Management of behavioral and psychological symptoms of dementia: The role of mood stabilizers

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INTRODUCTION

Alzheimer's disease (AD) and other dementias are associated with symptoms that extend far beyond cognitive deficits. The most distressing of these symptoms are known as the behavioral and psychological symptoms of dementia (BPSD) and include delusions, hallucinations, agitation and aggression, misidentification, and sexually inappropriate behaviors. As a result of BPSD, AD patients suffer a poorer quality of life, as do their caregivers.[1] Behavioral and psychological symptoms can be so distressing to the caregiver that they are a common reason for families placing their loved ones in long-term care. Approximately 60% and 80% of dementia patients living in the community and in long-term care settings develop BPSD, respectively.[1]

Aggression and agitation are characterized by increased or disruptive psychomotor activity, inappropriate verbal activity, or disorganized motor activity that is not explained by the patient's needs. Often times, dementia patients present with aggression and agitation as well as psychotic symptoms. Atypical antipsychotics have been the most widely studied agents for the management of psychotic symptoms as well as aggression and agitation.[1] Despite their noted efficacy for BPSD, their use has been curtailed over recent years due to concerns about an increase in cerebrovascular events and increased mortality with their use. This has led to an ongoing search for other effective pharmacologic treatments for BPSD. Several mood stabilizers including valproic acid, carbamazepine, oxcarbazepine, and topiramate have been studied in dementia patients.This paper aims to present the data on the efficacy of mood stabilizing drugs for the management of BPSD.

REVIEW OF THE ACNP WHITE PAPER

In 2007, the American College of Neuropsychopharmacology (ACNP) developed a white paper on the use of antipsychotics in elderly people with dementia for the purpose of treating psychosis and agitation.[1] This paper also reviewed the use of numerous other psychotropic drugs in this population. Evidence for atypical antipsychotic efficacy in psychosis of dementia indicated that these agents have modest efficacy. The data are difficult to interpret because these studies often included patients with psychosis and agitation. To further complicate the studies, the primary outcome was often a measure of global psychiatric symptoms, not a rating scale to assess psychosis or agitation only. There have been very few studies evaluating the use of atypical antipsychotics for agitation only. This is partly due to the fact it is difficult to recruit dementia patients with agitation only since it frequently overlaps with psychosis. Agents such as risperidone, olanzapine, and aripiprazole have reportedly shown some benefit for agitation in dementia patients.

Nearly 10 years ago, the FDA issued a warning regarding cerebrovascular events (CVEs) such as strokes and transient ischemic attacks (TIAs) associated with the use of risperidone. Soon after, the FDA evaluated CVE's with other atypical antipsychotics and the warning was added to olanzapine and aripiprazole. Furthermore, an analysis of pooled data indicated that the rates of CVEs were 1.9% for patients receiving atypical antipsychotics and 0.9% for placebo-treated patients (OR 2.1, 95% CI 1.2-2.8). Of course there are limitations to these data, most notably of which is that these studies were not powered to evaluate the relationship between drug and adverse events; they were powered to evaluate efficacy. In addition, the definition of CVE is not defined in the studies, nor were these events validated. Lastly, there is likely no difference in the rates of CVEs between typical and atypical agents.

In addition to the risk of CVEs, increased mortality rates in the elderly have been reported with atypical antipsychotics. These data led the FDA to issue a black box warning for antipsychotics in the elderly regarding the higher mortality rates, which were mostly due to cardiac or infectious disease. A meta-analysis reported that the elderly mortality rate was 3.5% with atypical agents compared to 2.3% with placebo. Again, there were numerous limitations cited including limited data regarding the circumstances around the deaths as well as controversy surrounding the mortality risk in patients receiving typical antipsychotics.

The study known as the Clinical Antipsychotic Trial of Intervention Effectiveness for Alzheimer's Disease

(CATIE-AD) evaluated the use of antipsychotics in elderly dementia patients under naturalistic conditions.[2] Patients were randomly assigned to receive olanzapine, quetiapine, risperidone, or placebo. The primary outcome was time to discontinuation of treatment for any reason as well as minimal improvement as noted on the Clinical Global Impression of Change (CGIC) scale at 12 weeks. Patients reportedly discontinued quetiapine due to lack of efficacy after a mean of only 9.1 weeks compared to olanzapine and risperidone where patients continued treatment for a mean of 22.1 and 26.7 weeks, respectively. Patients discontinued all treatments earlier than placebo due to adverse events.

