

The efficacy of mirtazapine in agitated patients with Alzheimer's disease: A 12-week open-label pilot study

Sibel Cakir
Isin Baral Kulaksizoglu

Istanbul University, Istanbul Medical School, Psychiatry Department, Geropsychiatry Unit, Istanbul, Turkey

Abstract: Agitation is one of the most devastating behavioral symptoms in demented patients but there is little evidence about effective and safe pharmacotherapy. We aimed to determine the effectiveness and safety of mirtazapine in treatment of agitated patients with Alzheimer's disease (AD). The consecutive patients with AD who have significant agitation were assigned to a 12-week open-label, prospective study. Patients received mirtazapine 15–30 mg/day. The changes in Cohen-Mansfield Agitation Inventory-Short form (CMAI-SF) scores were primary outcome measurement. The change in Clinical Global Impression-Severity scale (CGI-S) scores and tolerability-safety profile were the secondary efficacy variables. Thirteen of 16 (81.25%) patients completed the study. There was a significant reduction in CMAI-SF and CGI-S between the pre- and post-treatment with mirtazapine ($p < 0.001$). The mean baseline score was 26.54 (± 5.4) and mean reduction was 10.6 (± 7.5) in CMAI-SF. There was no significant side effect and cognitive deterioration. The results of this open-label pilot study suggest that mirtazapine may be an effective choice for treatment of agitated patients with AD.

Keywords: agitation, Alzheimer's disease, treatment, mirtazapine, safety, open-label

Introduction

Patients with Alzheimer disease (AD) present various psychological and behavioral symptoms. Agitation is commonly seen and has exhaustive effects on both patients and caregivers; it causes high morbidity, low quality of life, disturbances in medical care, and higher costs. The estimated prevalence of agitation in patients with AD is changing between from 67.5% to 82% (Ballard et al 2001; Tractenberg et al 2002). The variability of the symptom distribution causes diagnostic difficulties and makes ineffective management interventions more likely. The pharmacological treatments need careful evaluation because of fluctuating nature of the agitation, unwanted drug interactions, and serious adverse events in elderly. Therefore intervention and treatment of agitation is essential in patients with dementia.

Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA) that acts as an antagonist at central presynaptic α_2 adrenergic inhibitory autoreceptors and heteroreceptors. This interaction causes increase in central noradrenergic and serotonergic activity. Mirtazapine is a potent antagonist of 5-HT₂ and 5-HT₃ receptors. The 5-HT₂ blocking effect is related to its anxiolytic effects and its benefits on sleep. It was reported that depressed elderly patients on mirtazapine treatment were less likely to be taking a sedative/hypnotic drugs (Gardner et al 2004). The enhancement effect of serotonergic neurotransmission may be associated with the antiagitation, antiimpulsivity effect of the molecule. Antidepressant effects of mirtazapine in geriatric patients were studied but there is no study of its effects in treatment of agitation with dementia (Schatzberg et al 2002; Roose et al 2003). The present study was conducted

Correspondence: Sibel Cakir
Istanbul University, Istanbul Medical School, Psychiatry Department, 34390, Capa – Istanbul, Turkey
Tel +90 2125312621
Fax +90 2126351204
Email cakirsbl@istanbul.edu.tr

to investigate the efficacy of mirtazapine in agitated patient with AD.

Materials and methods

This 12-week open-label, prospective study was conducted between January 2006 and July 2007. Informed consents were obtained from patients and families. Sixteen community dwelling consecutive patients (having a close supervision or caring assistance) with AD (DSM-IV criteria) who had clinically significant agitation were enrolled to the study. Diagnosis of AD was done by a comprehensive neuropsychiatric evaluation that consists of clinical examination, neuropsychological tests, magnetic resonance imaging scans, and blood biochemistry.

Agitated patients who had delirium, severe or uncontrolled medical illness, and liver or kidney dysfunctions were excluded from the study. Other comorbid primary psychiatric diagnoses such as schizophrenia and bipolar disorder were also exclusion criteria.

The four different types of agitation: physically aggressive behaviors, physically nonaggressive behaviors, verbally aggressive behaviors, and verbally nonaggressive behaviors were assessed by Cohen-Mansfield Agitation Inventory-Short form (CMAI-SF) (Cohen-Mansfield et al 1986; 1996). It includes 14 aggressive behaviors graded on a 5-point scale. The caregivers were educated to complete the CMAI-SF at baseline and during the study they were checked by another physician.

