An Approach to the Patient with Cognitive Impairment: Delirium and Dementia

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Reading the diagnostic criteria for the various psychiatric disorders that present with cognitive impairment may lead to the misperception that diagnosis is relatively easy to achieve when dealing with the cognitively impaired patient because this population can be divided into 2 broad groups: those with chronic cognitive decline (most likely diagnosable with a dementia) and those with acute cognitive changes (most likely experiencing a delirium). As is often the case, diagnosis in clinical practice is far more complicated than it is in textbooks.

Perhaps the greatest hurdle in evaluating the cognitively impaired patient is the clarification of a cohesive history. As the choice of one diagnosis over another may hinge almost entirely on the chronicity of symptoms, gaining some insight to this aspect of the patient’s illness is vital. Unfortunately, the cognitively impaired patient is most often unable to provide such a history, and in the absence of a reliable family member, friend, or caregiver to fill in the gaps, diagnostic clarity can be difficult to achieve.

In this article, the authors outline the broad diagnostic spectra of delirium and dementia, review current understanding of their pathogenesis, and discuss useful diagnostic and therapeutic techniques.

DELIRIUM

Delirium is likely the most frequent cause of acute-onset cognitive impairment in the inpatient general hospital setting. Unfortunately, delirium is often either mis- or
undiagnosed due to more prominent symptoms that obscure the detection of the cognitive decline. From a psychiatric perspective, delirium has been called “the great imitator” by virtue of clinicians frequently mistaking it for depression (due to patients appearing quiet or withdrawn), mania (due to agitation or sleep disturbance), psychosis (due to hallucinations or other perceptual disturbances), or anxiety (due to restlessness or fearfulness). Indeed, studies of general hospital psychiatric consultation services have demonstrated misdiagnosis of delirium by nonpsychiatric hospital staff in at least 46% of cases.

Delirium is a common complication of general hospital admission, presenting in 31% of all patients being admitted to the intensive care unit (ICU) and in 82% of those requiring intubation and mechanical ventilation. Delirium has been shown to independently predict a 39% increase in ICU cost per patient and a 31% increase in the cost of hospital care alone.

Financial matters aside, timely identification of delirium is of paramount importance for several reasons. Primarily, delirium represents a somatic (or “medical”) disturbance presenting with a variety of possible cognitive and psychiatric symptoms. Delirium may present before other symptoms manifest, thus serving as an “early warning system,” alerting treaters to the presence of systemic illness. Early recognition of delirium allows for early intervention, potentially forestalling progression to more disturbing psychiatric symptoms and resultant agitation or aggression. Aside from the immediate risks that agitation poses for both patient and hospital staff alike, unchecked delirium has also been associated with the later development of posttraumatic stress disorder (PTSD) due to the experience of horrifying delusions and hallucinations.

**Clinical Presentation**

As defined by the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition—text revision (DSM-IV-TR), delirium is a syndrome presenting with a disturbance of consciousness with deficits of attention and changes in cognition or perception that develop over a short period and fluctuate over the course of the day. The diagnosis also requires evidence from history, physical examination, or laboratory results that these findings are caused by an underlying medical condition. Of these features, inattention and the fluctuating (or waxing and waning) course are probably the most pathognomonic of the diagnosis. As already mentioned, the various “accessory” symptoms of delirium (eg, agitation, social withdrawal, fearfulness, flattening of affect, hallucinations, sleep disturbance) often result in misdiagnosis. No other psychiatric diagnosis presents with the inattention seen in delirium, leading many experts to identify this symptom as the hallmark of the condition. Indeed, bedside diagnosis often hinges on tests of attention.

**Pathophysiology**

Current understanding of the pathophysiology of delirium centers on a final common pathway of the effects of oxidative stress on the brain, which allows for the hallmark features of delirium to present in cases with underlying somatic causes as diverse as urinary tract infection, traumatic brain injury, or drug reaction. Indeed, delirium may result from conditions spanning the entire breadth of medical practice. The immediately life-threatening causes of delirium can be remembered by the mnemonic “WHHHHIMPS” (Box 1).

