Olanzapine as a possible treatment for anxiety due to vascular dementia: An open study

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Abstract

Disabilities caused by behavioral problems can be potentially devastating in cognitively impaired patients. These behavioral symptoms can be a major cause of stress, anxiety, and concern for caregivers. While psychotropic drugs are frequently used to control these symptoms, they can be accompanied by significant side effects, which include sedation, disinhibition, depression, falls, incontinence, parkinsonism, and akathisias. Agitation is a major problem in older patients with dementia. Agitation and aggression have always been difficult behaviors to manage, and when it is severe, agitation can be a behavioral emergency that requires urgent and immediate intervention.

This six-month study included a group of 94 outpatients (48 men and 46 women) who had a diagnosis of subcortical vascular dementia (VaD). To be eligible for the study, patients needed a score of at least 3 for agitation/aggression on the Neuropsychiatric Inventory (NPI), suggesting at least moderate frequency and/or severity, and 0 for delusions and hallucinations. Patients were divided into two homogenous groups. Group A received olanzapine (2.5-5 mg/day) and Group B received bromazepam (0.25 percent, 15 drops, three times per day). Patients in both groups were allowed to continue any previous therapy. Patients receiving olanzapine at an average dose of 3.21 ± 1.02 mg/day showed statistically significant improvement on the anxiety rating compared with those receiving bromazepam. Our patients had a host of medical conditions and received numerous concomitant medications. Given the potential complications associated with these therapeutic agents, these patients tolerated olanzapine quite well. It appeared that adverse events, particularly somnolence, postural instability, and postural hypotension, were mild and transient. Moreover, no anticholinerigic effect was registered. These findings suggest that olanzapine could be a safe and effective treatment for anxiety in cognitively impaired patients.

Key words: agitation, behavior, vascular dementia, BEHAVE-AD, NPI

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Introduction

Agitation can be defined as an excessive verbal and motor behavior. It cuts across the boundaries of diverse diagnostic categories, including primary psychiatric disorders and somatic conditions, but its phenomenology is relatively consistent across various diverse states.[1] Common examples of agitation include hyperactivity, lack of cooperation, irritability, verbal outbursts or abuse, communicated distress, threatening gestures and language, and physical destructiveness. In more severe forms, agitation may lead to violent and destructive behavior, which can readily escalate to verbal or physical aggression.

Behavioral problems are common in people with dementia, and progressive cognitive disruption with a resultant loss of functional capacity is a core feature of all types of dementia. In addition, noncognitive behavioral problems, such as depression, disruptive agitation, psychosis, personality change, emotional lability, and social misconduct are seen in most demented patients during the course of the illness. These noncognitive problems create an additional disability that could be potentially devastating. In the spectrum of behavioral symptoms in dementia,[2] agitation occurs somewhat frequently and is often cited as an important factor for drug therapy introduction. Precipitating factors (such as physical discomfort that could not be expressed by the patient, excessive sensory stimulation, or an improper environment) should be considered when dealing with agitation in older and cognitively disrupted persons. Mild outbursts can sometimes be handled behaviorally by distracting patients or allowing them to wander in an enclosed place. However, agitation that is sufficiently troublesome and without obvious cause, which can be remedied, must be treated.

Agitation may contribute to the overall morbidity of the disease and is the major cause of institutionalization,[3,4] negatively impacting nutrition and sleep, and enhancing cognitive disruption. In particular, these behavioral symptoms can be a major cause of stress, anxiety, and concern for caregivers. However, clinicians view anxiety in dementia as synonymous with other behaviors, notably agitation and aggression,[5] or as a component of a broader syndrome, such as psychosis or depression.

