

The treatment of behavioral disturbances and psychosis associated with dementia

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Summary

Behavioral disturbances and psychosis associated with dementia are becoming an increasingly common cause of morbidity in patients with dementia. Approximately 70% of individuals with dementia will experience agitation, and 75% will experience symptoms of psychosis such as delusions or hallucinations. The goal of this article is to review the pharmacologic treatment options for behavioral disturbances and psychosis associated with dementia. A literature review was conducted on PubMed/Medline using key words of “dementia” and “interventions.” The results were filtered for meta-analysis, clinical trials, and systematic reviews. The results were then reviewed. At this time, the most evidence exists for the use of a second generation antipsychotics (SGAs), but consideration should be given to their collective boxed warning of morbidity/mortality. The evidence for second line treatments are limited. There is limited evidence to support the use of first generation antipsychotics (FGAs), antidepressants, anticonvulsants, cognitive enhancers, and analgesics. Additional randomized control trials are needed to guide clinical decision making regarding the behavioral disturbances and psychosis associated with dementia.

Key words: dementia, psychosis, behavioral disturbances

Introduction

Dementia has been described as a progressive and irreversible cause of cognitive decline. It affects approximately 20% of those over the age of 80 in the severe form [1]. It can be classified as either cortical or subcortical in etiology. The most common

cause of cortical dementia is Alzheimer's disease, which is commonly associated with aphasia and apraxia. Subcortical dementias include conditions such as Parkinson's disease and Huntington's disease, which are more commonly associated with movement disorders. As the population ages, dementia is becoming a major global public health burden.

Behavioral disturbances and psychosis associated with dementia are becoming an increasingly common cause of morbidity in this patient population. These behavioral disturbances often include aggression, agitation, wandering, verbal aggression, hostility, irritability, and psychosis. Approximately 70% of individuals with dementia will experience agitation, and 75% will experience symptoms of psychosis such as delusions or hallucinations [1]. Unfortunately, a large majority of individuals with dementia will develop behavioral disturbances and psychosis. There is not an accepted gold standard for the pharmacologic treatment of these behavioral disturbances. These behaviors may be distressing to the patient, dangerous, and place a burden on caregivers.

Aim

The goal of this article is to review the pharmacologic treatment options for behavioral disturbances and psychosis associated with dementia. It should be noted that nonpharmacologic interventions should be tried first and are likely to be beneficial [2]. However, pharmacologic treatments should be considered when first line treatments are not successful. At this time, there are no FDA-approved medications for the treatment of the behavioral disturbances and psychosis associated with dementia. It is our intention to provide a review of the treatment options, and a discussion of the associated risks and benefits of these treatments.

Method

A literature review was conducted on PubMed/Medline using key words of "dementia" and "interventions." The results were filtered for meta-analysis, clinical trials, and systematic reviews. Inclusion criteria included pharmacologic studies. The non-pharmacologic trials were excluded. Additional searches were later performed to gather information regarding second line treatments "gabapentin," "trazodone," "haloperidol," "anticonvulsants," "memantine," "prazosin," "cholinesterase inhibitors," and "analgesics." These terms were searched with "dementia." The resulting articles were then reviewed.

Second Generation Antipsychotics

The SGAs have been used to treat behavioral disturbances and psychosis. Providers may use SGAs to decrease aggression, agitation, hallucinations and delusions [3]. The SGAs have been used with increasing frequency compared to First Generation Antipsychotics (FGAs) owing to perception that they are associated with fewer adverse side effects, notably motor related. There continues to be questions regarding the safety and effectiveness of their use in this population. There is conflicting evidence regarding whether the benefits outweigh the risks of using these medications. It has been established by numerous trials that SGAs are associated with increased risk of death, stroke, and cardiovascular symptoms [4]. As a result, all of the SGAs are associated with an FDA issued black box warning of increased mortality.