It is theorized that because the neurons most vulnerable to oxidative stress are the dopaminergic and cholinergic ones, oxidative stress results in a state of hyperdopaminergia (due to release of endogenous dopamine) and hypocholinergia (due to loss
of cholinergic transmission). Excess dopamine results in hallucinations and agitation (because dopamine potentiates the action of the excitatory neurotransmitter glutamate), while a lack of acetylcholine leads to deficits of alertness and attention (because acetylcholine is the primary neurotransmitter of the reticular activating system that governs these functions via its projections to the thalami and inputs from the neocortex and limbic circuit). Baseline deficits of cholinergic function in the elderly (particularly those already diagnosed with a dementia) are believed to underlie the increased risk of delirium in this population.

**Diagnosis**

Accurate diagnosis of delirium is typically made by bedside cognitive testing. The Mini-Mental State Examination (MMSE) has long been used as a brief and easily administered test of cognitive function, though some have criticized its use of serial 7s (counting back from 100 in intervals of 7) or spelling of “world” backward as tests of attention because they are too reliant on baseline level of education rather than current ability to attend. Asking the patient to recite the days of the week and the months of the year in reverse order have been proposed as purer tests of attention, because almost every patient (regardless of educational achievement) can recite the days and months forward. The draw-a-clock task, in which the patient is presented with a circle drawn on a piece of paper and asked to fill in the numbers and to set the hands to a particular time (eg, ten to two), is also a method of bedside cognitive testing frequently used by general hospital psychiatrists to gauge multiple neuropsychiatric domains (including attention, planning, visuospatial reasoning, and impulsivity).

In terms of diagnostic studies, perhaps no test is more reliable in the diagnosis of delirium than the electroencephalogram (EEG). Originally described by Engel and Romano more than 50 years ago, the classic EEG findings in delirium are generalized slowing to the theta-delta range, the consistency of this slowing regardless of underlying cause, and the resolution of this slowing with treatment. The EEG may further delineate the underlying cause of the delirium if it reveals patterns characteristic of

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**Box 1**

<table>
<thead>
<tr>
<th>WWHHHHIMPS: A mnemonic for life-threatening causes of delirium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal</td>
</tr>
<tr>
<td>Wernicke encephalopathy</td>
</tr>
<tr>
<td>Hypoxia or hypoperfusion of the brain</td>
</tr>
<tr>
<td>Hypertensive crisis</td>
</tr>
<tr>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Hyper- or hypothermia</td>
</tr>
<tr>
<td>Intracranial hemorrhage or mass</td>
</tr>
<tr>
<td>Meningitis or encephalitis</td>
</tr>
<tr>
<td>Poisons (including medications)</td>
</tr>
<tr>
<td>Status epilepticus</td>
</tr>
</tbody>
</table>

certain conditions (such as the rapid beta activity seen in sedative-hypnotic toxicity, triphasic waves associated with hepatic encephalopathy, or the periodic spike-wave discharges that occur with Creutzfeldt-Jakob disease). The EEG is also, of course, the optimal diagnostic test to diagnose delirium that results from epilepsy (including partial complex status epilepticus and post-ictal conditions).

Because early recognition of delirium allows for more timely identification and treatment of the underlying cause, several scales have been developed and validated for use by nursing staff to enhance the detection of the condition. Perhaps the most commonly used is the Confusion Assessment Method (CAM), which also has a version refined for use in the ICU (CAM-ICU). The abbreviated screening version of the CAM and the CAM-ICU focus on 4 cardinal symptoms of delirium, and can be administered rapidly at the bedside. The brevity of the tool allows for multiple assessments per day, an important quality given the inherent waxing and waning course of delirium (because diagnosis may be missed if the patient is "caught on the wane").

Treatment

The only definitive treatment for delirium is identification and resolution of the underlying cause. While such diagnostic and therapeutic efforts are under way there are approaches to the management of delirium that should be used. Given the hyperdopaminergic/hypocholinergic hypothesis of delirium, it makes sense that pharmacologic interventions should be directed to diminishing dopaminergic activity while optimizing cholinergic function.

