Review Article

Managing Agitation in Alzheimer Disease and Related Disorders

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Abstract

**Background:** Alzheimer disease (AD) will affect increasing numbers of subjects as the population ages. Patients with AD and related disorders often develop agitation during the moderate to severe stages of their dementia. Agitation is often the reason that dementia patients need to be institutionalized. This review will address the natural history of agitation in AD, dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD). It will also discuss the use of antidepressants, antipsychotic agents and anticonvulsant drugs in preventing and treating agitation in dementia patients.

**Results:** Atypical antipsychotic drugs are sometimes needed in mild to moderate stages of DLB and FTD to manage agitation, whereas they are not usually needed until moderate to severe stages of AD to control psychotic thinking or agitated behaviors. Citalopram has recently been shown to prevent agitation in AD patients. Divalproex does not work well to prevent agitation in dementia patients when it is used as monotherapy, but it is usually effective when used in combination with antipsychotic or antidepressant drugs. Serotonergic agents such as trazodone and selective serotonin uptake inhibitors (SSRIs) are useful to reduce disinhibition and repetitive behaviors in FTD patients.

**Conclusion:** Agitation can be treated in dementia patients by using a combination of antidepressant, antipsychotic and anticonvulsant drugs.

ABBREVIATIONS

AD: Alzheimer’s Disease; DLB: Dementia With Lewy Bodies; FTD: Frontotemporal Dementia; SSRI: Selective Serotonin Uptake Inhibitor

INTRODUCTION

Dementia is a problem that affects 25 million people around the world today, about 50% of whom have AD [1]. The annual number of incident cases of AD is projected to increase from 377,000 cases/yr in 1995 to 959,000 cases/yr in 2050 [2]. Agitation and aggression are common features of dementia as the disease progresses [3]. Common symptoms of agitation include motor restlessness, pacing, excessive fidgeting, repetitive behaviors and abnormal vocalization. Atypical antipsychotic drugs (risperidone, olanzapine and quetiapine) are commonly used to control agitation in AD patients [4,5]. This review will discuss the use of other agents that have been shown to prevent agitation in AD patients, such as citalopram, trazodone and divalproex. It will also review other types of dementia, such as DLB and FTD, as well as the drugs that are unique to treating agitation in those conditions.

CASE 1 VIGNETTE: AGITATION IN ALZHEIMER DISEASE

This 65 year old right-handed woman had severe symptoms of AD. She had a memory disorder that had progressed slowly over a seven year period. An MRI of the brain supported the diagnosis of AD (it showed marked atrophy of both hippocampi and enlargement of both temporal horns). When she was placed in a nursing facility in the Fall, she was taking donepezil 10mg/d, memantine 10mg bid, and citalopram 20mg/d (she scored 6/30 on the MMSE at that time). She needed quetiapine 25mg tid then to control her agitation. By the Spring, she was pacing the halls of the nursing home and was becoming more and more agitated and restless. She walked into other patients’ rooms and attempted to remove them from their beds. The patient’s behavior improved in about a week after the addition of divalproex 250mg bid. Citalopram has been shown to reduce agitation in patients with AD. The starting dose is 10mg/d, then it can be increased to 30mg/d over three weeks. Cardiac and cognitive side effects sometimes limit the dosage range to 10-20mg/d [6]. The other drug that is useful for preventing agitation in severe AD patients is valproic acid, or divalproex. Meta-analysis of pooled results
of trials with valproic acid for agitation in dementia patients showed that valproate was not effective as monotherapy, and it had an unacceptable rate of adverse effects [7]. Nevertheless, when used in combination with other psychotropic drugs, valproic acid has been shown to be effective as treatment for the agitation associated with dementia [8].