A dual approach is necessary when dealing with agitation: acute management focuses on calming the agitated patient, and chronic management focuses on the reduction of the frequency and intensity of agitation episodes. Environmental interventions include the removal of objects that could be used as weapons, limiting extraneous stimulation, and the "talk down" calming approach. Early on, nonspecific sedation is often used in the management of acutely agitated patients. Until now, the choice of intramuscular medication for behavioral emergencies has been limited to intramuscular preparations of typical antipsychotics (e.g., haloperidol or chlorpromazine) or intramuscular preparations of benzodiazepines (principally lorazepam or diazepam). However, regardless of their efficacy, benzodiazepines are not recommended as first line treatments in this patient population for behavioral symptoms such as anxiety and sleep disturbances[6,7] because of their negative impact on cognition. The use of conventional antipsychotics has been reported to be efficacious, but these drugs are associated with unwanted effects including hypotension and extrapyramidal symptoms.[8,9] The atypical antipsychotics (e.g., risperdone, quetiapine, and olanzapine) have been shown as efficacious in the treatment of psychosis and agitation/aggression with a more favorable safety profile for the elderly.[10-13] A post hoc analysis of a previously published study was performed.[5] The analysis evaluated the response of a subgroup of Alzheimer's disease (AD) patients with significant anxiety symptoms to olanzapine treatment. The study suggested that olanzapine could be a safe and effective treatment for anxiety in AD patients. The authors clearly stated that the statistically significant improvement of anxiety was not secondary to an improvement in hallucinations, treatment emergent somnolence, or benzodiazepine use. However, patients enrolled in the study needed a score of at least 3 on any of the agitation/aggression, delusions, or hallucinations items on the Neuropsychiatric Inventory/nursing home version (NPI/NH).[14] The purpose of our study was to assess the efficacy and tolerability of an atypical, antipsychotic olanzapine in the treatment of anxiety as an isolated symptom, in patients with vascular subcortical dementia (VaD).

Methods

Patients

Men and women, aged 75 to 88, with Mini-Mental State Examination (MMSE) scores of at least 14, who satisfied the dementia criteria in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), participated in the study. Study subjects also satisfied the criteria for probable vascular dementia, in accordance with the National Institute of Neurological Disorders and Stroke Association Internationale pour la recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria.[15] A patient was diagnosed as having subcortical VaD when the CT scan showed moderate to severe ischemic white matter changes[16] and at least one lacunar infarct. Patients were not included in the study if

Table 1. Baseline characteristics of patients in the two treatment groups		
	Group A: Olanzapine	**Group B: Bromazepam**
Number of patients	47	47
Gender (male/female)	25/22	23/24
Age (mean ± SD)	74.56 ± 3.4	75.8 ± 0.3
Education level, years (mean ± SD)	8.69 ± 3.21	8.89 ± 1.23
Left- or right-handed	Right	Right
Hachiniski score	8.7 ± 1.9	8.71 ± 1.45
Concomitant illnesses (percentage of patients)		
Essential hypertension	23.2	25.2
Diabetes mellitus, type 2	17.8	15.3
Ischemic cardiopathy/valvular failure	15	11
Chronic renal failure	6	4.97

they showed signs of nonlacunar territorial infarcts or radiological signs of normal pressure hydrocephalus. Brain CT scans and MRI images were randomized and assessed independently by two neurologists. In the case of disagreement, the scans were reassessed together with an experienced neuroradiologist, who made the final decision. Patients with previous psychiatric illness or central nervous system disorders and alcoholism were excluded.

Study design

The study subjects, men and women aged 75 to 88, who were not bedridden, were recruited from January 1, 2001, to August 31, 2002. Participants underwent a standardized baseline assessment that included a detailed history, a physical examination, laboratory tests, and psychiatric evaluations. The physical examination included evaluations of pulse rate and rhythm, blood pressure, heart size and sounds, peripheral pulses, retinal vessel and carotid artery evaluation, and chest x-ray. To be eligible for the study, patients needed a score of at least 3 (suggesting moderate frequency and/or severity) for agitation/aggression on the NPI, and 0 for delusions and hallucinations. Patients were divided into two homogenous groups, with similar age and education levels. Group A received olanzapine (2.5-5 mg/day), and Group B received bromazepam (0.25 percent, 15 drops, three times per day). Bromazepam is a benzodiazepine that is absorbed well after oral administration. Its most common indication is its anxiolytic effect. Bromazepam is metabolized mainly by the liver, its initial biotransformation pathway is oxidation, and the usual range of blood elimination half-life is 15 to 25 hours. Bromazepam can be considered as an intermediate-acting benzodiazepine. Drops of bromazepam are quite simple to administer, accepted well by patients, and easily managed by caregivers.

