abstract



Alzheimer's disease (AD) is the most common cause of dementia, affecting nearly 18 million people around the world. Alzheimer's disease is characterized by cognitive, functional, and behavioural decline. As the condition progresses the affected individual becomes increasingly dependent on others for assistance in performing all activities of daily living. Neuropsychiatric symptoms (NPS) such as agitation, psychosis, and apathy are very common in dementia and especially in AD. Agitation and apathy contribute to a tremendous amount of caregiver distress. Treatment guidelines recommend utilizing nonpharmacologic behavioural approaches in all instances. When behavioural interventions fail or when the behaviour is severe, medications are recommended. At present, no psychotropic agent presently available within the United States is FDA-approved for use in dementia complicated with behaviour disturbance.

Key words: *agitation, apathy, behaviour interventions, atypical antipsychotics, dementia*

Pharmacologic Treatment of Agitation and Apathy in Dementia

Shailaja Shah, MD, *Clinical Assistant Professor, Assistant Director Geriatric Psychiatry Fellowship, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Piscataway, NJ, USA.*

Gautam Rohatgi, DO, *Geriatric Psychiatry Fellow, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Piscataway, NJ, USA.*

Daniela Ganescu, MD, *Geriatric Psychiatry Fellow, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Piscataway, NJ, USA.*

Introduction

Neuropsychiatric symptoms (NPS) also known as behavioural and psychological symptoms of dementia (BPSD) are common and have been reported in more than 80% of subjects in most studies.[1] These features of the disorder contribute to poor outcomes for individuals with dementia and their caregivers, and may include depression, agitation, aggression, apathy, hallucinations, and delusions. Neuropsychiatric symptoms are commonly seen with various types of dementia including Alzheimer's disease, vascular dementia, Lewy body dementia, and frontotemporal dementias. This review will focus on the treatment of agitation and apathy in Alzheimer's disease.

Agitation

Inappropriate behaviours are defined as verbal, vocal, or motor activities not judged to be clearly a consequence of the needs of the individual or the requirements of the situation.[2] Inappropriate behaviours can be divided into four categories: physically aggressive behaviours (e.g., hitting, kicking, biting); physically nonaggressive behaviour (e.g., pacing or inappropriate touching); verbally nonaggressive agitation (e.g., repetitive phrases or demands); and verbally aggressive behaviours (e.g., cursing or screaming).

Lyketsos and colleagues[3] reported findings from a study of 5,092 community residents who represented 90% of the older adult population of Cache County in Utah, USA. Several disturbances (delusions, anxiety, apathy, irritability, elation, and disinhibition) were reported with similar severity at all stages of dementia. In contrast, aggression/agitation and aberrant motor behaviour (restlessness and pacing) were more common at later stages of dementia. The study also identified a slightly increased occurrence of depression and hallucinations in moderately severe dementia as compared to mild stage dementia.

Assessment of the Individual with Agitation in Dementia

Psychiatric assessment of the individual with dementia complicated by agitation involves a thorough search for all biological, psychological, social, and environmental factors that may contribute to the disturbed behaviour. Assessment involves a comprehensive review of medical records, interview of the caregivers, and a physical and mental status examination of the patient. The assessment is focused on ruling out underlying medical etiologies (e.g., urinary tract infection) in an effort to rule out delirium, and looking for any environmental factors that could have triggered the symptoms. Important evaluation components include a pain assessment, exploration of sensory deficits, investigation of drug interactions and side effects, and a determination of whether the NPS represent

Table 1: Side Effects of Commonly Prescribed Psychotropics in the Treatment of Neuropsychiatric Symptoms in Dementia