The concerns regarding the safety of SGA in patients with Alzheimer's disease have been supported in recent studies. The following trial was part of the National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness – Alzheimer's Disease (CATIE-AD). A 42-site, double-blind, placebo-controlled trial of over 400 patients with Alzheimer's disease randomly assigned to receive either quetiapine, olanzapine, risperidone, or placebo showed adverse effects were greater than benefits. The participants of this study were followed over 36 weeks, and outcome measures included time to discontinuation or treatment and number of patients with improvement on the Clinical Global Impression of Change (CGIC) scale. Individuals were treated with relatively low doses to minimize adverse effects, olanzapine (mean dose of 5.5 mg per day), quetiapine (mean dose of 56.5 mg per day), and risperidone (mean dose of 1.0 mg per day). Those treated with SGA had a greater incidence of sedation, confusion, and weight gain. There were not statistically significant differences in the Clinical Global Impression of Change scale between any of the treatment groups and placebo [5].

A meta-analysis examined 18 randomized clinical trials of SGA treatment of aggression in dementia [6]. This study showed “modest” effects from risperidone, which at 2 mg per day was associated with a decreased in 1.5 points (95% CI -2.05 to -0.95 points) on the Behavioral Pathology in Alzheimer's Disease rating scale. A double-blind, randomized controlled trial showed that patients with Alzheimer's disease with psychosis or agitation had a higher rate of relapse when transitioned to placebo (60%) vs. those continued on risperidone (33%) [7].

A multicenter, double-blind, placebo-controlled, 6-week study was conducted with nursing home residents with Alzheimer's disease and associated psychosis or behavioral disturbances. This study compared placebo to fixed dose olanzapine, and found that low dose olanzapine was effective. However, olanzapine was associated with higher rates of somnolence and gait disturbance [8]. There is limited evidence

to support improvement in aggression with aripiprazole [9]. The literature regarding other SGA being effective for treating behavioral disturbances long term is also limited [10].

According to a meta-analysis published in JAMA the SGAs were associated with an overall relative risk of 1.65 (95% CI, 1.19–2.29; $p = 0.003$) of death when all SGAs were pooled [11]. This has been further supported by the DART-AD trial that also showed an increased mortality in patient's prescribed SGAs [12]. The SGAs have been associated with increased delirium, attributed to the anticholinergic effects.

Clinicians should closely monitor all patients with dementia prescribed an SGA for side effects, and should limit use of these medications to short term treatment if possible. However, for patients with severe behavioral disturbances and psychosis clinicians must carefully weigh the risks of treating these symptoms, as untreated psychosis and agitation is associated with considerable morbidity.

First-Generation Antipsychotics

The first-generation antipsychotics (FGAs) have been used “off label” to treat psychosis and agitation associated with dementia. This literature search was able to identify randomized controlled trials that have shown improved aggression in patients treated with haloperidol [13]. Recent studies have raised the concern the FGAs are similarly associated with increased risk of mortality. A retrospective cohort study found that haloperidol was associated with a 1.5 times the risk of mortality when compared to SGAs [14].

A multi-center trial that was a randomized, double blind controlled trial compared flexibly dosed haloperidol to risperidone. This study showed improvements in behavioral disturbances and psychosis in both groups, and there were no statistically significant differences in efficacy between groups. However, risperidone was associated with fewer extra pyramidal side effects [15].

There are considerable side effects that must be considered when prescribing FGAs for the treatment of dementia associated behavioral disturbances. The FGAs are associated with dystonia, parkinsonism, prolongation of the QTc interval, and tardive dyskinesia. Current evidence suggests that FGAs have lesser efficacy and equivalent or greater risk of mortality compared to SGA. As a result, clinicians should consider the FGAs a second line agent for the treatment behavioral disturbances and psychosis associated with dementia [16].

Prazosin

Behavioral disturbances in those with dementia may be partially mediated by increased responsiveness to norepinephrine release in the central nervous system.

Alzheimer's disease is associated with increased density of postsynaptic alpha-1 adrenergic receptors in the prefrontal cortex, which is associated with aggressive behavior [17]. It is proposed that antagonizing this system may reduce behavioral symptoms associated with dementia. Prazosin antagonizes these norepinephrine effects at brain post synaptic alpha-1 receptors thus may be helpful in treating agitation [18].

