

*Treatment in Psychiatry begins with a hypothetical case illustrating a problem in current clinical practice. The authors review current data on prevalence, diagnosis, pathophysiology, and treatment. The article concludes with the authors' treatment recommendations for cases like the one presented.*

# Psychosis in the Elderly

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Ms. A, an 85-year-old Caucasian woman, was hospitalized for increased paranoia, visual hallucinations, and agitation. According to her son, Ms. A had had "strange thoughts" for as long as he could remember. For example, for a time, Ms. A would eat only foods that were white. Still, in her adult life, she had actively participated in developing and running a successful family business with her husband and had raised two sons. When her husband died 5 years ago, Ms. A developed a major depressive disorder, single episode, severe with psychotic features. She moved to an assisted living facility and did well there until she was hospitalized 2 years ago with agitation. At that time, she was diagnosed with late-onset Alzheimer's type dementia with delusions, depressed mood, and behavioral disturbance. She returned to the assisted living facility and was stable until a few months before her current hospitalization, which was precipitated by gradually worsening paranoid delusions, visual hallucinations, severe restlessness, and difficulty in being redirected.

At admission, Ms. A's responses to questions were largely irrational or irrelevant to the topic at hand. In a more lucid moment, Ms. A conveyed that she had pain, gesturing to her stomach. Her vital signs were stable; she was afebrile and normotensive. Initial mental status examination revealed Ms. A to be an unkempt, distraught, elderly woman with poor eye contact and poor attention span. She was restless and would intermittently grasp imaginary objects in the air, uttering brief phrases or nonspecific sounds in response to questions. Her thought processes were disorganized as she conveyed vague thoughts with themes of

fears of dying and of being harmed. She was irritable and had a labile affect and clouded sensorium that fluctuated between periods of lucidity and of obtundation. Her insight and judgment were severely impaired.

Ms. A's psychotropic medications at the time of admission included 400 mg of quetiapine daily in divided doses for delusions, hallucinations, and agitation; 500 mg of divalproex daily for mood instability and agitation; 100 mg of sertraline daily for depression and agitation; and 4–6 mg of lorazepam daily in divided doses for anxiety and agitation. Her medical history was significant for hypothyroidism, coronary artery disease, atrial fibrillation, hypertension, hypercholesterolemia, and gastroesophageal reflux disease. For these conditions, she was taking 25 µg of levothyroxine daily, 0.125 mg of digoxin daily, 40 mg of enoxaparin daily, 325 mg of aspirin daily, 50 mg of metoprolol twice daily, 40 mg of simvastatin daily, and 40 mg of pantoprazole daily. Ms. A also had a history of recurrent urinary tract infections, chronic constipation, frequent falls, and osteoporosis. She had no known drug allergies.

## Challenges in Diagnosis and Evaluation

### Differential Diagnosis

The differential diagnosis in an elderly patient such as Ms. A who presents with delusions, hallucinations, and behavioral disturbance can include psychosis related to delirium, general medical conditions, affective illness, dementia, schizophrenia or other primary psychotic disorders, and substance abuse or dependence.

From the initial interview and mental status examination, we can judge that there were three leading conditions that may have been contributing to Ms. A's presentation of paranoid delusions, visual hallucinations, restlessness, and difficulty in being redirected: delirium; major depressive disorder, recurrent, severe with psychotic features; and dementia with delusions, depressed mood, and behavioral

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disturbance. Ms. A suffered from medical conditions that could predispose her to a delirium or a psychotic disorder due to a general medical condition. Because she presented with a clouded sensorium, which supported a diagnosis of delirium, a diagnosis of a psychotic disorder due to a general medical condition could not be fully supported at initial presentation.

There may be interactions among delirium, depression, and dementia. Elderly patients with dementia may have a lower threshold for delirium, and delirium has been associated with the development of dementia (1). Similarly, depression may be a risk factor for developing dementia or be a prodrome of dementia (2).