Neuroleptics (originally developed for the treatment of schizophrenia) function primarily through the blockade of dopamine receptors and are thus a natural choice to accomplish the former of these goals. Of the neuroleptics, intravenous (IV) haloperidol has accumulated the greatest amount of data and empirical clinical experience supporting its efficacy and safety in the treatment of delirium, resulting from its regular use in this regard over the past 3 decades. Haloperidol is a strong antagonist of the D2 receptor and carries relatively little anticholinergic activity, thus limiting the hallucinations and agitation that result from endogenous dopamine release without exacerbating the deficits of alertness and attention due to hypocholinergia. Indeed, it this combination of strong dopamine antagonism with negligible cholinergic activity (along with a low likelihood of inducing hypotension) that first prompted trials of IV haloperidol for management of the agitated delirious ICU patient.

Although haloperidol has never received a formal Food and Drug Administration (FDA) indication for IV administration, it is considered the standard of care. An initial dose is typically in the range of 0.5 mg (for elderly patients) to 2 mg in cases of “quiet” delirium or mild agitation, though more significant agitation may require starting doses in the 5- to 10-mg range. Subsequent doses should occur after a 30-minute interval to allow for distribution of the medication (11 minutes in healthy subjects, typically longer in the medically ill). If calm is not achieved with the initial dose, subsequent doses should be roughly doubled (ie, 1 mg, 2 mg, 5 mg, 10 mg, and so forth) until agitation is effectively managed. The effective dose can then be repeated on a 4- to 6-hour schedule with additional doses available as needed. Once calm has been maintained for a period of 24 hours, the regimen can be tapered.

As with most neuroleptic medications, chronic use of haloperidol has been associated with the development of extrapyramidal symptoms (EPS), however, these seem to be rare when the medication is administered IV. Clinicians may also be loath to use haloperidol because of concerns of prolongation of the corrected QT interval (QTc) and the risk of torsades de pointes. It should be noted that of the commonly used neuroleptic medications, haloperidol is associated with among the lowest
per-dose-equivalent prolongation of the QTc. Furthermore, a large number of non-neuroleptic medications are also strongly associated with prolonged QTc, including antibiotics (fluororquinolones), antiarrhythmics (amiodarone, flecainide), and pain medications (methadone). Nonetheless, care should be taken with the administration of IV haloperidol including close monitoring of the QTc (via telemetry if needed), regular assessment and requisite replenishment of potassium and magnesium (because hypokalemia and hypomagnesemia independently predispose to QTc prolongation), and potential replacement of other QTc prolonging agents if necessary.1

The development of parenteral formulations of the newer, so-called atypical neuroleptics has resulted in interest in their utility in the management of delirium. Of this group, risperidone has accumulated the most data indicating safety and efficacy in the treatment of delirium. Some of the other drugs in this class (olanzapine, quetiapine, aripiprazole, and ziprasidone) have more limited supporting data, but some smaller studies have shown some potential benefit of their use. All of these drugs, however, are limited to oral or intramuscular (IM) (for olanzapine and ziprasidone) administration. When faced with a confused and potentially agitated patient, oral dosing may not be an option, and repeated painful IM injections are unlikely to create the desired sense of calm or therapeutic trust. Quetiapine and clozapine occupy a niche role in the treatment of patients with Parkinson disease or dementia with Lewy bodies who become delirious, because the minimal antagonism of these drugs at the dopamine receptor is less likely to exacerbate their underlying parkinsonian symptoms.26

Although there are several agents available to address the first half of the hyperdopaminergic/hypocholinergic hypothesis, there is very little evidence that medications intended to increase cholinergic transmission are useful in the management of delirium. Small studies of the cholinesterase inhibitors approved for the treatment of dementia have shown some potential delirioprotective effect, but randomized, double-blind, placebo-controlled trials have failed to demonstrate any benefit of these agents in either preventing or treating postoperative delirium. Physostigmine has proved efficacious in reversing delirium from several causes, but due to a narrow therapeutic window and brief duration of effect, its use is limited to presentations of delirium due to anticholinergic poisoning.

Prevention

Because delirium is a systemic manifestation of a somatic illness, definitive prevention of delirium would require prevention of all illness and injury. More realistically, we can limit agents and interventions that place our patients at greater risk for delirium, because in most cases, delirium results from a series of stressors placed on the body and brain rather that a single “hit.” Perhaps most easily managed are the medications administered to patients that may result in delirium. While almost all medications can provoke delirium, the “usual suspects” often include anticholinergics, opiates, and benzodiazepines. Limiting the doses of the medications or replacing them with less deliriogenic alternatives can be of great benefit to the patient.

