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 Special Report

Comorbidity: Psychiatric Comorbidity in Persons With Dementia

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The assessment and treatment of psychiatric symptoms in persons with cognitive dysfunction are becoming increasingly important. Prevalence estimates of dementia in the United States range from 5% in those aged 71 to 79 years to 25% to 50% in those 90 or older. Up to 90% of patients with dementia have psychiatric comorbidities.^{1,2}

Physicians who treat patients with dementia must remember that dementia is not merely a problem with memory. The presence of one or more additional cognitive disturbances, including aphasia, apraxia, or agnosia, is required to make the diagnosis according to DSM-IV-TR criteria. Furthermore, some patients may present with changes in personality or deficits in executive function rather than memory impairment, which complicates the initial diagnosis.³ Additional mental and behavioral disturbances often affect patients and caregivers as much as memory deficits and may influence quality of life, the need for institutionalization, mortality, and caregiver burden.^{2,4,5}

This article emphasizes neuropsychiatric disturbances with the greatest prevalence and morbidity in persons with dementia. It also addresses comorbid depressive and anxiety disorders, as well as psychological and behavioral disturbances associated with dementia—psychosis and agitation/aggression.^{3,6}

Depression

Depression affects 20% to 32% of persons with dementia; the prevalence is higher in patients with vascular dementia than in patients with Alzheimer disease (AD).⁶ Assessing depression in dementia patients poses several challenges. Depressive symptoms can be the initial manifestations of dementia and may fluctuate over time.^{2,3} Compared with older patients with intact cognition, patients with dementia are more likely to report a diminished ability to concentrate or indecisiveness during a major depressive episode.⁴ On the other hand, patients with dementia are less likely to report insomnia/hypersomnia, feelings of worthlessness and guilt, or thoughts of death/suicide.⁴

To account for these differences, revised diagnostic criteria have been proposed for depression in patients who have AD. Specifically, participants in the NIMH Depression of Alzheimer Disease Workshop suggested adding irritability, social withdrawal, and isolation.^{7,8}

Further confounders of assessment include symptoms of apathy and anxiety. These symptoms frequently coexist with depression but are also independent behavioral dimensions.⁹

Several measures are available for screening and diagnosing depression. In the early stages of the disease, the Geriatric Depression Scale, which relies on patient self-report, can be used.¹⁰ In more advanced stages, clinician-administered instruments, such as the Hamilton Ratings

CHECK POINTS

- ✓ Several measures are available for screening and diagnosing depression: the Geriatric Depression Scale can be used in early stages of disease; the Hamilton Rating Scale for Depression and the Cornell Scale for Depression in Dementia can be used in later stages.
- ✓ A variety of approaches can be used to treat depression in patients with dementia, including pharmacotherapy, electroconvulsive therapy, and psychosocial modalities.
- ✓ The Worry Scale and the Rating Anxiety in Dementia are available to evaluate anxiety in patients with dementia.
- ✓ Behavioral and environmental interventions, including redirection and reassurance, are recommended as first-line treatment for psychotic symptoms that do not cause significant danger or distress.

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Scale for Depression or the Cornell Scale for Depression in Dementia, are more practical. Both have been validated in patients with broad ranges of cognitive impairment.^{11,12}

Treatment of depression

A variety of approaches can be used to treat depression in patients with dementia. These include electroconvulsive therapy (ECT), pharmacotherapy, and psychosocial modalities. Antidepressants. Although placebo-controlled studies of antidepressants have produced contradictory results, the American Psychiatric Association (APA) practice guidelines support a trial of an antidepressant to treat clinically significant depressive symptoms in patients with dementia.^{2,3} SSRIs are generally first-line agents because they have a better safety and tolerability profile than tricyclic antidepressants or monoamine oxidase inhibitors, which have cardiovascular and anticholinergic adverse effects. Among the SSRIs, citalopram and sertraline appear to have an edge in efficacy based on limited clinical trials. They may also be preferable because they are least likely to induce or inhibit cytochrome P-450 enzymes and interact with other drugs.^{2,3}

Alternative agents, including serotonin norepinephrine reuptake inhibitors (venlafaxine, duloxetine), mirtazapine, and bupropion, may be second-line treatment options. However, data from controlled studies are lacking. Patients with dementia are particularly prone to medication adverse effects; whichever agent is chosen, the paradigm of "start low and go slow" should be followed.