According to her son, Ms. A had a history of "strange thoughts" since early adulthood, raising the question of a possible primary psychotic disorder, such as schizophrenia, schizoaffective disorder, or delusional disorder, as part of her differential diagnosis. However, her premorbid social/occupational functioning and her course of illness did not support these diagnoses. It was judged that Ms. A's "strange thoughts" were in fact unique overvalued ideas that were unlikely to have been truly psychotic in nature. Because she had not abused alcohol or other illicit substances in the past, and these were not accessible to her recently, substance abuse or dependence was not considered a likely cause of Ms. A's psychotic symptoms. Alcohol and prescription drugs seem to be the main substances of abuse in the elderly, although illicit recreational drug abuse or dependence may become more prevalent with the aging of the baby boomers, who have an overall increased prevalence of illicit drug abuse that persists as this generation ages (3).

Misuse or abuse of potentially addictive prescription drugs (benzodiazepines, opiates, and the like) and other drugs cited in the updated Beers criteria (4) for potentially inappropriate medication use in the elderly is of growing concern, as many elderly hospital admissions may be related to medications or toxic effects of medications. Inappropriate use of or withdrawal from centrally active prescriptions, over-the-counter and alternative medications, alcohol, and other psychoactive substances may trigger psychotic symptoms.

### **Comprehensive Evaluation**

To determine or confirm what may be causing or interacting to cause the psychotic symptoms and to rule out additional etiologies, a thorough workup incorporating psychiatric, neurologic, and medical aspects of the history of the present illness, as well as blood, urine, brain, cardiac, and radiographic studies and other specialty assessments, was carried out.

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Ms. A's blood electrolytes, renal and liver function tests, fasting glucose and glycosylated hemoglobin levels, lipid profile, vitamin B<sub>12</sub> and folate levels, calcium level, rapid plasma reagin screen, and toxicology screen were all within normal limits.

Ms. A's urinalysis with cultures and sensitivities revealed an *Escherichia coli* urinary tract infection. Consistent with infection, the CBC with differential showed an elevated WBC count with left shift, and the erythrocyte sedimentation rate and C-reactive protein levels were elevated. Free T<sub>4</sub> and total T<sub>3</sub> were low, with an elevated thyroid-stimulating hormone level. EEG showed nonspecific generalized slowing, and a brain scan revealed mild age-related atrophy and no acute intracranial process. A chest x-ray showed cardiomegaly, hypoinflation, and no acute changes. ECG showed atrial fibrillation with a ventricular response rate of 95. Echocardiogram revealed left ventricle inferior wall hypokinesis with an ejection fraction of 50%. Mini-Mental State Examination and neuropsychological testing were attempted but could not be completed because of Ms. A's poor attention and concentration abilities. Occupational therapy functional assessment showed that Ms. A needed total assistance with activities of daily living. The neurologist diagnosed an acute confusional state, and an internal medicine evaluation revealed constipation but no other acute physical findings. Pertinent findings are discussed in conjunction with associated interventions in the next section.

The evaluation was prioritized according to clinical acuity and intervention impact, as indicated by the history and initial examination. Of the three leading conditions (delirium, depression with psychosis, and dementia), delirium was the most acute, emergent problem for which intervention would have great impact if a medically based reversible cause could be identified and addressed in a timely fashion. As described below, when Ms. A's delirium cleared, signs and symptoms of her depressive illness with psychosis became more prominent. Once her depression with psychosis was stabilized, her underlying dementia was more clearly apparent and interventions related to it were considered.

### **Treatment and Intervention**

The management of psychosis in the elderly is a multidisciplinary endeavor that includes concurrent pharmacologic and nonpharmacologic medical-psychiatric evaluation and interventions.

Pharmacologic interventions for psychosis in the elderly include conventional or atypical antipsychotic medications; in acutely agitated elderly patients, there may be a role for benzodiazepines as well (5, 6). For those with Alzheimer's type dementia, antipsychotics seem to be more effective for paranoia, anger, and aggression (5). Cognitive enhancers such as cholinesterase inhibitors also have been reported to be helpful (6). The choice and dos-

ing of medications for elderly patients is guided not only by efficacy but primarily by potential adverse interactions with other medications or illnesses, susceptibility to unwanted side effects, and the usefulness of some side effects for certain patients (for example, an antipsychotic that increases appetite may be desirable for a patient with weight loss due to anorexia). It is recommended that doses be titrated up or down slowly, according to clinical response and the development of side effects. Once a patient starts to show a positive response to a medication, it may be best to hold the dosage steady and monitor the patient for further improvement before attempting to change the dose to a recommended therapeutic dosage. Medication starting doses for the elderly are commonly one-fifth to one-quarter of those recommended for younger adult patients (7). Ease of use (e.g., once-a-day dosing) and insurance coverage for medications are practical concerns that may influence treatment adherence.

