Safety and Efficacy of Pharmacological Management of Agitation in Alzheimer’s Dementia - A Review

Anjali N Kalore, Dhananjay Medappa, Eukesh Ranjit, Sandeep S Nayak,

ABSTRACT

Agitation is a common and distressful symptom in Alzheimer’s dementia. Pharmacological treatment is frequently needed when symptoms are moderate to severe. Basic etiology and pathogenesis of agitation is not well understood and this makes targeted pharmacotherapy challenging. Many drugs have been tried but FDA has not approved any drug for treatment and there is lack of consensus. We review the principles, indications and current Level I evidence on the safety and efficacy of various drugs used for treatment of agitation in Alzheimer’s Dementia. We find that newer drugs like citalopram and prazosin have greater efficacy and are better tolerated than antipsychotic medications.

Keywords: Safety, Efficacy, Pharmacological Management, Agitation, Alzheimer’s Dementia
**INTRODUCTION**

Alzheimer’s Dementia (AD) is a progressive neurodegenerative disease with characteristic changes in the brain that include extracellular beta amyloid deposition, intracellular neurofibrillary tangles, inflammation, loss of neuronal connections and death of neurons. Clinically, AD is characterized by a gradual onset, progressive decline in multiple cognitive functions. AD affects 5%–15% of the population over 65 years and 20% of individuals over 80 years. Over 40% of patients with AD develop psychosis, which is characterized by delusions or hallucinations and may be associated with agitation. Agitation is a cluster of related symptoms that includes anxiety, irritability, and motor restlessness, leading to behaviors such as pacing, wandering, shouting, and aggression. Agitation is seen in 24% of people with AD in the community and 48% of those in residential care facilities. Agitation may be caused by neurodegeneration of the frontolimbic regions, distress due to environmental changes, illness, pain, poor sleep, depression or a side effect of medications. Agitation causes caregiver distress and increases risk of institutionalization. Non-pharmacologic management of agitation includes ensuring a safe, calm and predictable environment, music therapy, psychomotor therapy, behavioral therapy, and distraction and avoidance techniques. However, this is of limited benefit.

Pharmacological treatment of agitation in AD is frequently needed. There are a limited number of Level I studies evaluating the safety and efficacy of various drugs. There are widely accepted recommendations that are based on limited data. FDA has not approved any medications for this purpose and there is no consensus on which drugs to use. The purpose of this manuscript is to examine the principles, indications and current Level I evidence on the safety and efficacy of various drugs used for treatment of agitation in Alzheimer’s Dementia. We searched MEDLINE (Ovid SP) (1966 to date) primarily for randomized controlled trials evaluating safety and efficacy of various drugs used for treatment of agitation in AD. We reviewed the articles about the safety and efficacy, indications for use and recommendations for use of various drugs for treatment of agitation in AD.

Antipsychotics are the most commonly used drugs for agitation in AD. Typical antipsychotic drugs were used for agitation and behavioral psychotic disorders in AD starting in the 1970s. Atypical antipsychotics replaced typical antipsychotics in the 1990s because of the lower risk of motor adverse effects like tardive dyskinesia. However, atypical antipsychotics were found to be associated with a significantly increased mortality rate. This prompted FDA to issue a black-box warning about use of atypical antipsychotic agents. In recent years, other psychotropic medications have undergone clinical trials. Newer research is identifying novel targets and approaches that may be more causally related to agitation in AD.

**Typical antipsychotic agents**

Typical antipsychotic agents were used for agitation and behavioral psychotic disorders in AD “off-label” based on their benefits in Schizophrenia. We found 11 RCTs that evaluated the impact of typical antipsychotics versus placebo on agitation. Most trials were small, had mixed dementias and had 4-12 weeks of treatment duration. There was a significant but modest improvement compared with placebo. The typical antipsychotic haloperidol was effective in improving aggression but not agitation in four RCTs. There is very little evidence base for other typical antipsychotics for treatment of these symptoms.
There are significant and numerous safety concerns associated with the use of typical antipsychotics in patients with Alzheimer’s disease. Adverse effects include parkinsonism\(^1\), dystonia, tardive dyskinesia, acceleration of cognitive decline and prolongation of the QTc interval on ECG, leading to added risk of cardiac arrhythmias. Most typical antipsychotic agents have been withdrawn with exception of haloperidol due to safety concerns\(^12\).