ECT. If pharmacological interventions are not effective or contraindicated, ECT can be considered. Risks (including high rates of delirium in dementia patients) and benefits (including improved cognition when depression is successfully treated) must be carefully weighed on an individual basis.²

Psychosocial modalities. Nonpharmacological interventions include supportive-therapy techniques, such as reminding the patient of earlier accomplishments, focusing on positive aspects of life, instilling hope, and promoting enjoyable recreational activities.¹³ Of 11 randomized controlled studies of psychosocial treatments of depression in older adults with dementia, 7 showed significant improvement in the treatment group compared with the control group. In 6 of these studies, improvements were maintained beyond the active treatment.¹⁴

The psychosocial treatments studied were diverse. They included interventions based on behavioral approaches that focus on training caregivers to problem-solve and communicate effectively. Structured programs were used to increase social engagement, and interventions were employed to modify sensory or environmental stimulation.¹⁴ Group reminiscence therapy also improved cognitive and affective function in a recent randomized controlled trial undertaken by Wang.¹⁵

Anxiety

Community prevalence of anxiety in patients with dementia is nearly 20%.⁶ Generalized anxiety disorder (GAD), one of the most frequently diagnosed anxiety disorders in later life, occurs in 5% of patients with AD; estimates of clinically significant anxiety are as high as 70%, depending on the clinical sample (higher for vascular and frontotemporal dementias) and screening modality (lower in studies that employed structured clinical interviews).¹⁶⁻¹⁹

As with depression, the assessment of anxiety disorders in individuals with dementia is challenging. First, geriatric patients tend to underreport psychological problems and overemphasize somatic complaints.²⁰ Another issue is the high comorbidity of anxiety with major depression in AD (more than 75%); this statistic raises the question of whether AD is independent from, or an epiphenomenon of, depression.^{16,17} A paucity of data validates criteria for anxiety disorders for patients with dementia. Findings from a study of GAD in patients with dementia indicate that restlessness, irritability, muscle tension, fear, and respiratory symptoms of anxiety significantly correlate with excessive anxiety and worry. Difficulty in concentrating, fatigue, and sleep disturbance do not.¹⁷ No studies to date have examined anxiety disorders other than GAD in this population.

Two instruments are available to specifically evaluate anxiety in dementia patients, although both correlate highly with measures of depression.²¹ The Worry Scale relies on self-report and can be used in patients with mild dementia.²² The Rating Anxiety in Dementia scale is based on information from all available sources, including clinical observation and caregiver reports; it has excellent reliability.²³

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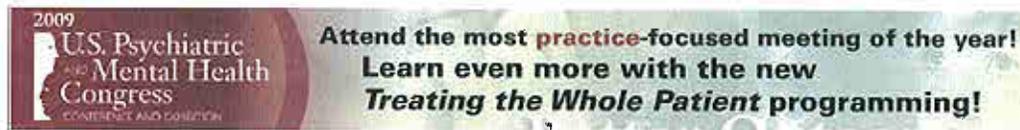
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Treatment of anxiety

Although pharmacological interventions are most frequently employed, no randomized clinical trials have evaluated the use of medication for treating anxiety disorders in persons with dementia. Thus, all recommendations for drug therapy must be cautiously interpreted.

Drug options. Among various options, SSRIs may be useful. One small, prospective, controlled study showed citalopram to be superior to placebo for elderly but cognitively intact patients with GAD.²⁴ The high comorbidity of depression with anxiety in dementia patients may further justify a trial of an SSRI.

Benzodiazepines may have an unacceptably high risk of cognitive adverse effects and falls in patients with dementia.

Psychosocial interventions. Psychosocial treatments for anxiety should be considered viable, safe alternatives to medications in patients with dementia although, again, research is limited. Outcome data on cognitive-behavioral therapy (CBT) for anxiety in dementia have shown promising results in several case studies.²⁵ Successful CBT in these patients relies on strategies to circumvent cognitive limitations in learning and applying new coping tools. These include simplifying skill training, repetition, and recruiting collaterals (eg, caregivers) to act as coaches.²⁵

Other non-drug interventions that show promising results in case series or small pilot studies include milieu therapy, addressing patients' specific environmental needs, and caregiver psychoeducation.^{26,27}

Psychosis

Psychotic symptoms of delusions and hallucinations have been shown to be present in 18% and 14%, respectively, of patients with dementia in a community-based cohort.⁶ Considerably higher estimates are often quoted in clinical samples, especially in patients with Lewy body dementia.