To that end, recent studies have demonstrated that dexmedetomidine (a centrally acting α2-adrenergic agonist sedative-analgesic agent) is significantly less likely to result in delirium than either midazolam or propofol when used as a postoperative sedative for mechanical ventilation. In addition, a recent large (N = 400) randomized, double-blind, placebo-controlled study of olanzapine and placebo in elderly patients with joint replacement revealed that 10 mg of olanzapine administered perioperatively reduced the incidence of postoperative delirium (from 40% to 14%) and
increased the likelihood of discharge to home (vs a rehabilitation facility). Other strategies to prevent or minimize the consequences of delirium are under way.

**DEMENTIA**

According to DSM-IV-TR, the essential feature of a dementia is the development of multiple cognitive deficits that must include memory impairment and at least one other cognitive disturbance including aphasia, apraxia, agnosia, or a disturbance of executive function. In addition (and of particular importance to this article), the diagnosis of dementia should not be made if the cognitive deficits occur exclusively during the course of a delirium. Although this is a potentially helpful way to differentiate between delirium and dementia, it is not uncommon for a patient with dementia to present with an acute onset of confusion (ie, delirium) because dementia is an independent risk factor for development of delirium. Therefore, this combination of conditions may be especially perplexing with respect to presentation, etiology, and treatment. From a practical perspective, however, the key features that may help to differentiate between delirium and dementia include the following: the cognitive deficits in dementia are generally chronic and develop slowly; the onset of cognitive deficits in delirium are much more acute; a “pure” dementia early in its course occurs in the presence of a clear sensorium; and a reduced ability to sustain or shift attention makes the diagnosis of delirium more likely. When evaluating a patient for dementia, it may be useful to view the condition as more than a cognitive disorder. In addition to cognitive deficits, disturbances in daily function and behavior as well as neurologic changes should be evaluated and tracked over time to serve as aids to diagnosis and response to treatment.

**Types of Dementia**

*Dementia of the Alzheimer type* or Alzheimer disease (AD) is the most common type of dementia, with a prevalence in those at age 65 years of approximately 1 per 100 individuals. This prevalence doubles with every 5-year increment or increase in age. Diagnostic criteria for AD include the “core” symptoms of dementia, namely a major impairment of learning, retaining, or recalling information and at least one of the following: aphasia, apraxia, agnosia, or disturbance in executive function (ie, planning, organizing, sequencing, or abstracting). The cognitive deficits must cause significant impairment in social or occupational function and represent a significant decline from a previous level of function. The course of the disorder is characterized by a gradual onset and by continuing cognitive decline. The average duration from onset of symptoms to death is 8 to 10 years. Disorders that must be ruled out before AD can be diagnosed include cerebrovascular disease, Parkinson disease, Huntington disease, normal-pressure hydrocephalus, hypothyroidism, B12 or folic acid deficiency, neurosyphilis, human immunodeficiency virus infection, and substance-induced cognitive impairment.

The 2 most important risk factors for development of AD include advancing age (after age 85 years the risk is as high as 50%) and a first-degree biologic relative with the early-onset type of AD (ie, with an onset before the age of 65 years). Additional risk factors include presence of the apolipoprotein-e4 (APOE-e4) gene, a history of head injury (even remote history), cardiovascular disease (including atherosclerosis, stroke, hypertension, or carotid artery disease), elevated levels of homocysteine, and very low educational achievement (ie, < an eighth-grade education). Protective factors include use of nonsteroidal anti-inflammatory drugs (NSAIDs), wine consumption (in moderation), coffee consumption, and regular physical activity. These
factors should be carefully considered because some studies have found no increased risk for AD in those with a family history of dementia, or a history of depression, estrogen replacement therapy, head trauma, smoking, hypertension, heart disease, or stroke. Psychiatric or behavioral disturbances in AD are common and include depression, anxiety, agitation (including physical aggressiveness and wandering), sleep disturbances, delusions, and hallucinations.