Patients in both groups were allowed to continue any previous therapy (e.g., cholinesterase inhibitors, antihypertensive, antidyslipidemic, or antidiabetic drugs) as shown in Table 1. Overall, the two treatment groups were similar, and no significant differences were observed between groups. All patients completed the six-month study, and periodic neurological and neuropsychological examinations were scheduled to take place one, three, and six months after the start of treatment. The results of a complete neuropsychological examination performed at baseline and at the last visit were compared.

The trial was conducted in accordance with the Declaration of Helsinki and with the ethics guidelines of the institute. Written informed consent was obtained from all participants or their responsible caregivers prior to the study. Caregivers monitored treatment compliance, controlled the intake of drugs, and reported problems when they occurred.

Outcome measures

Global performance was assessed using the Clinical Dementia Rating[17] at every visit. Global cognitive function

Table 2. Mean (± SD) baseline test scores in the two treatment groups		
Test	**Group A: Olanzapine**	**Group B: Bromazepam**
MMSE	20.23 ± 2.37	19.40 ± 2.48
BEHAVE-AD	40.46 ± 7.72	39.93 ± 7.21
NPI	11.21 ± 3.97	11.25 ± 3.93
RSS	23.85 ± 6.64	23.31 ± 6.68
CIRS	5.08 ± 0.88	5 ± 0.97

was assessed using the MMSE[18] at each visit. Behavioral symptoms were assessed using the NPI[19] and the Behavioral Pathology in AD Rating Scale (BEHAVE-AD)[20] at every visit. In addition to the total BEHAVE-AD score, seven items from the scale were assessed individually: delirium (maximum score 21), hallucinations (maximum score 15), activity disorders (maximum score 9), aggressiveness (maximum score 9), sleep disturbances (maximum score 3), affective disorders (maximum score 6), and anxiety and phobias (maximum score 12). Global health condition was assessed using the Cumulative Illness Rating Scale (CIRS)[21] at every visit. Finally, the caregivers' stress was evaluated using the Relative Stress Scale (RSS)[22] at every visit.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 10.0). Because of the small number of patients enrolled, within-group changes from baseline to six months were tested using the Wilcoxon Signed Ranks test. Between-group comparisons of changes from baseline were tested using the Wilcoxon two-sample test. This was done for the overall scores for each efficacy variable. In addition, subanalyses of behavioral data obtained at baseline and at six months using the BEHAVE-AD were performed to identify scale items that showed particular improvement or deterioration. Spearman's rank correlation analyses were performed on caregiver stress and behavioral outcome measures. Results are presented as mean changes from baseline with standard deviations, and P-values are presented where appropriate.

Results

Patients

The study included 94 patients, 48 men and 46 women, with a mean age of 74.98 ± 3.23 years. Participants had a mean education level of 8.1 ± 3.09 years (Table 1).

The diagnosis was based on historical information and neuropsychological assessment and supported by CT scan or MRI findings. Subsequent follow-up review of subjects has reinforced the clinical diagnoses in all cases. Brain CT scans or MRI images were available for all patients, and there was 94 percent inter-rater agreement for the two neurologists assessing the scans (kappa = 0.79). All patients completed the full six-month study. Of the 94 patients, 47 were randomized to receive olanzapine (Group A) and 47 were randomized to receive bromazepam (Group B). Patients receiving olanzapine began treatment on a low dose of 2.5 mg/day and were titrated to a higher dose of 5 mg/day, when symptoms required it. The average dose was 3.21 ± 1.02 mg/day. Two patients from Group A died (myocardic infarction and fatal ischemic stroke). One Group B patient was excluded from the study because of lack of compliance. Patients in both groups were allowed to continue any previous therapy (e.g., antihypertensive, antidyslipidemic, and antidiabetic drugs). The two groups were similar with respect to comedications and concomitant illnesses. Six patients from Group A (12.7 percent) and seven from Group B (14.9 percent) were receiving ACE inhibitors (mean dose 23.46 ± 2.37 mg/day) for the treatment of essential hypertension. Ten patients from Group A (21.27 percent) and nine patients from Group B (19.14 percent) received calcium antagonists (mean dose 6.4 ± 4.12 mg/day). Three other patients from Group A and B (6.38 percent) showed signs of diabetes mellitus type 2 and were receiving oral medication (mainly glibenclamine, 5 ± 2.34 mg, twice per day) for their conditions. Four patients from Group A (8.51 percent) and three from Group B (6.38 percent) received isosorbide mononitrate (mean dose 37.5 ± 10 mg/day). Four patients in Group A (8.51 percent) and five patients from Group B (10.63 percent) received a combination of the above therapies.