The psychosis of patients with dementia is typically characterized by persecutory and misidentification delusions.⁵ The latter include phenomena such as Capgras syndrome (belief that a close relative or friend has been replaced by an impostor) and "phantom boarder syndrome" (belief that strangers are living in the home), that may be associated with agnosia.⁵ In patients with hallucinations, visual hallucinations are more than twice as common as auditory hallucinations.⁵ Psychosis in AD is frequently comorbid with other cognitive symptoms (global deficits, anosognosia), affective symptoms (depression, elevated mood), and behavioral symptoms (agitation and overt aggression).²⁸

The presence of psychotic symptoms is typically elicited from a history (from the patient and caregiver) and a mental status examination. The Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) scale can aid in assessing behavioral and psychotic symptoms.²⁹ Another instrument is the Dementia Psychosis Scale, rated with the caregiver to quantify the severity and types of delusions.³⁰

Treatment of psychosis

Behavioral and environmental interventions, including redirection and reassurance, are recommended as first-line treatment for psychotic symptoms that do not cause significant danger or distress. Such interventions can also be important adjuncts to psychopharmacological therapy.^{3,31}

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Behavioral measures. A large randomized controlled study stressing nonpharmacological management in older adults with AD demonstrated the effectiveness of collaborative care in reducing behavioral symptoms, reflected by significant improvements in neuropsychiatric inventory scores.³² The study's research protocol included caregiver instructions and handouts to address hallucinations and delusions; these entailed using reassuring touch, establishing a daily routine and adequate light, and avoiding arguments and changes in surroundings.

Pharmacotherapy. When behavioral measures are insufficient, the APA practice guidelines support use of antipsychotic medication for treating psychosis in patients with dementia.³ However, one must exercise a great deal of caution when starting these medications. Increased mortality, particularly from cerebrovascular events, has now been well documented in a large meta-analysis of randomized clinical trials.³³ In June 2008, the FDA mandated a black-box warning about increased risk of death in elderly patients with dementia who are taking conventional or atypical antipsychotics.

The multicenter, double-blind, placebo-controlled Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), which assessed the efficacy of atypical antipsychotics in outpatients with AD, further suggest that the risk of adverse effects may outweigh the benefits. The discontinuation rate because of lack of efficacy was lower with olanzapine and risperidone than with placebo.³⁴

Once the decision to initiate pharmacotherapy is made, the choice of medication should be individualized. For instance, patients with Parkinson disease or dementia with Lewy bodies are highly sensitive to extrapyramidal adverse effects. Quetiapine is preferable to higher-potency antipsychotics. In general, among antipsychotics, atypical agents are better tolerated than conventional neuroleptics.³¹ Still, the therapeutic window can be quite narrow; and it is necessary to closely monitor patients for adverse effects, such as parkinsonism, sedation, anticholinergic effects, delirium, postural hypotension, and increased risk of falls.³

Alternatives to antipsychotic medications include SSRIs. There are data that, at least with AD, serotonergic deficits may contribute to depression and also to psychosis and aggression.³⁵ One short-term, randomized, double-blind, placebo-controlled study demonstrated that citalopram was more effective in diminishing psychosis and agitation than either placebo or perphenazine.³⁵

As always, start with the lowest dose and titrate slowly. The goal of pharmacological treatment in this setting should be to reduce behavioral disturbances rather than to eliminate psychosis altogether.³¹

Agitation/Aggression

Among individuals with dementia in the community, 27% exhibit agitation/aggression.⁶ The prevalence increases as dementia progresses (13% in mild dementia; 24% in moderate dementia; and 29% in severe dementia).⁶ In persons with dementia, agitation may manifest in a variety of behavioral disturbances, from intermittent psychomotor hyperactivity and disinhibition to physical aggression and combativeness.³ These symptoms often have multiple causes; they may reflect underlying pathophysiology of dementia (eg, serotonergic deficiency) or arise as a result of an inability to communicate needs (eg, hunger) or physical discomfort (eg, pain, constipation).^{35,36} Agitation may stem from psychosocial stressors, such as a change in living situation, caregiver, or environment.³