A diagnosis of AD may be confirmed at autopsy. Its characteristic microscopic findings include neuritic plaques (NPs; also called senile plaques) and neurofibrillary tangles (NFTs). The NPs are generated by a deposition of fibrils of the β-amyloid peptide, Aβ, a fragment derived from the proteolysis of amyloid precursor protein (APP), in the brain. NFTs are composed of paired helical filaments (PHFs), which are composed of the microtubule-associated protein tau. In NFTs, tau is excessively phosphorylated, which leads to the aggregation of tau molecules and their ultimate transition to insoluble NFTs. AD is the quintessential cortical dementia (Table 1). A helpful mnemonic to remember the characteristics of a cortical dementia is the “4 As”: amnesia, apraxia, aphasia, and agnosia; in comparison, subcortical dementia is characterized by defects in arousal, attention, motivation, and the rate of information processing.

Vascular dementia (also called multi-infarct dementia or vascular cognitive disorder) is characterized by cognitive deficits thought to be etiologically related to cerebrovascular disease, as demonstrated by either focal neurologic signs and symptoms or laboratory findings. Although overall it is the second most common type of dementia, comprising 10% to 20% of all dementia cases, it is much less common than AD. In most cases the onset of symptoms is abrupt, but some patients may have so-called silent strokes that at first do not present with obvious signs and symptoms. As more areas of the brain become damaged, symptoms begin to appear. The disease is more common in men than women.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Delirium</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Abrupt</td>
<td>Usually insidious; abrupt in some strokes/trauma</td>
</tr>
<tr>
<td>Course</td>
<td>Fluctuates</td>
<td>Slow decline</td>
</tr>
<tr>
<td>Duration</td>
<td>Hours to weeks</td>
<td>Months to years</td>
</tr>
<tr>
<td>Attention</td>
<td>Impaired</td>
<td>Intact early; often impaired late</td>
</tr>
<tr>
<td>Sleep-wake</td>
<td>Disrupted</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Alertness</td>
<td>Impaired</td>
<td>Normal</td>
</tr>
<tr>
<td>Orientation</td>
<td>Impaired</td>
<td>Intact early; impaired late</td>
</tr>
<tr>
<td>Behavior</td>
<td>Agitated, withdrawn/depressed, or both</td>
<td>Intact early</td>
</tr>
<tr>
<td>Speech</td>
<td>Incoherent, rapid/slowed, or both</td>
<td>Word-finding problems</td>
</tr>
<tr>
<td>Thoughts</td>
<td>Disorganized, delusions</td>
<td>Impoverished</td>
</tr>
<tr>
<td>Perceptions</td>
<td>Hallucinations/illusions</td>
<td>Usually intact early</td>
</tr>
</tbody>
</table>

Diagnostic criteria for vascular dementia include the core criteria for dementia listed above. In addition, focal neurologic signs and symptoms or laboratory evidence of cerebrovascular disease felt to be etiologically related to the disorder must be present. These indicators include exaggeration of deep tendon reflexes, gait abnormalities, weakness of an extremity, and imaging studies that demonstrate multiple infarctions of the cortex and underlying white matter.

Risk factors for vascular dementia include male gender; African American ethnicity; hypertension; history of stroke, diabetes, and heart disease; and high cholesterol levels. Psychiatric or behavioral symptoms include depression, apathy, mania, anxiety, emotional lability, agitation, psychosis, and delusions. Vascular dementia is the most common type of mixed dementia; it presents with signs and symptoms of both cortical and subcortical dementia (Table 2).

Dementia with Lewy bodies (DLB) is the second most common type of dementia in the elderly. DLB is characterized by marked impairments in visuospatial, attentional, and executive functions, and may be differentiated from AD because DLB often presents with relatively well-preserved memory in its early stages. Additional features of DLB include persistent, well-formed visual hallucinations in up to 80% of cases, and parkinsonism.41 Lewy bodies are intranuclear collections of \(\alpha\)-synuclein protein in the neurons in brain regions responsible for memory and motor control. Furthermore,