Efficacy of olanzapine

At baseline, there were no statistical differences between the two groups on any of the scales, indicating that there

Table 3. Mean (± SD) baseline scores of BEHAVE-AD items in the two treatment groups		
BEHAVE-AD item	**Group A: Olanzapine**	**Group B: Bromazepam**
Delusions	0	0
Hallucinations	0	0
Activity disorders	6.7 ± 1.17	6.89 ± 1.14
Aggression	4.6 ± 1.07	4.87 ± 1.05
Sleep disturbances	2.04 ± 0.29	2.68 ± 0.47
Affective disorders	4.19 ± 1.26	3.95 ± 1.51
Anxiety	10.72 ± 1.54	10.95 ± 1.45

was no significant difference between the groups with regard to baseline symptoms (Table 2 and Table 3).

When assessed at six months with the MMSE, patients in both treatment groups showed similar deterioration in general cognition when compared with baseline (Table 4). On the BEHAVE-AD and NPI, total scores in the olanzapine group were significantly improved over baseline and over the bromazepam group at six months ($p < 0.01$). This finding was evidenced by the significant decrease in the RSS score for the olanzapine group ($p < 0.01$ compared with the bromazepam group). Spearman's rank correlation analyses indicated that there was a significant correlation between caregiver stress and NPI and BEHAVE-AD scores at six months ($p < 0.01$). Further analysis of the BEHAVE-AD individual items indicated that olanzapine provided benefits on all items of the scale (Table 5 and Figure 1). Scores for delusions and hallucinations got significantly worse in both groups compared with baseline, although this was more evident in the bromazepam group (Table 5). There was a decrease in activity disorders, aggression, sleep disturbances, and affective disorders in the olanzapine group when compared with baseline and the bromazepam group, as reflected by the specific scores. Anxiety decreases in the olanzapine group (-8.17 ± 1.12, $p < 0.01$) compared with baseline and the bromazepam group. Spearman's rank correlation analyses indicated that there was no significant correlation between anxiety and hallucinations/delusions at six months ($p = 0.123$). No effect was detected in the comorbidities evaluation. The CIRS scores were unvaried in both groups.

Tolerability of olanzapine in patients with VaD

Of the patients in Group A (olanzapine), 31.78 percent reported transitory sleepiness during the titration phase.