Patients who exhibit agitation warrant a medical evaluation to rule out occult medical problems, medication side effects, and delirium—all potential culprits.³

Instruments to quantify agitation/aggression and monitor target behaviors in patients with dementia include BEHAVE-AD and the Cohen-Mansfield Agitation Inventory. The latter is a clinician- or caregiver-rated questionnaire that categorizes disruptive behaviors (either verbal or physical) on a spectrum from nonaggressive to aggressive.³⁷

Therapy for agitation/aggression

The effectiveness and safety concerns of medication use, especially antipsychotics, argue for greater emphasis on nonpharmacological interventions in treating behavioral disturbances.

Behavioral approaches. A systematic "ABC" approach to implementing a behavioral plan helps individualize treatment and monitor improvement. This entails identifying specific Antecedents of target problem Behavior and their

Consequences and devising specific strategies to address these.³ For example, repetitive screaming (depending on the antecedent identified) can be treated by fulfilling unmet needs (eg, pain, toileting), providing increased socialization, or reducing overstimulation in the environment.³⁸

In addition to individualized behavior plans, some persons with dementia also benefit from activity or sensory-oriented psychosocial treatments. In a recent review of 5 randomized clinical trials and 14 observational studies of activity interventions, significant decreases in problem behaviors or aggression/agitation were seen with sensory-stimulating and sensory-calming activities, physical activity-based interventions (including exercise and walking programs), and recreational activities.³⁶ A review of 3 randomized clinical trials and 21 observational studies of sensory therapy interventions, many of which involved music interventions, also largely favored intervention groups on measures of agitation.³⁶

Pharmacotherapy. The consequences of untreated agitation/aggression can be dire; agitation may lead to excess disability, threats to personal health and the safety of others, increased caregiver burden, and institutionalization.³⁸ Thus, despite the well-established risks of pharmacotherapy in this population, when behavioral measures alone are insufficient, the APA guidelines support use of antipsychotic medication for treating agitation, as with psychosis.³ The atypical antipsychotics risperidone and olanzapine have the best evidence for efficacy.³⁹

Antidepressants (SSRIs and trazodone) have not been well studied for symptoms other than depression, although their relative safety profile may warrant a therapeutic trial, especially for nonpsychotic patients with mild agitation.³ Results from a small, randomized, clinical trial with trazodone showed promising results for decreasing problematic behaviors in patients with frontotemporal dementia.⁴⁰

There is also evidence of modest, but statistically significant, efficacy of cholinesterase inhibitors.³⁹ There is limited evidence of efficacy for anticonvulsants, lithium, and α -blockers. All these agents can cause significant adverse effects and thus are not recommended, except for patients who have not responded to other treatments.³

The use of physical restraints should be restricted to behavioral emergencies if the patient is combative and puts self or others at imminent risk.³ Their use beyond these circumstances may increase risk of falls and contribute to cognitive decline.

In fact, restraint reduction has been shown to decrease serious injuries in nursing home residents.⁴¹⁻⁴³

Conclusion

Psychiatric comorbidity in persons with dementia reflects phenomenology and diagnostic treatment challenges that are distinct from those in elderly, cognitively intact individuals with psychiatric illness. To date, large systematic reviews of available pharmacological treatments highlight their lack of efficacy and increased adverse effects.³⁹

Systematic reviews of nonpharmacological interventions fault many studies for lack of methodological rigor; most are single-case designs.⁴⁴ Given the rising incidence of dementia, the ubiquitous nature of associated neuropsychiatric disturbances, limits of current pharmacological treatments, and modest effect of pharmacological and nonpharmacological interventions, more randomized controlled studies are needed to establish consensus treatment guidelines and improve care for this underserved patient population.

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 Duloxetine (Cymbalta)
 Lithium (Eskalith, Lithane, Lithobid)
 Mirtazapine (Remeron)
 Olanzapine (Zyprexa)
 Perphenazine (Etrafon, Trilafon, Triavil)
 Quetiapine (Seroquel)
 Risperidone (Risperdal)
 Sertraline (Zoloft)
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