Nonpharmacologic interventions include individual, group, couples, and family psychotherapies; behavioral and milieu management; occupational therapies; expressive therapies, such as music and art therapies; and case management. Emphasizing nonpharmacologic interventions may allow patients to receive maximum benefits from minimal effective dosages of medication and avoid side effects that can be more prominent as medication dosages increase.

### ***Psychosis Due to Delirium***

Delirium has been reported to be the third most common cause of psychosis in elderly outpatients, associated with 12.2% of diagnoses (8). Delirium-related psychosis is characterized by thought disturbance with themes that tend to be from the current environment and situations, with poverty of thinking and irrationality, and with hallucinations (often visual) (9, 10).

Ms. A was worked up and treated for conditions that can cause delirium, such as inappropriate drug use, withdrawal from drugs, infection, urinary retention, constipation, physiologic abnormalities, cardiovascular problems, intracranial strokes, seizures or hemorrhages, and sensory deprivation.

The medications that Ms. A was taking at the time of admission were reviewed. Because of modest efficacy and minimal effectiveness of most psychotropic agents in managing behavioral disturbances, multiple drugs are often used in the hope that there will be some combined efficacy. This all too often has the unintended consequence of exacerbating behavioral difficulties. For Ms. A, it was noted that sedative, antipsychotic, anticonvulsant, and antidepressant medications (lorazepam, quetiapine, divalproex, and sertraline) had been prescribed in relatively large doses for agitation, anxiety, delusions, hallucinations, mood instability, and depression. At high doses and in combination, they were judged to be adding to her acute confusional state. Thus, a psychotropic "drug holiday" was initiated. Psychotropic medications were tapered down in dose and then discontinued, despite Ms. A's history of major depression with psychosis and Alz-

heimer's type dementia with behavioral disturbance. Ms. A would then be monitored for emergent psychiatric signs and symptoms as her delirium cleared, and psychotropic medications would be reintroduced sequentially if clinically appropriate as her delirium resolved.

Ms. A also was found to have an *E. coli* urinary tract infection and constipation, both of which may contribute to delirium, especially in elderly persons with dementia. To treat the infection, Ms. A received antibiotics according to the results of the urine culture antibiotic sensitivities. Fluid intake was encouraged, and she was started on a probiotic. For constipation, a bowel regimen with a high-fiber diet, increased oral fluids, a bulk former, a stool softener, and an intestinal stimulant was initiated.

Her levels of free T<sub>4</sub> and total T<sub>3</sub> were low, and the thyroid-stimulating hormone level was elevated, suggesting that Ms. A had not been taking adequate doses of her thyroid medication. A hypothyroid state can cause a delirium and resemble a dementia. Endocrinologic consultation was obtained and levothyroxine dosages were readjusted.

In her more lucid moments, Ms. A conveyed that she had pain, which can contribute to delirium. She gestured on separate occasions to her stomach. In the light of such cardiac risk factors as chronic atrial fibrillation, hypertension, and hypercholesterolemia, aspirin had been prescribed to prevent ministrokes. After reviewing Ms. A's clinical condition and medications further, it was judged that the aspirin might be causing her abdominal discomfort, despite the use of medication for gastroesophageal reflux disease. In her current situation, it was judged that the risks outweighed the benefits of continuing on aspirin therapy, and the aspirin was discontinued. Within a few days, her complaints of abdominal distress declined. Reducing pharmacologic treatments when appropriate may be more helpful than adding more medication.