Clinical Global Impression-Severity scale (CGI-S) and adverse effects-tolerability profile were secondary outcome measures. The changes in depressive symptoms and cognition were followed up with Geriatric Depression Scale (GDS) and Mini-Mental State Examination (MMSE) during the study. All these measurements were done by a another physician independently from the prescribing physician.

The antipsychotic, antidepressant, and anxiolytic medications that were given for agitation treatment and gave the impression they were ineffective despite an optimum time and dosage were stopped before the study. After a wash-out period, the study drug was started. The concomitant cholinesterase inhibitors and memantine were continued during the study.

Mirtazapine was started with 15 mg/day orally at bed time. In the patients who did not respond to 15 mg, the dosage were increased to 30 mg at the end of the 2nd week. The dosage was flexible between 15–30 mg and the maximum dosage was 30 mg. Follow up visits were done at 1 week (over the telephone), and at 2, 4, 8, and 12 weeks. The study

group was checked for interim adverse events at every visit. Safety assessments were done with collecting all adverse events, laboratory tests. Liver enzymes, kidney function, and other biochemical tests were checked before the study and at the end of the study.

Data analysis

Descriptive and comparison statistics from baseline to post-treatment were used as a primary method to conclude the results. Changes in primary and secondary efficacy measurements were collected to asses the effectiveness. Paired *t* tests were used to analysis of effectiveness between the baseline and 2, 8, and 12 weeks. *P* value lower than 0.05 was considered significant.

Results

Demographic and clinical features

Sixteen patients were enrolled and 13 patients completed the study (81.25%). The demographic and clinical data are summarized in Table 1. Twelve female (75%) and 4 male (25%) patients, aged between 66–86 (mean 73.6, $SD \pm 6.36$), with moderate ($n = 10$) or severe ($n = 6$) AD had significant agitation. The mean duration of agitation was 7.2 weeks at baseline. Half of the patients had psychotic symptoms; 4 patients had delusions, 3 patients had both delusions and hallucinations, and 1 had only hallucinations. In 6 of 8 patients, agitation was started after the psychotic symptoms. Verbal agitation was significant ($n = 12$). Twelve of the patients were on cholinesterase inhibitors (7 donepezile, 5 rivastigmine), 4 patients were on cholinesterase inhibitors and the *N*-methyl *D*-aspartate-receptor antagonist, memantine.

Six patients had been taking 15 mg/day mirtazapine, the dosage was increased to the 30 mg/day in 7 patients at the end of second week. Three patients discontinued in the first week of the treatment.

Improvements on the outcome measurements

The CMAI-SF score was 26.54 (range: 17 to 36, $SD \pm 5.4$), CGI-S was 4.54 (range: 3 to 6, $SD \pm 0.9$) at baseline (Table 1). Mean GDS score was 10.5 (range: 6 to 16, $SD \pm 3.3$) and MMSE was 16.8 (range: 9 to 23, $SD \pm 3.9$) at baseline. Among the completers, 11 patients were much or very much improved, 2 patients were minimally improved.

Table 2 shows the changes in primary and secondary outcome measurements. Total CMAI-SF score significantly

Table 1 Demographic and clinical features of study group

The number of patients participated (n)	16
The number of completers (n)	13
Mean age (SD)	73.6 (± 6.36)
Female gender n (%)	12 (75%)
Severity of AD	
– Moderate (n)	10
– Severe (n)	6
Mean duration of agitation (weeks)	7.2
Mean mirtazapine dosage (mg/day)	23.08
– Patients with psychotic symptoms (n)	8
– Delusions	4
– Hallucinations	3
– Delusions and hallucinations	1

Abbreviations: AD, Alzheimer's disease; SD, standard deviation.

decreased starting from the 2nd week of treatment ($p < 0.002$). Total CMAI-SF improved by 20%–45% at second week and by 41.35% at the end of study.

There was a statistically significant improvement between baseline and 12th week in both CGI-S and CMAI-SF scores ($p < 0.001$). The mean change in CMAI-SF was -11.0 ($SD \pm 7.5$) and -2.0 ($SD \pm 0.9$) in CGI-S, p value was < 0.001 in both. The mean change was 0.85 at GDS, it was not significant ($p = 0.055$). There was no correlation between the GDS and CMAI-SF ($r = 0.03$).

Safety, tolerability, and adverse events

Three patients could not tolerate the study drug and dropped out because of sedation ($n = 2$), fatigue ($n = 1$), or dizziness ($n = 1$). These complaints were seen with 15 mg in 3 patients at the first week of the treatment. Sedation disappeared when the dosage was increased from 15 mg to 30 mg in a patient and they could continue the study.