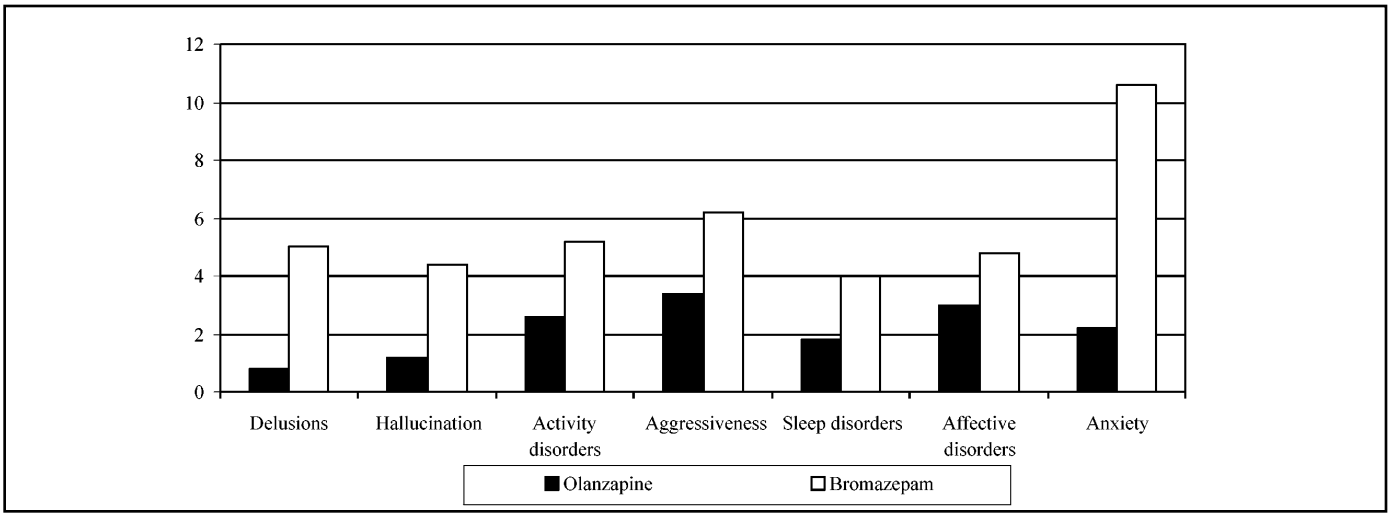

Figure 1. Differences in subitems of BEHAVE-AD in the two groups, at six months.

Table 4. Mean (± SD) changes in test scores, compared with baseline, in the two treatment groups at six months		
Test	**Change vs. baseline at month six**	
	Group A: Olanzapine	**Group B: Bromazepam**
MMSE	-3.56 ± 1.2[a]	-3.05 ± 1.65[a]
BEHAVE-AD	-16.95 ± 0.52[c,d]	+5.38 ± 0.01[c]
NPI	-4.097 ± 0.73[c,d]	+2.79 ± 0.90[c]
CIRS	-0.08 ± 0.17	+0.17 ± 0.06
RSS	-3.2 ± 0.2[a,d]	+7.92 ± 1.12[c]
[a] $p < 0.05$ versus baseline; [b] $p < 0.05$ versus the bromazepam group; [c] $p < 0.01$ versus baseline; [d] $p < 0.01$ versus the bromazepam group.		

This symptom resolved spontaneously within 11.3 ± 1.64 days. Of the patients in Group B (bromazepam), 37.2 percent reported sleepiness, which lasted longer (32.45 ± 9.2 days). Gait unsteadiness was reported by 4.5 percent of patients in Group A and by 7.2 percent of patients in Group B. Of the patients in Group A, 5 percent manifested episodes of postural hypotension during the titration phase, without cardiac involvement. Of the patients in Group B, 3.65 percent also exhibited postural instability. Of the patients in Group A, 2.4 percent fell repeatedly and 9.6 percent of patients in Group B fell repeatedly, especially at night. Of the patients in Group A, 6.5 percent exhibited oral craving, with a slight weight increase (mean 2.34 ± 0.32 kg) during the follow-up evaluation; in Group B, 11.5 percent reported nausea during the first week of the study, associated with anorexia. Although patients were allowed to continue any previous medication, no side effects thought to be the result of drug interactions were reported.

Discussion

While cognitive impairment is a consistent clinical feature of dementia, neuropsychiatric symptoms are also characteristic of the disease and represent a major cause of morbidity in dementia patients. Neuropsychiatric disturbances have been associated with more rapid cognitive decline,[23,24] increased caregiver burden,[24] increases in patient care costs due to earlier institutionalization, and more extensive institutional staffing needs.[25] Non-cognitive symptoms of dementia include abnormal behaviors (e.g., sleep disturbance, emotional incontinence, wandering, and restlessness) and abnormal mental experiences (e.g., depression, delusions, and hallucinations) that can lead to abnormal behaviors. Since the mechanisms for these behaviors are not well-known, most treatment is currently empirical.[26] It is not uncommon for patients with dementia to exhibit agitation, aggression, and violence. Agitation is very common and presents a complex clinical challenge to the neurologist who works with a cognitively disturbed, older population. A key step in the initial evaluation is to identify whether a medical etiology for the agitation is present and to determine the general category of the problem (e.g., delirium, intoxication, or other causes). Often, anxiety represents an isolated behavioral symptom, which may warrant an indication for pharmacological treatment.[5]