Ms. A's sensorium continued to clear, and she had fewer episodes of psychosis and purposeless hyperactivity. When such episodes occurred, they were intermittent and consisted of brief periods of delusions with pacing, during which times she was redirectable. She was more responsive to interactive and milieu interventions, occupational therapy, and physical therapy.

### ***Psychosis Due to Major Depressive Disorder With Psychotic Features***

Major depression has been reported to be the second most common diagnosis in elderly outpatients, accounting for most psychosis in this population (8). In contrast to psychosis associated with delirium, depression-related psychosis in the elderly is often characterized by themes of somatic troubles, persecution, guilt, and poor self-esteem (11).

As Ms. A's delirium cleared, she became more lucid, focused, and coherent in her conversation. However, she started to have periods of increased depression and tearfulness and clearly indicated that she was afraid that she was dying. No amount of explanation could convince her otherwise. This fixed, false belief was judged to be delusional in nature. Somatic causes of depression with psychosis were ruled out with the workup for delirium with

psychosis. There was concern that Ms. A was having a recurrence of the major depressive disorder with psychotic features (mood-congruent delusions) that had been previously diagnosed, especially in the light of the discontinuance of antidepressant and antipsychotic medications over concerns with delirium when Ms. A was first admitted. Extended-release venlafaxine (37.5 mg/day) and then aripiprazole (2 mg h.s., titrated to 5 mg h.s.) were started, and the depression and delusions gradually remitted. The antidepressant and antipsychotic were chosen primarily on the basis of patient tolerance, side effect profile, ease of dosing schedule, and insurance coverage/affordable cost. Recent studies have reported that in patients with psychosis related to dementia, both conventional and atypical antipsychotics are associated with a greater risk of death, cerebrovascular incidents, and cardiovascular events (6, 12). In patients with dementia, it is essential to evaluate the benefits versus risks to the patient, to obtain informed consent from the patient and/or the patient's surrogate, and to monitor closely the use of antipsychotics with careful assessment of comorbid conditions (13). The patients (or their health care proxies) and the treatment team must be aware of the pros and cons of usual treatments, alternative interventions, and no treatment. Because Ms. A was judged unable to provide informed consent, this consent was given by her health care proxy, her son.

Nonpharmacologic approaches included individual, group, and family psychotherapies, expressive therapies such as art and music therapy, behavioral and milieu interventions, and case management (14, 15). Appropriate family members were included as part of the treatment team to encourage communication and cooperation from those serving as patient surrogates. ECT, considered a treatment of choice for depression with psychosis, was not pursued because the potential risks, such as increased confusion, outweighed the potential benefits, especially since Ms. A responded well to low dosages of antidepressant and antipsychotic medications.

### *Psychosis Due to Alzheimer's Type Dementia*

Psychosis is an important aspect of dementia and poses a major health concern for the elderly. Dementia has been reported to be the most common diagnosis accounting for psychosis in elderly outpatients (8). Estimates for the prevalence of delusions in dementia have ranged from 9% to 63% (median, 36%), and for hallucinations, 4% to 41% (median, 18%) (16). The treatment prevalence of delusions and hallucinations in dementia has been reported to be 25%, with hallucinations remitting over a few months and delusions being more persistent (17). Often, delusions of patients with Alzheimer's type dementia are simple, probably because of cognitive impairments that preclude the elaboration of complex ideas. They are often of a paranoid nature, where patients believe that items are being stolen from them, that they are being abandoned, or that their spouse and children are being disloyal to them.

Once Ms. A's delirium had cleared and her major depressive disorder with psychotic features was more stable, functional testing revealed moderate to severe dementia-related chronic deficits in short- and long-term memory, activities of daily living, and instrumental activities of daily living. Treatment with cognitive enhancers was con-

sidered. There was the possibility that at this juncture any remaining psychosis and behavioral disturbance may be due primarily to Alzheimer's type dementia, in which case a cognitive enhancer might be helpful by potentially stabilizing both the cognitive and noncognitive aspects of the dementia. If this were the case for Ms. A, then there was the possibility that with cognitive enhancer treatment, the antidepressant and antipsychotic medications could be decreased in dose and even discontinued.