We did not observe significant weight gain. Two patients had mild orthostatic hypotension but the relation between the hypotension and study drug was not clear, since hypotension continued after the end of study. One patient reported headache with 30 mg, which disappeared with a decrease of dosage to 15 mg. At the end of study, there was no change

in blood biochemistry in any of the patients. There was also no change in MMSE scores.

Discussion

This open-label pilot study indicated that mirtazapine could be an option for treatment of agitation in patients with AD. To our knowledge this is first study in the literature to research the efficacy of mirtazapine in the treatment of agitation in patients with AD.

Thirteen of 16 patients completed the study and 3 dropped out within the first week of the study. The drop-out rate (18.8 %) can be considered as minimal in this study as in other dementia studies with atypical antipsychotics drop-out rate was reported 1/3 and 77%–85% (Schneider et al 2006a, 2006b).

The side-effect profile of mirtazapine was mild in this study. Sedation, headache, and mild hypotension were seen and these were managed with close monitoring. A more regular appetite was reported by caregivers but no difference in weight was found. Agitation may precipitate the loss of appetite. The increased appetite and weight gain with mirtazapine in elderly can be less than in young patients as a report in elderly depressed patients showed (Nelson et al 2006).

The recent pharmacologic studies to manage the agitation in dementia showed unsatisfactory results. Atypical antipsychotics have serious side effects such as cerebrovascular events and extrapyramidal symptoms (Schneider et al 2005; Ballard et al 2006). The remained options also do not have promising effectiveness. Benzodiazepines are known to increase the cognitive impairments and falls (Golombok et al 1988; Ray et al 1989). Donepezil also did not show any difference than placebo for the treatment of agitation (Howard et al 2007). Despite the recent positive result of valproate in some selective physical aggression and irritability subitems, a placebo-controlled study did not show its effectiveness in management of agitation (Herrmann et al 2007).

Table 2 Scores and changes in efficacy variables

	Baseline	2nd week	8th week	12th week	p*
CMAI-SF (SD)	26.50 (5.4)	21.08 (4.4)	15.62 (3.9)	15.54 (3.8)	< 0.001
CGI-S (SD)	4.56 (0.9)	3.46 (0.9)	2.62 (0.65)	2.54 (0.6)	< 0.001
GDS (SD)	10.5 (3.3)	10.46 (2.7)	9.8 (2.5)	9.65 (2.8)	ns
MMSE (SD)	16.8 (3.9)	18.15 (2.5)	18.6 (2.4)	18.53 (2.5)	ns

Note: p* baseline and 12th week.

Abbreviations: CGI-S, Clinical Global Impression-Severity scale; CMAI-SF, Cohen-Mansfield Agitation Inventory-Short form; GDS, Geriatric Dementia Scale; MMSE, Mini Mental State Examination; SD, standard deviation.

There are some reports showed serotonergic psychotropic agents like trazadone, citalopram, or paroksetin could be useful in treatment of agitation (Pollock et al 1997; Ramadan 2000). In our opinion, mirtazapine could make a step forward for previously studied agents. While selective serotonin reuptake inhibitors activates serotonin receptors of the 2 and 3 subclasses, mirtazapine blocks them, and this feature may result in fewer complaints related to sleep and arousal and this may work as an advantage. In addition, endocrine effects of mirtazapine, particularly on the hypothalamic-pituitary-adrenal system and melatonin, may be related to its sleep-promoting action and helps improve the agitation (Schmid et al 2006).

It was thought that agitation was related to the sleep disorders (Cohen-Mansfield et al 2000). Our observations were also similar; agitation was seen during the night in most of patients. The sedative effects of mirtazapine may help to decrease the agitation during the night. If sleep disturbances are solved, agitation can be decreased also during the day. The results of this study are in line with this opinion. Mirtazapine could be beneficial especially in those who need a sedating agent or in patients whose agitation is significant at night time. In this study the depression is not significant among the patients and was not the main target of the treatment. Psychotic symptoms, depression, and agitation can make an amalgam that induces each other and create complexity especially in the later stages of dementia. To start the treatment for agitation with this complex would be beneficial as a urgent and safe intervention. A double blinded study found that antidepressant effect of mirtazapine started earlier than paroxetine in elderly depressed patients (Schatzberg et al 2002). This study supports our suggestion that mirtazapine with its short action time may improve current therapeutic practices.