In addition to reporting the efficacy of antipsychotics in dementia patients with psychosis and agitation, the ACNP white paper also reported on the use of other psychotropic drugs for these symptoms.[1] There were three trials that evaluated the efficacy of VPA for agitation or aggression in dementia patients.[3-5] Two of the studies were completed in patients with agitation and one with patients with aggression. All three studies failed to show any benefit of VPA over placebo for management of aggression or agitation. Additionally, two trials evaluated the short-term (6 week) use of carbamazepine (CBZ) for agitation. Both CBZ trials were small (n of 51 and 21), and reported mixed results. Total Brief Psychiatric Rating Scale (BPRS) scores indicated that CBZ was more effective than placebo in one study[7] but no difference was found in the other.[6] Olin and colleagues actually reported that there was a significant improvement on the hostility item of the BPRS but a worsening of the hallucination item in CBZ-treated patients.[6] The authors also reported that their study lacked statistical power and that they would have needed 69 patients in order to confirm the findings regarding the total BPRS scores.[6]

Unfortunately, the long-term use of CBZ is limited by its poor tolerability, including ataxia and disorientation, and the risk of significant drug-drug interactions.

REVIEW OF VPA FOR BPSD

Since the publication of the ACNP white paper, there has been one further study that evaluated the efficacy of VPA in agitation and aggression.[8] This study included patients with moderate to severe AD and were experiencing agitation or aggression based on Neuropsychiatric Inventory Scores (NPI). Patients had to meet Diagnostic and Statistical Manual, 4th edition (DSM-IV)[9] criteria for AD, have a mini-mental status exam (MMSE) score of < 15, and an NPI > 8. This was a randomized, double-blind, placebo-controlled, cross-over study. Each treatment period was 6 weeks with a 2 week wash-out period. Forty patients were referred, but consent was obtained from only 16. Two patients dropped out prior to enrollment, leaving 14 in the study (8M, 6F). Prior to starting the study, patients underwent a wash-out of current psychotropic medications for a period equal to 5 half-lives of the drugs. Treatment was initiated with VPA 125 mg twice per day for one week and increased to 500 mg twice per day during week two. The dose was increased according to symptom response and patient tolerability to a maximum of 1,500 mg per day. The dose could be decreased, as needed. Loxapine 2.5 mg up to 4 doses per week was permitted as a rescue medication. The primary outcome was the NPI agitation score. Secondary measures were the NPI total score and the Cohen-Mansfield Agitation Inventory (CMAI). Primary and secondary outcomes were measured using the Wilcoxon signed ranks tests comparing the change in scores for VPA vs. placebo.The results indicated that the NPI agitation scores decreased for VPA-treated patients and increased for placebo-treated patients (1.43+/-3.87 vs -2.08 +/-4.05, p=0.043). The change in scores for the VPA group represents a worsening of symptoms. Worsening of symptoms was also seen on the total NPI and CMAI scores, but was significant only for the CMAI (NPI p=0.075 and CMAI p=0.039). Twelve VPA patients had adverse effects such as falls (5), sedation (4), thrombocytopenia (2), and loose stools (2). The placebo group had 2 patients with sedation and 1 fall. The conclusion is that VPA was ineffective for agitation and aggression and was poorly tolerated in elderly AD patients.

A second study was designed to evaluate the efficacy of VPA for preventing agitation and aggression in AD patients.[10] Patients had to meet criteria for possible or probable AD by the National Institute of Neurological and Communicative Disorders and Stroke AND the Alzheimer's Diseaseand Related Disorders Association criteria (NINCDS-ADRDA), have a MMSE of 12-20, and be free from agitation or psychosis as defined by NPI < 1 on items assessing delusions, hallucinations, or agitation. This was a prospective, placebo-controlled, parallel-arm flexible-dose study. Patients received VPA for two years in a double-blind fashion, and then had a two-month,single-blind placebo treatment period. The VPA target dose was 10-12 mg/kg and used identical appearing VPA and placebo tablets. The primary outcome was defined as the development of a score of at least 3 on one or more NPI items assessing delusions, hallucinations, and agitation for 2 weeks. Other scales used to assess secondary outcomes included the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog), CMAI, Alzheimer's Disease Cooperative Study activities of daily