**Atypical antipsychotic agents**

Overall, atypical antipsychotic drugs appear to have modest efficacy for treating the psychosis of AD\(^13,14\). However, some studies found no significant advantage over placebo in terms of psychotic symptoms\(^15,16\). Schneider et al.\(^15\) reviewed 15 RCTs of atypical antipsychotics for agitation and/or psychosis of dementia (3 with aripiprazole, 4 with olanzapine, 4 with risperidone, 1 comparing olanzapine and risperidone, and 3 with quetiapine). Eleven trials were conducted in nursing homes and four in outpatient settings. A total of 3353 patients were randomized to atypical antipsychotic treatment and 1757 to placebo group. A vast majority of subjects included had AD (87%), were women (70%) and had a mean age of 81 years. Overall, atypical antipsychotics, especially risperidone and aripiprazole improved general neuropsychiatric symptoms. However, it is difficult to separate the efficacy of these drugs on agitation or psychosis because of heterogeneity in sample (outpatient versus inpatient) and outcome measures. Subgroup analysis revealed better overall response in patients with psychosis, nursing home residents and those with severe cognitive improvement. Adverse events were mainly somnolence and urinary tract infections or incontinence with drugs and extrapyramidal symptoms or gait abnormalities with risperidone and olanzapine. There was a significant risk for cerebrovascular events especially with risperidone.

In the Clinical Antipsychotic Trial of Intervention Effectiveness study for Alzheimer's disease (CATIE-AD trial), the largest (N=421) non-industry sponsored study of atypical antipsychotics for psychosis or agitation/aggression in people with dementia, olanzapine, quetiapine, and risperidone were no better than placebo for the primary outcome (time to discontinuation for any reason) or the secondary outcome (Clinical Global Impression or CGI)\(^17\). Time to discontinuation due to lack of efficacy favored olanzapine and risperidone, while time to discontinuation due to adverse events favored placebo. The CATIE-AD outcome measures assess effectiveness (not efficacy) in more clinically meaningful or relevant outcomes. This is in contrast to many previous trials, which used psychopathologic rating scales such as the Neuro-Psychiatric Inventory (NPI), Brief Psychiatric Rating Scale (BPRS), and BEHAVE-AD to assess efficacy\(^18-20\). The CATIE-AD trial had some limitations: 1) possible under-dosing of antipsychotics (especially regarding quetiapine) 2) the relatively high discontinuation rates compared to previous efficacy trials\(^15\) 3) all patients were outpatients and this group possibly responds less to atypical antipsychotics compared to nursing home residents or more cognitively impaired patients.

In a meta-analysis of large-scale RCTs of atypical antipsychotics in dementia, the “Number Needed to Treat” (NNT), ranged from 5 to 14\(^15\). The overall average treatment effect was about 18%, similar to that of typical antipsychotics\(^10\).

Only a few studies of antipsychotics specifically targeted agitation or aggression. Schneider et al.\(^15\) reported better response of atypical antipsychotics for dementia patients without...
psychosis; thus, patients with agitation alone may preferentially respond to these medications. Some, though not all, RCTs with risperidone, antipsychotics for dementia patients without psychosis; thus, patients with agitation alone may preferentially respond to these medications. Some, though not all, RCTs with risperidone, olanzapine, and aripiprazole have shown modest efficacy for reducing aggression and overall agitation in AD\textsuperscript{13,14}.

Adverse effects of atypical antipsychotics include somnolence, extrapyramidal symptoms, gait disturbances and an increased risk of cerebrovascular events (OR\~3) -nonspecific neurologic events rather than strokes\textsuperscript{21}. Also, there is an increased mortality (OR \~ 1.5) with atypical antipsychotic agents compared to placebo\textsuperscript{22}.

As per American Psychiatric Association’s Practice Guidelines for Treatment of AD, antipsychotics are recommended for the treatment of psychosis and agitation despite potentially serious adverse effects, with proper informed caregiver consent.

**Cholinesterase inhibitors**

Cholinesterase inhibitors (ChEIs) like Donepezil have been found to be useful for cognitive symptoms in AD. There is limited evidence that ChEIs may improve overall Behavioural and Psychological Symptoms of Dementia (BPSD)\textsuperscript{23} and BPSD may worsen after withdrawal of ChEIs\textsuperscript{24}. However, donepezil and rivastigmine showed no treatment benefit for the treatment of clinically significant agitation in two RCTs\textsuperscript{2,25}. Overall, ChEIs do not appear to be useful in the management of agitation but may be helpful for depression, apathy and anxiety\textsuperscript{26}.

