AD develop BPSD at some point during their illness, with relative persistence of agitation and psychosis (Ballard and Howard,

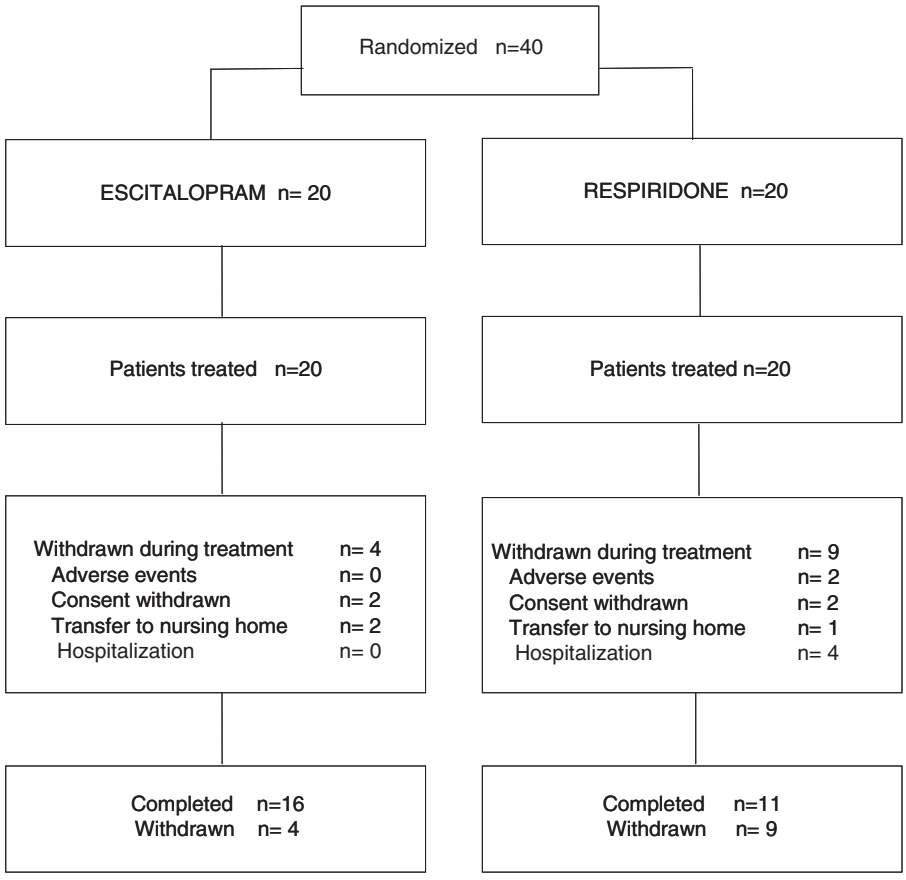

Figure 1. Patients recruited to the two treatment arms of the study and their outcomes.

2006). Despite its frequency and adverse impact, BPSD remains a major treatment challenge with no established treatment approach that is both well tolerated and effective.

In the present study, we compared the effectiveness of escitalopram and risperidone in reducing aggression, agitation and psychosis in patients suffering from AD. A decrease in the NPI total scores was observed in both treatment groups. The decrease was greater in the risperidone group, but there were fewer withdrawals in the escitalopram group. It is of interest that risperidone treatment began to show an effect sooner, which is an advantage with such distressing and time-sensitive symptoms.

Limitations inherent in the small sample size, the recruitment of inpatients and the fact that this was a single-center study need be taken into account when generalizing these findings. The higher than expected withdrawal rate, and the higher SD in NPI scores, means that this study was not powered to detect a 5-point difference in NPI scores. Caution must also be used in generalizing these findings, as no placebo arm was employed.

Recently, the Cochrane Database Systemic Reviews published their meta-analysis focusing on antidepressants for agitation and psychosis in dementia (Seitz *et al.*, 2011). Nine randomized, controlled trials comprising a total of 692 individuals were included in the review. Five studies compared SSRIs to placebo. Although there was a significant difference between antidepressants and placebo on measures of agitation the results were heavily weighted by one large study. Patients' withdrawals due to adverse events were lower for citalopram. The authors concluded that SSRIs and trazodone appear to be tolerated reasonably well when compared to either placebo or antipsychotics. Our findings are in line with these conclusions.

Any behavioral effects of SGAs in patients suffering from AD must be weighed against the adverse events and risks. Thus, we need to ask: "Are there pharmacological alternatives to antipsychotics?" Citalopram was associated with an improvement in BPSD in a double-blind, placebo-controlled trial (Nyth and Gottfries, 1990) and in two more recent blinded studies by Pollock and colleagues (Pollock *et al.*, 2002; 2007). We conclude that the present study with escitalopram needs replication in a much larger study, perhaps as second-line treatment after withdrawal from less well-tolerated treatment.

Conflict of interest

None.

Description of authors' roles

Y. Barak wrote the protocol, supervised the data collection, and wrote the first draft of the paper. I. Plopski and S. Tadger collected the data and assisted with writing the article. D. Paleacu was responsible for designing the study and helped in writing the paper. All authors contributed to and have approved the final paper.

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