The 12-week duration was considered an optimal period to decide the efficacy of the study drug even although there may be a fluctuating nature of agitation because of the unwanted effects of psychotropic drugs in elderly.

Similarly to the other studies which included elderly AD patients, this study had some methodological difficulties; small case numbers, being an open study, a lack of placebo control, and the short duration.

In conclusion, even though it was an open-label study, this prospective, pilot study indicated that patients with AD who have significant agitation can be treated with mirtazapine without significant adverse events or cognitive deterioration. Therefore controlled studies with a larger number of cases are needed.

Disclosure

The author reports no conflicts of interest or financial support in this work.

References

- Ballard CG, Margallo-Lana M, Fossey J, et al. 2001. A 1-year follow-up study of behavioral and psychological symptoms in dementia among people in care environments. *J Clin Psychiatry*, 62:631–6.
- Ballard C, Waite J. 2006. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. *Cochrane Database Syst Rev*, 25:CD003476.
- Cohen-Mansfield J. 1986. Agitated behaviors in the elderly. II. Preliminary results in the cognitively deteriorated. *J Am Geriatr Soc*, 34:722–7.
- Cohen-Mansfield J. 1996. Assessment of agitation. *Int Psychogeriatr*, 8:233–45.
- Cohen-Mansfield J, Garfinkel D, Lipson S. 2000. Melatonin for treatment of sundowning in elderly persons with dementia – a preliminary study. *Arch Gerontol Geriatr*, 31:65–76.
- Gardner ME, Malone DC, Sey M, et al. 2004. Mirtazapine is associated with less anxiolytic use among elderly depressed patients in long-term care facilities. *J Am Med Dir Assoc*, 5:101–6.
- Golombok S, Moodley P, Lader M. 1988. Cognitive impairment in long-term benzodiazepine users. *Psychol Med*, 18:365–74.
- Herrmann N, Lanctôt KL, Rothenburg LS, et al. 2007. A placebo-controlled trial of valproate for agitation and aggression in Alzheimer's disease. *Dement Geriatr Cogn Disord*, 23:116–9.
- Howard RJ, Juszcak E, Ballard CG, et al; CALM-AD Trial Group. 2007. Donepezil for the treatment of agitation in Alzheimer's disease. *N Engl J Med*, 357:1382–92.
- Nelson JC, Hollander SB, Betzel J, et al. 2006. Mirtazapine orally disintegrating tablets in depressed nursing home residents 85 years of age and older. *Int J Geriatr Psychiatry*, 21:898–901.
- Pollock BG, Mulsant BH, Sweet R, et al. 1997. An open pilot study of citalopram for behavioral disturbances of dementia. Plasma levels and real-time observations. *Am J Geriatr Psychiatry*, 5:70–8.
- Ramadan FH, Naughton BJ. 1999. Paroxetine for verbal agitation. *Ann Long Term Care*, 7:282–86.
- Ray WA, Griffin MR, Downey W. 1989. Benzodiazepines of long and short elimination half-life and the risk of hip fracture. *JAMA*, 262:3303–7.
- Roose SP, Nelson JC, Salzman C, et al; Mirtazapine in the Nursing Home Study Group. 2003. Open-label study of mirtazapine orally disintegrating tablets in depressed patients in the nursing home. *Curr Med Res Opin*, 19:737–46.
- Schatzberg AF, Kremer C, Rodrigues HE, et al; Mirtazapine vs Paroxetine Study Group. 2002. Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. *Am J Geriatr Psychiatry*, 10:541–50.
- Schmid DA, WichnIak A, Uhr M, et al. 2006. Changes of sleep architecture, spectral composition of sleep EEG, the nocturnal secretion of cortisol, ACTH, GH, prolactin, melatonin, ghrelin, and leptin, and the DEX-CRH test in depressed patients during treatment with mirtazapine. *Neuropsychopharmacology*, 31:832–44.
- Schneider LS, Dagerman KS, Insel P. 2005. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA*, 294:1934–43.
- Schneider LS, Dagerman K, Insel PS. 2006a. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. *Am J Geriatr Psychiatry*, 14:191–210.
- Schneider LS, Tariot PN, Dagerman KS, et al; CATIE-AD Study Group. 2006b. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med*, 355:1525–38.
- Tractenberg RE, Weiner MF, Thal LJ. 2002. Estimating the prevalence of agitation in community-dwelling persons with Alzheimer's disease. *J Neuropsychiatry Clin Neurosci*, 14:11–8.