**CASE 2 VIGNETTE: AGITATION IN DEMENTIA WITH LEWY BODIES**

This 77 year old right-handed man had moderate DLB. A year after the onset of memory loss, he developed visual hallucinations, delusional ideas, shuffling gait and excessive daytime sleepiness. An MRI of the brain showed diffuse cortical atrophy, a sign consistent with this diagnosis. An examination a year prior to the index phone interview showed MMSE=16/30 and mild flattening of affect. He had mild dysarthria and moderate motor apraxia with the modified Luria test. Tone was moderately increased in both arms and there was moderate slowing of finger taps bilaterally. There was no tremor at rest. He walked with a stooped posture and had a shuffling gait. He had been taking donepezil 10mg/d for memory loss, carbidopa-levodopa 50/200 bid for the shuffling gait and quetiapine 25mg bid for delusional ideas (he became fearful in the evenings when his wife left the house). His wife called recently to report that the patient had become very agitated and restless. He was pacing about and unable to sit still. He improved somewhat when the dose of carbidopa-levodopa was reduced to 25/100 bid and the dose of quetiapine was raised to 25mg tid. A more satisfactory response was achieved a week later when divalproex was added at 250mg bid. DLB is the second most common cause of dementia after AD, with the estimated prevalence ranging from 15-25% of all dementing illnesses [9-11]. It is characterized by progressive dementia in addition to at least two other features: parkinsonism, visual hallucinations, daily fluctuation in cognition, and REM sleep behavior disorder [12]. Walker and others [13] showed that DLB patients have higher psychiatric symptom scores (Neuropsychiatric Inventory) than AD patients when they are still in the mild stage of dementia (mean baseline MMSE=21/30 in both groups). They found that in the mild stage, 16% of DLB patients needed neuroleptic medications for agitation, compared to only 4% of AD patients (p=0.01). Our patient needed quetiapine when he was still in the mild stage of DLB because of his delusional ideas. Delusions occur along with agitation in about 50% of DLB patients, and atypical antipsychotic drugs are often needed to manage the agitation [12,14,15]. Cholinesterase inhibitors such as donepezil, rivastigmine, or galantamine are used to treat DLB patients, and they are especially effective at managing the complex visual hallucinations and the nighttime behaviors [12,16]. Typical antipsychotic drugs should not be used in DLB patients, because of the increased neuroleptic sensitivity in this population, including worsening sedation, confusion, parkinsonism and reduced mobility. Caregivers should be warned of neuroleptic sensitivity in DLB patients, since in rare cases, both typical and atypical antipsychotic drugs can cause neuroleptic malignant syndrome, a condition that can be potentially fatal [17].

**CASE 3 VIGNETTE: AGITATION IN FRONTO-TEMPORAL DEMENTIA**

This 65 year old right-handed woman has FTD, delusional disorder, anxiety, depression and agitation. When her memory problems began four years prior to the index interview, her MRI showed frontal lobe atrophy that was consistent with the behavioral variant of FTD. Since the onset of her illness, she had had delusional ideas and frontal lobe behaviors (she showed disinhibited behaviors; she had an excessive appetite, and she put too much food on her fork when she ate her meals). An examination in the Fall prior to the index interview showed MMSE=9/30 and disinhibition (she slapped her husband at one point in front of the examiner). Her affect was flattened. There was no dysarthria, and she made no paraphasic errors. Cranial nerve exam was unremarkable, except for slowed and hypometric saccades and irregularities of smooth pursuit eye movements. Motor exam showed mild rigidity in the right arm, but there was no tremor at rest. She had motor apraxia when performing the modified Luria test. She had a normal regular gait, and she was able to walk on toes, heels, and in tandem. She had been taking citalopram 30mg/d for depression, lorazepam 1mg tid for anxiety, quetiapine 25mg qid for delusional disorder, divalproex 250mg bid for agitation and risperidone 0.5mg bid prn for severe agitation. A nurse from the nursing home called in the Spring to complain about the patient having falls that werein her words, “caused by divalproex”. The nurse asked the neurologist if the divalproex could be stopped. The quetiapine dose was reduced instead to 25mg tid, and this seemed to prevent the patient’s falls.

Valproic acid is a useful agent for preventing agitation in patients with dementia [8]. There have been several reports that valproic acid could cause signs of parkinsonism in the elderly, but there appears to be no relationship between drug dosage or plasma levels [18]. In this setting, the patient was on three drugs that could have been causing drug-induced parkinsonism

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
<th>Daily dose</th>
<th>Range of doses</th>
<th>Common side effects</th>
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<tbody>
<tr>
<td>quetiapine</td>
<td>Seroquel</td>
<td>100mg</td>
<td>25-200mg</td>
<td>sedation, dizziness</td>
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<td>250-1000mg</td>
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<td>citalopram</td>
<td>Celexa</td>
<td>20mg</td>
<td>10-30mg</td>
<td>dizziness</td>
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<tr>
<td>trazodone</td>
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<td>50-200mg</td>
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(quetiapine, risperidone and divalproex). The risperidone was only being given on a prn basis, so it was unlikely to be the culprit. This patient had some subtle signs of drug-induced parkinsonism at baseline (rigidity). Ideally, she should have been reassessed before changes were made in her treatment regimen. It is a matter of clinical judgment as to whether the dose of quetiapine or divalproex should have been reduced in order to prevent the patient’s falls.

FTD is the third most common cause of neurodegenerative dementia, following AD and DLB, but it is often more difficult to manage than either of the more common dementias [19]. There are usually profound alterations in social conduct in the behavioral variant of FTD. There may be signs of inertia and loss of volition in addition to disinhibited behaviors and loss of control over various appetites. SSRIs, such as citalopram, are useful in managing disinhibited and repetitive behaviors in FTD [20]. Trazodone is an alternative serotonergic agent that has also been shown to be useful in managing agitation in patients with FTD [21,22].

DISCUSSION AND CONCLUSION

Agitation is a common problem among dementia patients, especially moderate to severe AD [6] and mild to moderate DLB and FTD [12,13,19]. In the past, we used atypical antipsychotic agents for managing agitated behaviors in these patients [3,4], but now we have atypical agents and trazodone for FTD [21,22]. Valproic acid is also effective for reducing agitated behaviors when psychotropic drugs are already present [8], even though it is not useful as monotherapy [7].

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REFERENCES


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