

Treatment of Neuropsychiatric Symptoms in Dementia

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DEMENTIA IS A DISORDER CHARACTERIZED by cognitive or behavioral deficits that interfere with one's ability to function at work or in their usual activities and represents a decline from previous level of functioning. Most patients diagnosed with dementia develop neuropsychiatric symptoms at some stage during their illness.¹ Neuropsychiatric (NP) symptoms are associated with an accelerated decline in overall patient functioning, increased use of medications, frequent hospitalization and earlier entry into nursing homes or supportive living environment. They are highly disruptive to caregivers and family members, greatly affecting quality of life of those caring for patients with dementia. Quality of life is found to be lowest in those caring for patients with symptoms of agitation, aggression and irritability.²

NP symptoms are heterogeneous and not specific to dementia. While symptoms are associated with regional changes in glucose metabolism or neurotransmitter receptor populations, their presentation is shaped by interactions between the primary pathologic process, cognitive limitations, medical comorbidity, premorbid personality and coping style, environment and other psychosocial factors. The frequency of NP symptoms may vary depending on the cause and stage of the dementia. Apathy, dysphoria and irritability are common in **mild cognitive impairment (MCI)** secondary to **Alzheimer's disease (AD)** while agitation, delusions and hallucinations tend to occur in later stages of dementia.³ In dementia secondary to **frontotemporal dementia (FTD)**, aberrant motor behaviors and disinhibition may be common whereas in dementia with Lewy Bodies, visual hallucinations may be prominent in early stages. While symptoms may be transient, apathy for example, often persists through progressive stages of the illness.

NP symptoms not only lead to a lower quality of life of patients with dementia and their caregivers, they are also associated with progression of illness. Depression may manifest months before onset of clinically apparent cognitive symptoms and is a risk factor for MCI when present in the elderly without cogni-

tive impairment. When present in those with MCI, it is found to translate to more than twice the risk of conversion to AD over those without depression.⁴

Depression is a common syndrome in patients with cognitive impairment. Symptoms, however, must often be obtained from family and caregivers as patients may not report them. History taking should include attention to sleep pattern, appetite, weight changes, hedonic capacity, irritability and agitation. As the disease progresses, language problems and reduced awareness of symptoms may further limit report of symptoms.

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Treatment of depression in the cognitively impaired patient should incorporate a multimodal approach tailored to the patient's cognitive and physical abilities. Developing a daily routine with structured activities, education of caregivers and assessment of social and support networks are critical first steps. Adult day care centers may offer structured socialization as well as physical and cognitive based activities and should be part of the treatment.

Evidence based pharmacologic treatment for depression in patients with dementia is limited. The results have generally been mixed with some studies suggesting use of antidepressants only after non pharmacologic interventions have failed unless indicated by severity of symptoms or level of acute risk. SSRIs (e.g., sertraline or citalopram) should be considered first for treatment of depression associated with dementia.⁵ Initial dosing should be conservative though titration to maximum dosing may be necessary depending on response. Tricyclic antidepressants are less well tolerated and should be used with caution. Anticholinergic effects of the tricyclics may contribute to cognitive deficits mak-

ing their use less practical. Cholinesterase inhibitors have been found to improve mood and other non-cognitive symptoms in patients with dementia though the results are not robust. Electroconvulsive may be considered in patients with severe or refractory depression or in those with risk of suicide. ECT is associated with delirium though it has been shown to improve cognitive function when successfully treating depression in patients with degenerative dementia. A trial of stimulants may be warranted for patients who respond partially to SSRI or who display prominent psychomotor retardation.

Apathy is defined as diminished activity due to lack of motivation. Behaviors associated with apathy include 1) decreased goal directed executive functioning, for example initiating daily chores or hygiene; 2) decreased goal directed behaviors, for example socializing; and 3) decreased emotional expression. Depression and apathy have symptoms such as diminished interest and psychomotor retardation in common making differentiation difficult.⁶ Patients with cognitive decline may not complain of apathy. Apathy may be particularly frustrating for family members as patients with apathy may appear to be able to function to higher levels than they are. Family members and caregivers may mistakenly interpret their apathy as "lack of effort" or "oppositional."