<table>
<thead>
<tr>
<th>Characteristic or Function</th>
<th>Cortical eg, Dementia in Alzheimer Disease or Pick Disease</th>
<th>Subcortical eg, Dementia in Huntington Disease, Parkinson Disease, or HIV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alertness</td>
<td>Normal</td>
<td>“Slowed up”</td>
</tr>
<tr>
<td>Attention</td>
<td>Normal early</td>
<td>Impaired</td>
</tr>
<tr>
<td>Language</td>
<td>Aphasia early</td>
<td>No aphasia</td>
</tr>
<tr>
<td>Episodic memory</td>
<td>Amnesia</td>
<td>Forgetfulness</td>
</tr>
<tr>
<td>Visuospatial skills</td>
<td>Impaired</td>
<td>Impaired</td>
</tr>
<tr>
<td>Calculation</td>
<td>Involved early</td>
<td>Preserved until late</td>
</tr>
<tr>
<td>Personality</td>
<td>Unconcerned or disinhibited if frontal type, otherwise preserved</td>
<td>Apathetic, inert</td>
</tr>
<tr>
<td>Mood</td>
<td>Euthymic</td>
<td>Depressed</td>
</tr>
<tr>
<td>Speech</td>
<td>Normal articulation</td>
<td>Dysarthric</td>
</tr>
<tr>
<td>Movement disorders</td>
<td>Absent</td>
<td>Common</td>
</tr>
<tr>
<td>Pathology</td>
<td>Primary damage to neocortex and hippocampus</td>
<td>Primary damage to deep gray matter and white matter structures, including the thalamus, basal ganglia, brainstem nuclei, and frontal lobe projections</td>
</tr>
</tbody>
</table>

DLB may produce a waxing and waning pattern of cognitive impairment similar to that seen in delirium, thus rendering accurate diagnosis more difficult.

Dementia associated with depression or other psychiatric disorders is often incorrectly referred to as pseudodementia. However, the cognitive deficits caused by an underlying psychiatric condition may be indistinguishable from those in primary dementia and are quite real; the major difference between the 2 conditions is that dementia associated with a psychiatric condition improves or completely resolves with successful treatment (usually with an antidepressant medication, although some severe cases may require electroconvulsive therapy).

Dementia occurs in up to 40% of patients with Parkinson disease (PD), a condition characterized by progressive neurodegenerative disease that includes cardinal motor symptoms of bradykinesia, resting tremor, rigidity, and impaired postural reflexes due to loss of pigmented dopaminergic neurons in the substantia nigra pars compacta (SNpc). In some cases, cognitive and intellectual decline will not meet the full criteria for dementia; the most commonly affected domain, that of executive function, manifests as forgetfulness, poor attention, absent-mindedness, or disorganization. The mean time from onset of PD to dementia is approximately 10 years.

Reversible dementias are dementias that may resolve after appropriate therapy. There are many potential causes, and it is recommended that (even in situations where it is highly likely that a dementia is due to an “irreversible” cause, such as AD) other treatable causes be sought as it is possible that presenting symptoms may result from overlapping conditions. Causes of reversible dementias include, but are not limited to, vitamin (eg, B1, B12, folate, niacin) deficiencies, endocrine (eg, adrenal, parathyroid, thyroid) dysfunction, anemia, medications (eg, anticholinergic agents, H2 blockers, psychotropics), and paraneoplastic phenomena.

Dementia may be a component of many other conditions or insults including Huntington disease, Wilson disease, Pick disease, Creutzfeldt-Jakob disease, progressive supranuclear palsy, chronic substance abuse, and head trauma. Because both dementia and delirium are due to one or more medical conditions, clinicians should perform a thorough “rule-out” of likely (and sometimes not so likely) causes of these conditions to make certain that reversible or treatable causes are not overlooked. Table 1 summarizes the clinical features useful in the differentiation of delirium and dementia.

Treatment or Management

The strategies for treatment or management of dementia may be divided into 2 broad categories: pharmacologic and nonpharmacologic (ie, behavioral). As is true for delirium, a methodical step-wise approach is the best tactic, aimed at identifying all potentially reversible or treatable causes and addressing each one. An example of this first step might be suspecting that a dementia is due to a hypothyroid state: the approach here would be to normalize thyroid function and observe for improvement. In practical terms, this is unlikely to be of much immediate help given that it may take days to weeks for thyroid function to improve and other interventions not specifically aimed at the suspected cause of the dementia will be necessary.