The effectiveness of prazosin to treat agitation and aggression in patients with Alzheimer's disease was investigated using a double-blind, placebo controlled, parallel group study. There were a total of 22 participants, average age was 80.6, and they were equally randomized to receive either placebo or prazosin. The prazosin was titrated up to 6 mg daily, well tolerated, and associated with improvement in behavioral disturbances within 8 weeks using the Clinical Global Impression of Change (CGIC), Neuropsychiatric Inventory (NPI), and Brief Psychiatric Rating Scale (BPRS). However, this study excluded patients with persistent psychosis such as paranoid ideation and auditory hallucinations [19].

Prazosin rarely has the sedating properties often associated with increased morbidity in the elderly population. Clinicians should closely monitor individuals for orthostatic hypotension associated with alpha-1 adrenergic receptor blockade. The elderly population is at increased risk of falls, and should be monitored closely for any orthostasis associated with prazosin.

Gabapentin

Gabapentin is an anticonvulsant that works on the GABA system, and has been proposed as a potential treatment for behavioral disturbances associated with dementia. This is based on the hypothesis that anticonvulsants have anti-aggressive effects [20].

According to an open, baseline comparison study gabapentin was associated with decreased behavioral disturbances [21]. There were 20 participants with Alzheimer's disease who received gabapentin treatment for 15 months, titrated up to 300 mg three times daily, and then increased on an individual basis depending on behavioral response. Patients showed statistically significant improvements in scales assessing behavioral and psychotic symptoms, such as the NPI ($p < 0.001$), CMAI ($p < 0.001$), and CBI ($p < 0.001$). The results indicate that gabapentin was associated with decreased behavioral disturbances [21]. There are no published randomized control trials of the use of gabapentin in this patient population.

Valproate

Valproate has been thought to have some neuroprotective qualities such as reduced neuronal injury, activation of bcl-2 with decreased apoptosis, increased cell

survival, and possibly reduced neurofibrillary tangles [22]. As a result, it has been considered as an alternative treatment for the behavioral disturbances associated with dementia.

Recent studies have investigated if prophylactic treatment with valproate could delay the onset of psychiatric symptoms in patients with Alzheimer's disease [23]. This was a multicenter, randomized, double-blind, placebo-controlled trial of valproate use in patients with Alzheimer's disease who had not developed agitation or psychosis. Participants were randomly assigned to either placebo or valproate group with dose of 10–12 mg per kilogram. The study measured time to clinically significant psychosis or agitation. The participants receiving valproate had higher rates of unsteady gait, tremor, diarrhea, somnolence, and weakness. Those that received valproate were also found to have greater loss of hippocampus and brain volume on MRI. The use of valproate was not associated with a delay in behavioral disturbance or psychosis [23].

However, there have been small placebo controlled trials that have provided limited evidence of valproate treatment being associated with a decrease in behavioral disturbances [24, 25]. This evidence is limited thus valproate should only be considered a second line treatment option, and warrants further investigation [26].

Antidepressants

There is limited evidence to guide clinicians in the use of antidepressants to address behavioral disturbances associated with dementia. The rationale for using antidepressants comes from studies that suggest serotonergic deficits in Alzheimer's disease are associated with aggression, disturbed sleep, depression, and psychosis [27]. Patients with dementia often display significant confusion with associated anxiety that precedes behavioral outbursts, which may be amenable to the anxiolytic properties of antidepressants.

Of the antidepressants, citalopram has more data to support its use to treat primarily agitation. The Citalopram for Agitation in Alzheimer Disease Study (CitAD) was a randomized, placebo-controlled, double-blind, parallel group trial of 186 patients. The participants received either psychosocial intervention with citalopram or placebo for 9 weeks. The initial dose of citalopram was 10 mg daily and titrated up to 30 mg daily. Participants randomized to receive citalopram showed statistically significant improvements compared to placebo in scores on 18-point Neurobehavioral Rating Scale agitation subscale and Alzheimer Disease Cooperative Study-Clinical Global Impression of Change [28].