living (ADCS-Activities of Daily Living), the Quality of Life-AD, and the ADCS Clinical Global Impression of Change (ADCS-CGIC). The primary endpoint was evaluated using the cox proportional hazards model comparing time to end point in the drug and placebo groups and adjusted for variables such as age, sex, baseline MMSE, total NPI, total CMAI, and ADCS-Activities of Daily Living. All assessments were completed at baseline, and every three months until the 24th month, then at month 26. Five hundred thirteen patients were screened and 313 were randomized. At enrollment, the mean MMSE in both groups was 16.9 and the NPI subscales for agitation, delusions, and hallucinations were < 1.0. The mean modal dose of VPA was 250 mg/day and the mean VPA level at 12 months was 42.7 mcg/ml. Sixty-one percent of VPA and 62% of placebo patients discontinued treatment early. The time to the primary endpoint did not differ between the two groups (p=0.88). Twenty-nine placebo and 25 VPA patients reached the endpoint. The mean change in ADAS-cog scores indicated that there were some differences that favored placebo (VPA 9.4, PLC 6.8, p=0.01). The ADCS Activities of Daily Living scores at 18 months also favored placebo (VPA -19.3, PLC -14.4, p=0.02). More VPA than placebo-treated patients discontinued treatment due to adverse events (16% vs 7.5%). This study failed to show any benefit of VPA in preventing the development of agitation, delusions, or hallucinations.

REVIEW TOPIRAMATE FOR BPSD

Due to the intolerability and drug interactions noted in carbamazepine trials as well as the lack of efficacy reported with VPA, other mood stabilizers have been evaluated for controlling BPSD. Topiramate (TOP) is a viable option secondary to its reported efficacy in controlling irritability and aggression in other psychiatric populations.[11] However, there is concern with the use of TOP in the dementia population due to cognitive decline reported with its use.

To date, there is only one published, prospective trial of TOP for aggression in dementia patients.[12] This was an 8-week, double-blind, randomized clinical trial, comparing topiramate to risperidone (RIS) that included 48 patients with mild to moderate severity of AD defined by an MMSE score of 10-26. Patients were included if they had a complaint of behavioral disturbances and had an NPI score of greater than 1 in sub-items relating to delusions; hallucinations; agitation and aggression; and irritability and lability. Topiramate was initiated at 25 mg/day and increased to 50 mg/day after 2 weeks. Risperidone was initiated at 0.25 mg/day with a doubling in dose every week until target dose of 2 mg/day was achieved. In both groups, the dose could be reduced if adverse events occurred. The mean daily dose of TOP was 44.0 mg and RIS was 1.9 mg. Any improvement on NPI parts 1 and 2 or the CMAI were considered the primary outcomes. Part 1 of the NPI assesses behavioral disturbances and affective and psychotic symptoms; part 2 assesses caregiver burden and distress. Cognitive function was assessed with the MMSE.

Forty eight patients were enrolled, but 41 completed the trial. Seven patients dropped out due to adverse events; fatigue and loss of appetite were reported in the TOP group and GI disturbance and akathisia in the RIS group. Both groups showed improvements in the NPI parts 1 and 2 from baseline to week 8. However, no statistically significant differences were seen between groups (NPI part I: P<0.575, NPI part 2: P<0.456). Both groups also showed a decrease in agitation as assessed by CMAI scores but no statistically significant difference noted (P<0.927). Cognitive status on the MMSE was not found to change significantly in either group (P<0.479). In conclusion, the authors found that low dose TOP had comparable efficacy to RIS in treating behavioral symptoms in Alzheimer's dementia. However, nearly 15% failed to complete the study due to adverse events.

REVIEW OF OXCARBAZEPINE FOR BPSD

Carbamazepine has shown efficacy in treating BPSD, but carries a high risk for adverse events and drug-drug interactions.[1] Oxcarbazepine(OXC) has been hypothesized to be efficacious as it has a similar structure to carbamazepine, but with better tolerability. There are case reports suggesting that oxcarbazepine may be beneficial in treating BPSD. To formally evaluate the efficacy of OXC for BPSD, an 8 week, multicenter, randomized, double-blind, placebo control trial for the treatment of agitation and aggression in patients with a diagnosis of AD, vascular dementia, or mixed dementia was conducted.[13] This study included patients with moderate to severe dementia as defined by a MMSE of 0-20, a history of agitation or aggression for at least 1 week, a score of 6 or greater on Neurospychiatric Inventory-Nursing Home version (NPI-NH) subscale for agitation and aggression, and were in a nursing home for at least 4 weeks. Patients who were receiving psychotropic medications prior to the study could not have dose changes within 2 weeks before and throughout the study. New psychotropic agents could not be initiated during the study except for haloperidol if needed as a rescue medication. Patients were randomly assigned to receive OXC 300-900 mg/day or placebo. Oxcarbazepine