Drug	Side effect
Citalopram	Nausea, vomiting, diarrhea
Sertraline	Nausea, vomiting, diarrhea
Sodium valproate	Nausea, vomiting, ataxia, sedation, tremor thrombocytopenia, hair loss, elevated liver enzymes, rarely acute pancreatitis
Carbamazepine	Aplastic anemia, agranulocytosis, drowsiness, ataxia, rash, elevated hepatic enzymes, drug-drug interactions.
Atypical antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole)	Sedation, weight gain, extrapyramidal symptoms, hyperlipidemia, diabetes; orthostatic hypotension, slightly higher risk of stroke and mortality as a group.
ChEIs (donepezil, rivastigmine, galantamine)	GI distress (slightly more common with rivastigmine), sleep disturbance and muscle cramps (slightly more common with donepezil), sinus bradycardia, loss of appetite
Memantine	Sedation, fatigue, headache; rare: increase in confusion and irritability

an unmet physical need (e.g., hunger, need to void, or feeling too hot or cold).

Treatment of Agitation in Dementia

Initially, behaviour disturbances in dementia should be managed by nonpharmacologic interventions to avoid the potential adverse effects of psychotropic agents.[2] A wide spectrum of nonpharmacologic interventions has been studied for the treatment of NPS in AD.[2] Treatment of unmet needs (such as thirst, hunger, need to void, feeling too hot or cold) of the individual with dementia must be a priority over pharmacological treatment.[4] The consensus statement on improving the quality of mental health care in U.S. long-term care facilities by the American Geriatrics Society (AGS) and the American Association for Geriatric Psychiatry (AAGP) recommends utilizing nonpharmacological interventions as a first-line option if there are no psychotic symptoms and when there is no immediate danger to the individual or others.[5] The statement alludes to such forms of treatment as sensory therapy, activities therapy, social contact interventions, and environmental modifications. A comprehensive review of the pertinent literature is beyond the scope of this article; however, readers are referred to a review published by Forbes and colleagues.[6]

Pharmacotherapy of Agitation in Dementia

At present, no psychotropic agent available within the U.S. is approved by the Food and Drug Administration (FDA) for use in dementia with agitation. In Canada, Conn and colleagues recently published extensive guidelines for the assessment and treatment of seniors' mental health;[7] however, a thorough risk/benefit analysis must be made prior to prescribing psychotropic agents in the older adult population. In a recent review of the pharmacological treatment of NPS in dementia, Sink and colleagues[8] conducted a systematic review of English language articles published from 1996 to 2004. Twenty-nine articles met inclusion criteria (only double-blind placebo-controlled, randomized controlled trials [RCT] or meta-analyses of dementia trials reporting effects on NPS were included). Out of five trials of antidepressants, no efficacy was demonstrated for symptoms other than depression except one study of citalopram, which showed some efficacy for depression, agitation, and lability. For mood stabilizers, three trials of sodium valproate showed no efficacy. Two trials of carbamazepine showed mixed results. Four studies of typical antipsychotics showed small benefit and no differences among specific agents. Six trials of atypical antipsychotics were included. Results indicated modest, statistically significant efficacy of olanzapine and risperidone for agitation with psychosis in dementia. Two meta-analyses and six RCTs of cholinesterase inhibitors (ChEIs) showed small but statistically significant efficacy. Two randomized clinical trials of memantine had mixed results for the treatment of NPS. The evidence available is not sufficient to define best clinical practice. However, recent practice guidelines do recommend the use of ChEIs and memantine for treatment of behavioural symptoms in dementia.[9]

The use of atypical antipsychotic medications for the treatment of NPS in dementia has come under scrutiny due to modest efficacy and reports of significant adverse effects (Table 1). In April 2005, the U.S. Food and Drug Administration mandated the addition of a black box warning to the prescribing information for atypical antipsychotics regarding their use in older adults with dementia-related psychosis.[10] This recommendation came from the finding of increased death rates in drug-treated patients (1.6 to 1.7 times) versus placebo-treated patients. Given the black box warning, as well as increased cardiovascular risks (stroke), metabolic side effects such as weight gain, hyperlipidemia, insulin resistance, and diabetes, the clinician should very carefully consider the choice of pharmacological agent for the treatment of dementia-related psychosis and other NPS.