**Memantine**

Memantine is the first in a novel class of Alzheimer’s disease medications acting on the glutamatergic system by blocking NMDA receptors. Memantine has been found to be useful in the treatment of mild-to-moderate irritability, agitation or aggression for up to 6 months\textsuperscript{27-30}. Besides, memantine may be of value in reducing the emergence of overall BPSD\textsuperscript{30}. However, randomized controlled trials of memantine have contradictory findings. One recent trial, the Memantine for Agitation in Alzheimer’s Dementia trial, did not observe any improvement in agitation in 153 people treated with memantine or placebo over 6 and 12 weeks\textsuperscript{31}. However, in another recent RCT\textsuperscript{32} the Donepezil and Memantine in moderate to severe Alzheimer’s Disease trial, reported a 5.5-point significant advantage favouring memantine over placebo at 6-month follow-up on the total Neuropsychiatric Inventory\textsuperscript{32}. The current evidence indicates that memantine may have some benefit in the prevention and treatment of mild-to-moderate agitation. Further RCTs may be needed to clarify the role of memantine in the treatment of agitation in AD.

**Antidepressants**

There is limited evidence for the use of antidepressants to address agitation and aggression. Clinical trials have provided wide spectrum of results. Few trials have shown that use of citalopram leads to improvement in BPSD in AD with particularly notable effect on agitation or aggression\textsuperscript{33}. Besides, citalopram has far better tolerability compared to antipsychotics\textsuperscript{34}. RCTs of sertraline\textsuperscript{35} and trazadone\textsuperscript{36} have been less promising. Citalopram is relatively contraindicated in patients who have congenital long QT syndrome, hypokalemia, hypomagnesaemia, active heart disease. Also, overlapping with an antipsychotic medication for the first few weeks may be helpful as the SSRI may require that time frame for its actions to be evident.
Anticonvulsants
Initial RCTs of carbamazepine have shown some overall benefit\textsuperscript{26,37,38} in neuropsychiatric symptoms and good tolerability in people with Alzheimer’s disease. In contrast, valproate has not shown benefit for treatment of BPSD\textsuperscript{39}.

Alpha-adrenoceptor blockers
Postmortem studies have established a relationship between altered adrenoceptors and agitation and aggression in people with AD\textsuperscript{40}. The alpha adrenoceptor blocker prazosin has been found to be useful for treatment of BPSD in AD in a preliminary, small RCT\textsuperscript{41}.

Conclusions
Treatment of agitation in Alzheimer’s dementia is still evolving and the FDA has not approved any drugs for the same at the moment. Atypical antipsychotics have a role in short term management of these patients, but there is a significant risk of adverse events. Antidepressant agents are well tolerated but have limited evidence for efficacy in the treatment of neuropsychiatric symptoms of dementia other than depression. Overall, the published literatures based on preliminary studies support the greater efficacy of newer treatments like citalopram and prazosin and are far better tolerated than antipsychotic medications. Considering the potential for increased quality of life, these newer treatments should have a great impact on treatment of agitation worldwide. While prescribing these newer medications, doctors should work with their patients to develop a strategy that ensures maximum patient compliance. Strategies to tailor a regimen personalized to patient might serve useful. Where substitutions are not possible, supervised starts and dosage reductions may be needed.

To treat agitation in AD in more efficient and safe way, it is important to further investigate, systematically synthesize data from level I studies and estimate the safety and efficacy of various drugs used for treatment. Also, current evidences of drugs such as prazosin and citalopram are promising and large-scale clinical trials are needed. Besides, there is a need for better understanding of the basic etiology and pathogenesis of agitation and development of targeted pharmacotherapy.

Conflicts of Interest
The authors declare that there is no conflict of interests regarding the publication of this paper.

Author Contributions
Anjali N Kalore, MD: Conceived and designed the experiment. Analyzed the data. Wrote the first draft of the manuscript. Agree with manuscript results and conclusions. Developed the structure and arguments for the paper. Reviewed, made critical revisions and approved of the final manuscript.

Dhananjaya Medappa, MD: Contributed to writing the manuscript, was involved in the literature review.

Eukesh Ranjit, MD: Contributed to writing the manuscript, was involved in the literature review and critical revision.

Sandeep S Nayak, MBBS: Contributed to the writing of the manuscript. Developed the structure and arguments for the paper. Made critical revisions and approved final manuscript.

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