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Low-dose Lithium treatment for agitation and psychosis in Alzheimer's disease and Frontotemporal dementia: A case series

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INTRODUCTION

Symptoms of agitation, aggression and psychosis commonly occur in patients with dementia, are distressing to patients and caregivers, often lead to institutionalization, are associated with increased mortality, and are difficult to treat.[1,2,3,4] Among psychotropic medications studied in Alzheimer's disease (AD), the most common type of dementia, only antipsychotics have demonstrated efficacy consistently in randomized, double-blind, placebo-controlled trials to treat agitation and psychosis, but they are associated with several side effects and increased mortality.[5, 6] Antipsychotics are also used to treat behavioral symptoms in frontotemporal dementia (FTD), but the limited data fail to demonstrate efficacy.[7,8]

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Conflicts of interest

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Lithium is an established treatment for bipolar[9] and other psychotic disorders in which agitation can occur. Lithium has not been evaluated in placebo-controlled trials to treat agitation/aggression with or without psychosis in AD[9] or FTD.[7] In AD, lithium has been studied for its putative cognitive enhancing effects; patients with psychosis or agitation were typically excluded from these studies.[10,11] There are few case reports on lithium to treat agitation in dementia[11]. In one report, an 87 year-old woman with AD showed symptoms of agitation, aggression, and wandering. After four days of treatment with lithium 300 mg daily, symptoms decreased with a serum lithium level of 0.2 mmol/L. She was maintained on lithium 300 mg and 150 mg on alternating days with a level of 0.8 mmol/L. Her decreased behavioral symptoms allowed for transfer to an extended care facility.[12]

In the FTD-spectrum illnesses of Progressive Supranuclear Palsy (PSP) and Corticobasal Degeneration (CBD), a lithium trial to study its putative neuroprotective effects at a serum level of 0.4 to 1.2 mmol/L was stopped due to poor tolerability, including increased falls.[13] Effects of lithium on the behavioral symptoms of FTD have not been studied.

We report on three patients with AD and three patients with FTD presenting with agitation/aggression with or without psychosis who were treated with low-dose (150 mg–600 mg daily) lithium; all patients improved to varying degrees as determined by clinical judgment and/or objective rating scales, Clinical Global Impression Severity (CGI-S) and Change (CGI-C) scales, and the Neuropsychiatric Inventory (NPI).

CASE 1

A 77-year-old female residing at home with probable AD of moderate severity and history of depression for two to three years prior to the onset of AD, was evaluated for increasing agitation and psychosis. Caregivers reported that the patient was sleepless, had intense anger outbursts, persecutory auditory hallucinations, and paranoia. She continually paced, opening drawers, unpacking and repacking their contents.

At the time of evaluation, she was being treated with quetiapine 25 mg and paroxetine 10 mg daily. Based on the physician’s discussion with the patient and family the patient did not receive cholinesterase inhibitors. Lithium 150 mg was added and increased from 150 mg to 300 mg daily after two weeks. By week two she had a normal sleep cycle with a marked decrease in paranoia, auditory hallucinations, agitation, and aggression. Her serum lithium level was 0.32 mmol/L after 10 weeks of treatment and she experienced no adverse events.

CASE 2

A 67-year-old male with probable AD and a history of depression was evaluated for worsening auditory and visual hallucinations, paranoia, anxiety, anger and frustration. He presented with persistent agitation, anger outbursts and shuffling gait. The patient repeatedly called his son every day. At the time of evaluation, he was taking quetiapine 100 mg, memantine 20 mg and sertraline 100 mg daily; trazodone 50 mg was added for insomnia a few weeks later. Lithium 150 mg was added and titrated up to 600 mg daily in intervals of 150 mg every two weeks. After six weeks on lithium, olanzapine 15 mg daily was added, and quetiapine was stopped. At the final clinic visit he remained on olanzapine 15 mg,

sertraline 100 mg, trazodone 50 mg and lithium 600 mg daily. He exhibited marked reduction in symptoms with a decrease in anger outbursts, physical aggression, paranoid delusions and accusations, and improved gait after 12 weeks on lithium and 6 weeks on olanzapine. His serum lithium level was 0.30 mmol/L at 12 weeks and he experienced no adverse events. The patient's agitation was effectively managed during 24 months of follow-up, although he was institutionalized when his disease progressed.

CASE 3

A 79-year-old male with mild probable AD and a history of late-onset anxiety and depression was evaluated for uncontrollable anger outbursts and agitation. He had become extremely argumentative with both his wife and his co-workers at a part-time job. When unable to complete a task he would become uncontrollably angry and grabbed his wife's wrists once. At the time of evaluation, the patient was taking donepezil 10 mg, bupropion 300 mg, lorazepam 0.5 mg, and trazodone 50 mg daily. He was started on lithium 150 mg, which was increased to 300 mg daily after two weeks. After 12 weeks of lithium treatment, he exhibited a significant decrease in angry thoughts, frustration, and irritability. His last recorded serum lithium level, after 8 weeks of treatment, was 0.32 mmol/L. He remained on lithium and continued to work part-time without any adverse events. He continued to decline cognitively with persistent but less severe agitation.