The effectiveness of atypical antipsychotic drugs for individuals with AD was studied in a 42-site, double-blind, placebo-controlled trial (National Institute of Mental Health Clinical antipsychotic trials of intervention effectiveness [CATIE-AD]). The results of the first phase were

Table 2: Commonly Prescribed Drugs for Agitation and Apathy in Dementia, and Dosage Guidelines for Older Adults

Drug (mg)	Starting dose (mg)	Maximum dose
Donepezil	5 mg once daily for 4 weeks	10 mg
Rivastigmine	1.5 mg twice daily for 2 weeks	Titrate every 2 weeks to 3 mg twice daily, after 2 more weeks can go up to 4.5 mg twice daily and maximum up to 6 mg twice daily
Galantamine	4 mg twice daily for 4 weeks	8 mg twice daily for 4 weeks and may increase to 12 mg twice daily
Galantamine ER	8 mg once daily for 4 weeks	16 mg once daily
Memantine	5 mg once daily for 1 week Titrate up by 5 mg every week	10 mg twice daily at week 4
Bupropion	75 mg once daily	150–300 mg
Methylphenidate	2.5 mg once daily	10–20 mg
Risperidone	0.25 mg	1mg
Olanzapine	2.5 mg	5–10 mg
Quetiapine	25 mg	200–300 mg

published in October 2006.[11] Phase I included 421 patients who were randomly assigned to receive either placebo, risperidone, olanzapine, or quetiapine. Patients were followed for up to 36 weeks. No significant differences were noted among the groups with regard to improvement on the Clinical Global Impression of Change scale[11] at 12 weeks. In addition, 24% of patients who received olanzapine, 16% in the quetiapine treated group, 18% treated with risperidone, and 5% of patients who received placebo discontinued treatment due to adverse effects ($p = .009$). There were no significant differences among treatments with regard to the time to discontinuation of treatment. Phase II of the trial (as yet unpublished) compared 253 patients who discontinued treatment in phase I and who were then randomly assigned to receive either one of the atypical antipsychotics they had not received in the first phase or citalopram.

Only in the presence of sustained patient distress and danger to self or others due to psychosis (delusional thinking and hallucinations) is the use of atypical antipsychotic medications recommended.

Any treatment plan for the distressing symptoms of agitation in dementia must consider a trial of nonpharmacologic interventions. Once these have failed, a trial of psychotropic agents based on the target symptom must be initiated. The adage of starting medication for older adults at a low dose and titrating gradually only if needed is a simple but important guide that the clinician must adhere to. Monitoring adverse effects must be a priority on the clinician's care plan, as should reviewing the need for continuing medication at least every three months. Attempts to decrease the medication must be documented as well as the rationale for continuation, specifying the target symptoms listed at all times.

Apathy in Alzheimer's Disease

Apathy affects 70% of individuals with mild to moderate AD and over 90% of individuals with later-stage illness.[13] Apathy is defined as a lack of motivation relative to the patient's previous level of functioning, and is manifested by diminished goal-directed behaviour and responsivity.[14] Such symptoms are often attributed to depression. About half of AD patients with apathy have no concomitant depression.[15] Apathy in AD has been associated with faster progression of cognitive, functional, and emotional impairment and increased caregiver burden.[16]

Caregivers may misinterpret apathy as laziness, fatigue, or deliberate opposition.[17] Caregivers will often report that patients are less spontaneous, interactive, and affectionate. There is less involvement in household chores, self-care, recreation, and socializing. Several researchers have found that apathy correlates with severity of dementia and not depression.[18,19] Specifically, apathy has been shown to correlate with poorer naming, word list learning, verbal fluency, and set shifting.[19]