Currently, there are two classes of cognitive enhancer drugs available by prescription: cholinesterase inhibitors (tacrine, donepezil, rivastigmine, and galantamine) and the *N*-methyl-D-aspartate receptor antagonist memantine. Cognitive and noncognitive benefits from these medications may be subtle, may occur slowly, and may be difficult to evaluate consistently in a clinical setting. Their clinical effectiveness may be more apparent when these drugs are discontinued, such as due to a lack of perceived positive effect or because of side effects. In these situations, some patients suffer a clinically significant loss of clarity, behavioral stability, and function, which may be restored when the cognitive enhancers are restarted in a timely fashion. For Ms. A, memantine, which is indicated for treating moderate to severe Alzheimer's type dementia, was judged to have a more favorable risk-benefit profile than the cholinesterase inhibitors. Ms. A had atrial fibrillation and was on two atrioventricular nodal blocking medications (digoxin and the beta-blocker metoprolol, which had been started after a trial with a calcium channel blocker had failed to treat the arrhythmia). Bradycardia and heart block may be caused by acetylcholinesterase inhibitors and, if severe enough, might increase Ms. A's risk of sudden death. Ms. A also had a history of frequent falls, and increased cardiovascular compromise could increase her vulnerability to falling. In addition, Ms. A had gastroesophageal reflux disease. The cholinesterase inhibitors are known to increase gastric acid secretion, which might cause Ms. A more discomfort, despite her taking medication for gastroesophageal reflux disease. In contrast to the cholinesterase inhibitors, memantine, with its low incidence of relatively minor side effects, seemed to be a better choice. However, the possible side effects of increased confusion and hallucinations with memantine were of concern, as Ms. A had been very confused and was hallucinating when she was first hospitalized. Although not entirely free of all psychotic symptoms, Ms. A had finally reached a point where she was clearer and had some quality of life, as she was not in physical pain and could enjoy visits from her son. Given the severe consequences of the dementia, it was important to provide Ms. A with the opportunity for as much treatment and support as clinically appropriate and beneficial. After considering Ms. A's clinical history and progress and the advantages and disadvantages of treatment with cognitive enhancers, Ms. A's son and the treatment team decided that the potential risks of treatment with cognitive enhancers outweighed the potential benefits. Thus, Ms. A was discharged from the hospital to a skilled nursing facility in stable condition without starting a trial of cognitive enhancer therapy.



## Pathophysiology

In many elderly persons, it is within the context of frailty, limited reserve capacity, and increased vulnerability to adverse outcomes from stressors (18) that several interconnecting pathological mechanisms lead to psychosis. These mechanisms may incorporate neurobiological, genetic, and environmental models of dementia, delirium, general medical conditions, or primary psychiatric conditions that may ultimately lead to imbalances in the synthesis, discharge, and inactivation of neurotransmitters such as dopamine, acetylcholine,  $\gamma$ -aminobutyric acid, serotonin, and glutamate, which control cognitive function, behavior, and mood (19, 20). Adding to this complexity is the fact that over the course of illness, the degree to which any of these mechanisms drives the expression of psychosis in an elderly patient may vary because of aging and fluctuations in illness severity, which in turn influence the patient's reserve capacity and ability to adapt to ongoing physical and mental stress.

## Conclusion

The case of Ms. A illustrates the complex, multifactorial, and changing nature of psychosis in the elderly. The treatment goals included first identifying and treating reversible conditions that posed the greatest risk to the patient, such as delirium. For Ms. A, appropriate simplification of the medication regimen and treating a urinary tract infection, constipation, hypothyroidism, and pain helped clear the delirium and improve her clinical state. Concurrently, other co-occurring psychiatric conditions associated with psychosis, such as depression and Alzheimer's type dementia, were evaluated and managed. The signs and symptoms of such co-occurring conditions became clearer as other conditions, such as the delirium, remitted. Progressive treatments involved maximizing nonpharmacologic interventions while judiciously using sequential, minimal but effective doses of psychotropic medications for specific target symptoms. Engaging the family as part of the treatment team encouraged communication and cooperation, which is especially pertinent for patients who cannot provide informed consent.

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