CASE 4

A 77-year-old female with behavioral variant FTD was evaluated after staff at her assisted living facility identified severe agitation and aggression. She was physically aggressive and stole food from other residents. She was increasingly frustrated and repetitively grunted and yelled, upsetting staff and other residents. She stole a visitor's car at her assisted living facility, and crashed it resulting in injury. She also experienced repeated visual hallucinations about her doctor giving her an injection in her room. At the time of evaluation, she was taking paroxetine 20 mg, risperidone 1.5 mg, and trazodone 200 mg daily. She had been taking donepezil 5 mg, which was discontinued because it is not helpful for patients with FTD. She started lithium 150 mg, which was increased to 300 mg daily after two weeks. Symptoms decreased after one week of treatment with lithium 300 mg and the patient remained relatively stable without any adverse events in the assisted living facility. The last recorded non-trough lithium level was 0.8 mmol/L.

CASE 5

A 55-year-old male with semantic variant-primary progressive aphasia was evaluated for outbursts of severe agitation, skin picking, frequent elopement attempts, and multiple instances of shoplifting. At the time of evaluation, he was being treated by another psychiatrist with donepezil 23 mg, clonazepam 1 mg, duloxetine 60 mg, fluvoxamine 100 mg, venlafaxine 37.5 mg, lisdexamfetamine 30 mg, and lithium 600 mg daily. When behavioral symptoms did not fully resolve, lithium was increased to 1200 mg daily, which was reduced to 600 mg after one week when he became sedated and developed a tremor. The initial improvement in behavioral symptoms was maintained and all other psychiatric

medications were tapered and discontinued over time. The patient remained on lithium until his death two years after starting treatment. Serum lithium levels were not recorded.

CASE 6

A 65-year-old male with FTD was admitted via a hospital emergency room for episodes of agitation with increasing severity. The patient was physically violent, experiencing auditory and visual hallucinations, and was ingesting inedible materials. Prior to hospitalization, he was on galantamine 8 mg, which was discontinued upon the diagnosis of FTD. At admission he was receiving chlorpromazine 250 mg, sertraline 100 mg, and haloperidol 2 mg daily. He was started on lithium 300 mg daily for five days, which was increased to a maximum dose of 450 mg daily without any adverse events. While still hospitalized, the patient no longer required prn haloperidol after beginning lithium. Agitation, violent behavior, and other behavioral disturbances improved significantly. The last serum lithium level was recorded as 0.40 mmol/L on 450 mg daily.

DISCUSSION

Three patients with AD and three patients with FTD with agitation/aggression with or without psychotic features responded to treatment with lithium at daily doses ranging from 300 mg–600 mg with recorded serum levels of 0.2–0.6 mmol/L in five cases and 0.8 mmol/L (non-trough) in one case. Low oral lithium doses of 150–600 mg daily were associated with low serum levels and side effects were observed only when the lithium dose exceeded 600 mg daily (case 5). In a study of low-dose lithium (150 mg–600 mg daily with serum levels of 0.2–0.8 mmol/L) evaluated as a cognitive enhancer in elderly patients with dementia, lithium was tolerated well and the neurological side effects of tremor, gait disturbance and confusion were not consistently greater on lithium compared to placebo.[11,10,14]

In our case series, when low-dose lithium was used as an add-on to antipsychotic treatment, several symptoms improved: auditory hallucinations, visual hallucinations, paranoia, anxiety, anger/aggression, agitation, impulsivity, and physical violence. It remains unclear if lithium is effective in the treatment of symptoms of agitation and psychosis in dementia by itself or if its effectiveness is related to concomitant antipsychotic use. A common clinical scenario is the difficulty in increasing the dose of antipsychotics when side effects develop; our case series suggests that adding lithium is an option that should be considered. For example, case 6 became violent and self-injurious by ingesting inedible materials. Treatment with antipsychotics was unable to successfully treat these symptoms, but adding low-dose lithium markedly reduced these behavioral disturbances.

Lithium has inhibitory effects on glycogen synthase kinase-3 (GSK-3) and tau phosphorylation,[15,16] leading to interest in lithium as a possible neuroprotective agent for tauopathies including AD and subtypes of FTD. The mechanism of action for lithium as a treatment for agitation remains unclear, partly because lithium has a multitude of neurotransmitter effects in the brain.[9,15]

In patients without dementia, lithium is an effective treatment for agitation and other behavioral disturbances associated with several psychotic disorders.[9] In our case series,

short-term to intermediate-term follow-up indicated that lithium was effective in treating agitation and other behavioral disturbances. The findings support the need for a randomized, double-blind, placebo-controlled trial to evaluate lithium as a treatment for agitation in subtypes of dementia including AD and FTD.

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