Pharmacotherapy of Apathy in Dementia

Pharmacological interventions for apathy have included trials of psychostimulants, amantadine, buproprion, acetylcholinesterase inhibitors, memantine, and atypical antipsychotics (Table 2). Data supporting the use of the CHEI donepezil for treating NPS in moderate to severely impaired AD patients suggests that apathy is the symptom most consistently responsive to treatment. Feldman and colleagues[20] conducted a six-month randomized, double-blind, placebo-controlled trial of donepezil in 290 outpatients and individuals with AD in assisted living facilities. Results indicated significant ($p < .0005$) improvement in NPS at weeks four and 24 among the actively treated group as compared to the placebo-treated group. At week 24, the actively treated group showed significant reductions ($p < .05$) in apathy, anxiety, and depression. Adverse events such as diarrhea, headache, and arthralgia were noted in the donepezil treated group and were seen twice as frequently compared with the placebo treated group. Gauthier and colleagues[21] conducted a subanalysis

Key Points

Neuropsychiatric symptoms are common findings in dementia and cause tremendous caregiver burden.

A thorough assessment of these symptoms must include a comprehensive history, physical and mental status exam, and laboratory evaluation to rule out underlying medical etiologies.

Nonpharmacologic behaviour interventions are first-line options for treatment.

When psychotropic medications are used, patients must be closely monitored for adverse effects, and reassessment of the need for continued medication use must occur at least every three months.

of a large double-blind, placebo-controlled trial of donepezil in moderate-severely impaired AD patients. At baseline, apathy was the most common NPS (67% of the total sample). Treatment with donepezil was associated with statistically significant reductions in apathy, depression, and anxiety ($p< .05$).

Tariot and colleagues[22] conducted a six-month placebo-controlled, double-blind study to evaluate the effects of galantamine in individuals with mild to moderate AD, AD with cerebrovascular disease, and probable vascular dementia. The active treatment group (galantamine 24 mg/day) was associated with significant reductions in apathy and anxiety ($p<.05$).

In a 26-week study of rivastigmine in AD patients residing in a long-term care facility, Cummings and colleagues[23] noted significant reductions in NPS; however, apathy severity was not significantly reduced.

Cummings and colleagues[24] reported on the behavioural effects of combination treatment with memantine and donepezil in moderate to severe AD. Patients treated with memantine plus donepezil showed statistically significant improvements in agitation/aggression ($p=.001$), irritability ($p=.005$), and appetite disturbances ($p=.045$) when compared with patients treated with placebo/donepezil. There were statistical trends suggesting improvement in apathy and nighttime wandering.

In a retrospective chart review of 50 individuals with AD, Negron and Reichman[25] found that risperidone at a mean dose of 1.3 mg at 12 weeks showed significant improvement in negative symptoms (apathy).

Open-label treatment with methylphenidate among inpatients with AD and vascular dementia has been shown to improve negative symptoms.[26] Methylphenidate did not improve depression scores in this pilot study. Additional research is needed to determine the duration and magnitude of positive effect. Clinical observation of dementia patients indicates that stimulant effects may be short lived and side effects include agitation and irritability.

Some clinicians have used stimulating antidepressants such as bupropion to treat apathy in AD, but more research in this area is warranted.

Behaviour Interventions for Apathy in AD

As with the treatment of agitation, behaviour interventions for apathy have included activity interventions, music therapy, multisensory stimulation (Snoezelen). In a randomized, placebo-controlled trial of moderately to severely impaired individuals with AD, Holmes and colleagues[27] studied the quality of engagement in patients exposed to 30 minutes of music (live music versus passive prerecorded music versus silence). Of the individuals in the live music group, 69% showed active engagement compared with 25% in the pre-recorded music exposure group and 12.5 % in the silent placebo group.

Although the evidence for the effectiveness of some psychosocial interventions remains modest, more studies are necessary to identify optimal treatments.

Conclusion

Agitation and apathy are among the most frequently occurring neuropsychiatric symptoms in dementia and have been especially well described in Alzheimer's disease. Optimal treatment using nonpharmacological techniques and psychotropic medications remains elusive, and presents an opportunity for additional research.

No competing financial interests declared.

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