Treatment of apathy should begin with education of caregivers and engagement in repetitive structured activities in a social setting. Acetylcholinesterase inhibitors have been found to have beneficial effects in some clinical trials and case reports have suggested benefits from psychostimulants. SSRI's may increase apathetic syndrome thus caution is advised.

Agitation, aggression and psychosis have the most profound negative effect on overall level of functioning of patient and quality of life of caregivers and family. It is necessary to consider a broad range of causative factors including reversible causes such as pain syndromes, infection, metabolic derangement, medication effect and other psychosocial/environmental factors. Agitation and aggression are

often triggered by misinterpretations or misperceptions and are associated with frank psychosis and delirium. Behavior intervention should be initiated early however if the symptoms are associated with potential risk of harm or significant distress to patient, caregiver or community, pharmacologic management is indicated.

Much has been written about use of second generation antipsychotics for treatment of neuropsychiatric symptoms associated with dementia. Meta analysis of placebo controlled trials using second generation antipsychotics for elderly patients with dementia related agitation has shown an increased risk of mortality (odds ratio 1.5 – 1.7).^{7,8} In 2005 the FDA issued a public health advisory warning against increased mortality for second generation antipsychotics for the treatment of behavioral symptoms in elderly patients with dementia.

Effectiveness studies of antipsychotics for patients with neuropsychiatric disturbances in dementia have shown mixed results. The CATIE AD trial studied effectiveness of olanzapine, quetiapine, risperidone and placebo in outpatients with AD and psychosis or agitated/aggressive behavior. Medications were discontinued in 83% of patients by week 36 due to intolerability, side effects or perceived lack of efficacy. Parkinsonism or EPS was highest in those treated with olanzapine and risperidone. Sedation and confusion were noted with all three medications though particularly likely with olanzapine. Increase in body weight and body mass index were noted with all three antipsychotic medications though most prominent with olanzapine and risperidone. Overall no significant differences were noted among the groups with regard to improvement on the Clinical Global Impression of Change scale at 12 weeks. The group concluded that adverse effects offset advantages in the efficacy of atypical antipsychotic drugs for treatment of psychosis, aggression or agitation in patients with AD.⁹

Subsequent studies have noted improvement on measures of specific clinical symptoms for example measures of hostility, suspiciousness, mistrust and uncooperativeness¹⁰. Although few studies report improvement in functional abilities or quality of life, improvement in psychiatric and behavioral symptoms may be clinically meaningful for individual patients without affecting overall function. Given the paucity

of data supporting other classes of medications for treatment of agitation, aggression and psychosis in AD (anticonvulsants, mood stabilizers, benzodiazepines) and the frequent need for augmentation of non pharmacologic treatments, second generation antipsychotics continue to be frequently prescribed for neuropsychiatric symptoms in dementia.

Irritability/lability may be an early behavior symptom of cognitive impairment and may be influenced by underlying mood disorder, frustration with cognitive limitations, personality and coping style and quality of support network. Cholinesterase inhibitors and memantine, in addition to their cognitive enhancing effects, have been shown to have modest impact on irritability/lability of mood and should be considered along with SSRIs as pharmacologic intervention for irritability/lability in patients with AD. SSRIs have a broad range of effects including anxiolysis, anti-obsessional and anti-compulsive effects and should be considered for patients with cognitive impairment with anxiety syndromes. Benzodiazepines may worsen cognitive symptoms and are associated with increased risks of falls in the elderly population. Their use should be limited to situations that may require rapid onset with time limited effects while under close observation.

Personality changes may include coarsening or softening of personality characteristics. Disinhibition may present with impulsivity, tactlessness, violation of social boundaries, or sexually inappropriate behaviors. Primary treatment modality is behavior management aimed at identifying and avoiding triggers. Pharmacologic treatment has limited utility for personality changes or sexually inappropriate behaviors.

Non pharmacologic treatments should be considered first for NP disturbances associated with dementia. Such behaviors as wandering, hoarding, repetitive questioning, inappropriate behaviors will often respond to behavior therapy techniques though for limited periods of time. Day care centers, structured and semi-structured living environments will often provide an environment matched to the functional capacity while fostering independence, comfort and familiarity. A multidisciplinary approach with adequately trained staff providing multimodal treatment options that are patient specific

can be invaluable in helping patient, family and caregiver cope with the behavior and psychological symptoms of dementia.

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Statement of Off-Label Discussion

All of the medications discussed here are off-label.

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