To date, few medications can effectively target specific chemical “deficiencies” or “surpluses” in the central nervous system with dementia (Table 3). However, because there is convincing evidence that both the cholinergic and glutamatergic systems are dysregulated in AD, important exceptions are 2 drug classes (acetylcholinesterase inhibitors [AChEIs] and glutamate modulators) that are effective in AD. In addition, there is growing evidence that both classes may be beneficial in vascular dementia and in DLB. Currently available AChEIs include donepezil,
galantamine, and rivastigmine; all have beneficial effects on mild to moderate AD, although many clinicians (sometimes due to pressure from family members) prescribe these medications for severe disease or continue them in the presence of worsening symptoms. However, benefit is limited to slowing down the progression of the disease; it does not cure the condition. Likewise, memantine, the only available glutamate modulator, is effective in moderate to severe AD by delaying disease progression.51 It is not uncommon for both an AChEI and memantine to be prescribed at the same time.52,53

Pharmacotherapy for the other dementias, as well as for the behavioral changes accompanying AD, DLB, and vascular dementia, is generally aimed at co-occurring signs and symptoms (such as agitation, anxiety, depression, hallucinations, and delusions); it typically involves the use of drug classes commonly identified for these conditions (see Table 3).

Behavioral interventions for dementia may be as or more important than pharmacologic approaches. This therapy should focus on keeping the affected patient as

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Drug Class</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Agitation</td>
<td>Atypical antipsychotic; benzodiazepine; trazodone</td>
<td>Atypical antipsychotics are less likely to cause EPS; any antipsychotic may cause severe/fatal reactions in DLB (clozapine and quetiapine have lowest risk due to low affinity for the dopamine receptor); not approved for dementia-related psychosis—increased mortality risk; trazodone may cause orthostasis/&quot;hangover&quot;</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Antidepressants (SNRI; SSRI; TCA); benzodiazepines</td>
<td>Benzodiazepines may cause disinhibition in some patients</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>AChEI, memantine</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>SNRI; SSRI; TCA</td>
<td>TCAs are less desirable due to their anticholinergic potential</td>
</tr>
<tr>
<td>Mania or disinhibition</td>
<td>CBZ, VPA</td>
<td>May cause nausea or excessive sedation</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Atypical antipsychotics</td>
<td>Atypical antipsychotics are less likely to cause EPS; any antipsychotic may cause severe/fatal reactions in DLB; not approved for dementia-related psychosis—increased mortality risk</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>Trazodone, benzodiazepines, eszopiclone, zaleplon, zolpidem</td>
<td>Eszopiclone, zaleplon, and zolpidem carry a risk of worsening confusion, hallucinations, and sleep behavior disorders</td>
</tr>
</tbody>
</table>

Abbreviations: AChEI, acetylcholinesterase inhibitor; CBZ, carbamazepine; DLB, dementia with Lewy bodies; EPS, extrapyramidal symptoms; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; VPA, valproic acid.
comfortable, safe, and free of physical restraint as possible and on maximizing the patient’s dignity. Many of these interventions rely on family or other loved ones as well as on common sense for efficacy, and they include simple strategies (such as keeping the room well lit; using “orienting” items, such as a calendar or clock; placing pictures of well-known family members/friends/pets in the room; playing calming or well-known music; limiting the number of visitors to a few at a time to avoid “sensory overload”; making sure the affected patient has his or her eyeglasses and hearing aids on [and check the batteries in the hearing aids!]; keeping directions/explanations simple; straightforward, and unambiguous; avoiding excessive talk with other visitors that may lead to “defocusing” on the patient; visiting at times when the patient is at his or her best [eg, most alert, best pain control]; and allowing the patient plenty of rests and breaks from visitors).

SUMMARY

While identification of the cause of confusion in the cognitively impaired patient is important to guide further workup and prognosis, the care of this group of patients has a strong central theme. Whether the patient is suffering from a delirium or a dementia, their care calls for a careful step-wise approach to identifying and addressing somatic issues that may be either directly causing (in the case of delirium) or exacerbating (in the case of dementia) cognitive and behavioral issues. Furthermore, the environmental and behavioral cues discussed here can be of great benefit to many of these patients. Clinicians will do well by following these recommendations and additionally by helping to support the affected patient’s caregiver(s) through education, empowerment, and empathy.

REFERENCES