Table 1. Mood Stabilizers in BPSD

Title	Design/N	Results	Conclusion
Herrmann N, et al[3] Goal: to assess efficacy & tolerability of VPA for aggression & agitation in LTC residents with mod-severe AD	Patients met DSM-IV criteria for AD and NINCDS-ADRDA criteria for probable AD, < 15 MMSE, ≥ 8 NPI. RND, DB, PLC, 6 week crossover study with 2 week washout, followed by 6 more weeks. Loxapine 2.5 mg x 4 doses/week allowed for rescue medication Primary outcome: NPI agitation score N=40 (8M, 6F) VPA dose: 125 mg BID, increased to 500 mg BID in the first 2 weeks. Could increase or decrease with max dose of 1500 mg/day	Mean age 85.6yr MMSE average: 4.5+/-4.6 NPI total 33.4+/-23.6 NPI agitation 6.4+/-3.5 Mean dose VPA 1,134 +/-400 mg Mean VPA level 48.4+/-16.8 ug.ml No benefit from VPA found. Change in scores NPI agitation – VPA 1.43+/- 3.87 Plc -2.08+/-4.05 VPA did worse than PLC p=0.043 NPI total- VPA 12.50+/-18.39 PLC -5.77 +/-18.52 P=0.075 12 VPA patients had ADRs vs 8 PLC (no diff). Number of ADRs: VPA 4.15 +/- 3.67 Plc 1.23 +/- 1.69 P=0.005	VPA ineffective and poorly tolerated in elderly LTC patients with mod-severe aggression and agitation.
Tariot PN, et al.[4] Goal: VPA for prevention of agitation & aggression in AD.	Patients met criteria for probable or possible AD by NINCDS-ADRDA criteria, age>54 yrs, MMSE 12-20, absence of agitation or psychosis defined by NPI <1 on items assessing delusions, hallucinations, agitation. N= 313 Prospective, PLC, parallel-arm, flexible-dose trial. Patients received treatment for 2 yrin DB fashion, then had a 2 mo single-blind PLC treatment period. Target dose- 10-12 mg/kg VPA. 80% adherence rate required. Primary outcome: development of at least a 3 on NPI items for delusions, hallucinations, and agitation for 2 weeks.	Primary outcome: Time to end point did not differ between groups, p=0.88. 29 PLC and 25 VPA patients reached end point. There were some secondary measures that favored PLC. ADAS-cog: PLC 6.8, VPA 9.4; P=0.01 ADCS activities of daily living at 6 mo: PLC -4.5, VPA -7; P=0.02 ADCS activities of daily living at 18 mo: PLC -14.4, VPA -19.3; P=0.02 151 PLC pts (94%) vs 147 VPA pts (95%) had an ADR. 16% of VPA vs 7.5% PLC discontinued tx due to ADR VPA had more somnolence, gait disturbances, tremor, diarrhea, constipation, weakness, asthenia, dyspnea	No treatment effect on time to end point, or on any secondary measures.
Mowla A, et al.[6] Goal: Compare TOP with RIS for controlling behavioral disturbances in patients with DSM-IV diagnosis of AD.	8 wk,DB, RND trial. N=48 enrolled, 41 completed Primary outcomes: NPI Parts I and II and CMAI TOP initiated at 25 mg/day and increased to 50 mg/day after 2 weeks RIS initiated at 0.25 mg/day, dose doubled every week until target of 2mg/day	Mean age 74.7 years 61% female Avg TOP dose 44.0 mg/day Avg RIS dose 1.9 mg/day No difference found between treatment groups on any outcome: NPI I: P<0.575 NPI II: P<0.456 CMAI: P<0.927 Reported ADR: TOP: fatigue (50%), loss of appetite (50%) RIS: GI disturbance (33%), akathisia (66%)	Low dose TOP had comparable efficacy to RIS on behavioral symptoms of AD.
Sommer O, et al.[7] Goal: To evaluate efficacy of OXC versus PLC in treating agitation and aggression in patients with AD, vascular or mixed dementia.	8 wk, multicenter, DB, RND, PLC controlled trial Primary outcome: change in agitation and aggression subscore of NPI-NH N=103, 83 completed trial OXC initiated at 75 mg qam and 225 mg qpm with titrations up to 900 mg/day with highest, well-tolerated dose maintained	Avg age: 84 75% female Avg OXC dose: 536.6 mg/day No difference found between groups for primary outcome outcome: NPI-NH agitation/aggression: P=0.70 There was no difference between groups on use of haloperidol as rescue med: P=0.26 Adverse events: OXC- 39 pts (75%) PLC- 24 pts (47%) More OXC pts had falls, ataxia, fainting, sedation, UTIs, and decrease serum sodium	No significant effect of OXC for agitation and aggression in patients with dementia