There have been a number of studies investigating the treatment of anxiety in dementing illness, including AD.[27-29] Only one study has investigated an effective treatment for anxiety as an isolated symptom in AD.[5] The results of this study indicated that the improvement of anxiety in the subset of patients treated with olanzapine (5 mg/day) was not secondary to an improvement in hallucinations, treatment-emergent somnolence, or benzodiazepine use. Even if the post hoc analysis had been based on pilot evidence, it was conducted on a population who exhibited anxiety in addition to other behavioral symptoms, such as delusions and hallucinations. Our study subjects were elderly patients with subcortical vascular cognitive impairment, who had behavioral alterations (e.g., anxiety, aggressiveness, and sleep disturbances), but did not complain of delusions or hallucinations. The study's heterogeneous population of outpatients was vulnerable to drug effects and drug interactions. Our first conclusion is that anxiety can be found as an isolated symptom, which is unrelated to the presence of delusions or hallucinations in cognitively impaired

Table 5. Mean (± SD) changes in separate scores of BEHAVE-AD, compared with baseline, in the two treatment groups at six months		
BEHAVE-AD item	**Change vs. baseline at month six**	
	Group A: Olanzapine	**Group B: Bromazepam**
Delusions	+0.91 ± 0.77[c,d]	+5.04 ± 1.16[c]
Hallucinations	+1.23 ± 0.89[c,d]	+4.08 ± 1.11[c]
Activity disorders	-3.81 ± 0.53[c,d]	-1.41 ± 0.90[c]
Aggression	-1.72 ± 0.6[c,d]	+1.73 ± 1.16[c]
Sleep disturbances	-0.32 ± 0.4[c,d]	+1.09 ± 0.22[c]
Affective disorders	-0.98 ± 0.02[a,d]	+1.23 ± 0.89[c]
Anxiety	-8.17 ± 1.12[c,d]	-0.04 ± 0.01

[a] $p < 0.05$ versus baseline; [b] $p < 0.05$ versus the bromazepam group; [c] $p < 0.01$ versus baseline; [d] $p < 0.01$ versus the bromazepam group.

patients. Anxiety also represents a major cause of distress for patients and their caregivers, as evidenced by the high scores in RSS, which correlate significantly with NPI and BEHAVE-AD scores. Moreover, our study showed a double dissociation between delusions and hallucinations and anxiety. Although more evident in the bromazepam group, delusions and hallucinations scores got significantly worse in both groups at the end of the study compared with baseline. In contrast, anxiety decreased in the olanzapine group.

Spearman's rank correlation analyses indicated that there was no significant correlation between anxiety and hallucinations and delirium at six months. Our second conclusion is that olanzapine, when used at a mean dose of 3.21 ± 1.02 mg/day, is efficacious in the treatment of anxiety. Also, improvement in neuropsychiatric symptoms resulting from olanzapine treatment has a positive impact on the caregivers at nursing facilities.

Our third conclusion is that olanzepine is safe, even when administered over a long period of time. Reflective of the geriatric population in general, our patients had a host of medical conditions and received numerous concomitant medications. Given the potential complications associated with these therapeutic agents, these patients tolerated olanzapine quite well. Adverse effects, particularly somnolence, postural instability, and postural hypotension, were mild and transient, and they did not result in withdrawal from treatment. Moreover, no anticholinerigic effect was observed. These results are supported by recent previous studies that found when compared with placebo, patients treated with olanzapine did not demonstrate a significant decline in cognition at any dose.[13,30,31] These data support the finding by Mintzer et al.[5] that treatment with olanzapine results in a statistical improvement in anxiety, which is definitively not secondary to an improvement in hallucinations and delusions. Therefore, it may offer a safe, well-tolerated treatment option for cognitively impaired patients with anxiety. The results obtained from this study could be considered limited since it is an open-label comparative study based on a small number of patients. However, the population was sufficient to provide statistically significant differences between the two groups of patients, and may be viewed as a good basis for further research into olanzapine. The results of an ongoing, larger, randomized double-blind study of olanzapine may help provide a safe and efficacious treatment option for a group of patients who have had few therapeutic options.

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