A small trial compared citalopram to placebo, and found citalopram was superior in regards to decreased agitation. Another study compared citalopram to risperidone,

and citalopram was shown to have similar improvements on agitation [29]. Further studies have compared citalopram with placebo and perphenazine, and found that citalopram was associated with significantly greater improvement in total neurobehavioral rating scale score and scores of agitation [30]. The evidence for the use of SSRIs in the treatment of behavioral disturbances is limited as the majority of participants in these studies are included regardless of baseline depression. Furthermore, clinicians must take into consideration the risks of cardiac and cognitive adverse effects from citalopram.

There has been a randomized trial investigating the use of trazodone, and it was found to be effective [31]. However, a double-blind comparison of trazodone and haloperidol for treatment of agitation in patients with dementia found no significant difference in improvement between the groups [31]. The improvement was measured on the Cohen-Mansfield Agitation Inventory (CMAI) and CGI scale. However, the data is limited and some research has suggested that trazodone is no more effective than placebo [32]. It should be noted that trazodone may be associated with lethargy, orthostasis and sedation, which should be monitored closely in an elderly population.

Cognitive enhancers

The limbic cortices that control emotional regulation receive extensive cholinergic innervations, Alzheimer's disease is associated with cholinergic deficits in these areas [33]. This is the basis for the use of cholinesterase inhibitors to treat behavioral disturbances associated with dementia. A multicenter, blinded, randomized trial found no significant differences between placebo and donepezil. The primary outcome measure of this study was the Cohen-Mansfield Agitation Inventory (CMAI) [34]. Support has been limited to small studies, such as a withdrawal study that found increased agitation when patient's donepezil was discontinued [35].

Memantine is an N-methyl-D-aspartate (NMDA) antagonist, which reduces glutamatergic dysfunction. The Memantine for Agitation in Alzheimer's Dementia Trial did not show a difference in agitation between participants treated with placebo versus memantine. A meta-analysis that included randomized, parallel-group, double-blind studies showed improvements on the Neuropsychiatric Inventory (NPI) for patients on memantine compared to placebo [36]. However, this meta-analysis was limited in that it reviewed studies with patient populations that did not have severe behavioral disturbances. Additional studies have found memantine is associated with improvements in aggression and irritability [37, 38]. Further research is needed to evaluate the clinical value of using cognitive enhancers to treat the behavioral disturbances associated with dementia.

Analgesics

There is limited evidence that the prophylactic use of analgesics is associated with improved behavioral outcomes. The hypothesis is that untreated pain leads to agitation, and aging is associated with a high prevalence of painful conditions such as arthritis. A randomized, double-blind, placebo-controlled, crossover trial investigated the effect of acetaminophen on behavior of patients with dementia [39]. This study compared daily acetaminophen (3000 mg per day) with placebo, and found that participants receiving acetaminophen were better able to perform personal care, engage in activities as evidenced by improvement in the Dementia Care Mapping measures. However, there was no difference in the Cohen-Mansfield Agitation Inventory. The data is limited, but does suggest clinicians should focus on alternative pain assessments as self report may be limited in dementia patients, and pain may contribute to behavioral disturbances [40].

Conclusions

The behavioral disturbances and psychosis associated with dementia often lead to decreased quality of life, increased mortality, poor prognosis, earlier placement in a nursing home, and increased utilization of healthcare resources [41–43]. The first line treatment is to develop a comprehensive management plan that addresses the needs of the patient and caregivers. It is also crucial to modify environmental factors that may contribute to behavioral disturbances, and develop the skills of caregivers.

Pharmacologic interventions are controversial given the limited data and associated risks. However, medications should be considered when first line treatment is not successful, symptoms are severe, and/or behaviors are dangerous. At this time, the most data is available to support the use of SGAs [44]. The use of SGAs should involve a thorough discussion of risks and benefits with the patient and caregivers. Treatment should aim to use the lowest possible dose of medication, and clinicians should consider tapering medication when symptoms improve. There is insufficient evidence for second line treatments. There is limited evidence to support the use of FGAs, cognitive enhancers, antidepressants, anticonvulsants, and analgesics. Additional randomized control trials are needed to guide clinical decision-making regarding the treatment of behavioral disturbances and psychosis associated with dementia.

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