KEY: AD- Alzheimer's disease, ADAS-cog – Alzheimer's disease assessment scale –cognitive subscale, ADCS- Alzheimer's disease cooperative study –activities of daily living, DB- double-blind, DSM-IV – Diagnostic and Statistical Manual Fourth edition, LTC – long-term care, MMSE- Mini Mental Status Exam, NINCDS-ADRDA -National Institute of Neurological and Communicative Disorders and Stroke AND the Alzheimer's Disease and Related Disorders Association Criteria, NPI – Neuropsychiatric Inventory, NPI-NH- Neuropsychiatric Inventory – Nursing Home, OXC – oxcarbazepine, PLC – placebo, RIS – risperidone, RND – randomized, TOP – topiramate, VPA – valproic acid

was initiated at 75 mg in the morning and 225 mg in the evening with dose increases up to a total of 900 mg/day after 3 weeks with the highest, well-tolerated dose maintained. The mean daily dose of OXC was 536.6 mg/day. The primary outcome was the change in the agitation and aggression subscore of NPI-NH. Secondary outcomes included change in agitation measured by the Brief Agitation Rating Scale (BARS) and change in burden of care measured by NPI-NH.

A total of 103 patients were enrolled and received at least one dose of study medication with 83 patients completing the study. No significant difference was found between groups for any of the outcomes assessed regardless of whether the intention to treat or per protocol population analysis was used (NPI-NH agitation and aggression subscore P=0.70, BARS P=0.07, NPI-NH P=0.58). Interestingly, there was also no significant difference between groups in the use of haloperidol (P=0.26). The most common side effects occurring in the active treatment group included urinary tract infections, falls, a decrease in serum sodium, ataxia, fainting, and sedation. In conclusion, the study failed to show any benefit of OXC for the management of agitation or aggression in patients with moderate to severe dementia.

NONRANDOMIZED TRIALS WITH OTHER MOOD STABIIZER AGENTS

There have been some smaller, open studies and case studies published on this topic involving other mood stabilizers not already mentioned in this review. A recent case series showed benefit with low dose gabapentin 200-600 mg/day in treating aggressive behavior in seven patients with the vascular or mixed dementia.[14] Gabapentin was well tolerated and produced sustained results at follow up varying from 2-6 months.[14]

Lamotrigine has shown to be effective and well-tolerated over six months in a case report of a patient diagnosed with frontal lobe dementia who was demonstrating verbal and physical aggression.[15] Another case series of five patients with dementia, manic-like symptoms, and agitation treated with lamotrigine reported improvements on the Young Mania Rating Scale (YMRS) after five months of treatment.[16] None of the patients had to discontinue therapy due to adverse events.

Two small, open-label trials with less than 20 patients each reported the effectiveness of levetiracetam for the management of behavioral disturbances in patients with dementia. Both trials found significant improvement from baseline in the NPI and YMRS.[17,18] One report indicated that three patients required a dose reduction of levetiracetam as two patients experienced lethargy and one had an increase in agitation.[17] The second study noted that no patient had to discontinue therapy due to adverse events, but did not mention if any dose reductions were required.[18]

CONCLUSION

Since the publication of the ACNP White Paper in 2007, there have only been three randomized clinical trials studying mood stabilizers for treatment of BPSD. Low-dose TOP and RIS were reported to be equally effective for BPSD. Prospective, placebo-controlled trials of OXC and VPA failed to show any benefit in patients with BPSD. Open trials and case studies have shown some limited effectiveness for gabapentin, lamotrigine, and levetiracetam and require further evaluation in a controlled setting.

Due to a paucity of data indicating efficacy and safety, no mood stabilizer is currently FDA approved for the management of BPSD. If a mood stabilizer is indicated for patients with dementia showing aggressive or agitated behavior, their use should only be considered in cases where the symptoms pose serious risk to the patient or their caregivers. Antipsychotics have the most data indicating some moderate efficacy for BPSD, but their use is associated with serious adverse events, like CVEs, and an increased mortality in the elderly. Carbamazepine also has reported mixed efficacy but is associated with poor tolerability and a risk of drug-drug interactions. Gabapentin, lamotrigine and levetiracetam may hold promise, but further research using placebo controlled trials are needed before recommendations can be made with these agents. Overall, no single pharmacologic agent has shown efficacy and tolerability in the elderly patient with BPSD. Their use should be carefully considered on an individual basis in patients with clearly identified target symptoms followed by close monitoring for improvement.

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