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Dementia (J Pillai, Section Editor)

The Diagnosis and Management of Reversible Dementia Syndromes

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Abstract

Purpose of Review This article discusses the diagnostic evaluation and management of reversible dementia syndromes. It highlights clinical syndromes and explores the recent literature implicating certain reversible factors in Alzheimer's disease pathogenesis.
Recent Findings The prevalence of fully reversible dementia is low, but there is growing awareness for potentially reversible contributors to neurodegenerative disease. In particular, exposure to anticholinergic medications, obstructive sleep apnea, and depression have emerged as potentially modifiable targets in the pathogenesis of preclinical and early Alzheimer's disease. Treatment of these factors may not only reverse any direct cognitive effects but also prevent downstream neurodegeneration.
Summary There is substantial opportunity to improve outcome in patients with dementia due to reversible etiologies. Even in the setting of primary neurodegenerative disease, conscientious effort is required to recognize and address reversible contributors.

Introduction

In 1927, the Nobel Prize in Medicine was awarded for the development of malaria therapy to treat neurosyphilis [1]. Just 5 years prior at the International Medical Congress in Paris in 1922, dementia paralytica

due to syphilis had been deemed incurable [2]. Over the following decades, there were considerable advances in the recognition of reversible dementia syndromes. In the 1930s, thiamine deficiency was discovered as the cause of Wernicke's encephalopathy. In 1965, Hakim and Adams were the first to describe normal pressure hydrocephalus (NPH) as a treatable syndrome [2]. In 2007, Josep Dalmau described anti-NMDA receptor encephalitis [3], sparking interest in autoantibodies with central nervous system (CNS) targets.

Today, there is a wide differential of entities that might cause a cognitive impairment or dementia that is at least partially reversible, spanning metabolic, infectious, autoimmune, toxic, structural, epileptic, psychiatric, and other etiologies (Table 1). The American Academy of Neurology (AAN) recommends screening for vitamin B12 deficiency, hypothyroidism, and structural abnormalities in the standard assessment of all dementia patients. Certain clinical features suggest a potentially reversible etiology and should prompt further investigation: acute onset, rapid deterioration, younger than expected age, prominent fluctuations, high-risk exposures, focal findings on the neurologic exam, and an incongruence between neurocognitive testing and clinical history [4].

Despite the wide differential, the actual prevalence of fully reversible dementia remains low. In the 1970s and 1980s, it was projected that 40% of dementias might be reversible. A 1988 review estimated the prevalence was closer to 10%. While a 2003 meta-analysis showed that a similar 9% of dementia cases might have a potentially reversible cause; less than 1% actually reversed with treatment [2]. Although rare, the potential to cure these cases demands heightened awareness. Furthermore, dementia is often multifactorial, with both reversible and irreversible contributors. Such cases may not be curable, but there remains substantial opportunity to temper the overall disease trajectory and improve quality of life.

There has been a paradigm shift as some processes classically thought to be fully reversible have recently been implicated in irreversible neurodegeneration. Specifically, certain medications, sleep dysfunction, and depression may play a role in Alzheimer's disease (AD) pathogenesis. It was previously hypothesized that the impairment caused by these entities was transient, fully reversible and independent of—though often concomitant with—neurodegeneration. With accumulating data supporting a more direct association, treatment has the potential not only to reverse any direct cognitive effects of the offending factor but also to mitigate downstream neurodegeneration. In this way, certain reversible dementia syndromes have gained new relevance as modifiable targets in neurodegenerative disease.

In this review, we will explore the recent literature linking reversible factors to AD pathogenesis, highlight several reversible dementia syndromes, propose a diagnostic algorithm, and discuss treatment options.

Reversible etiologies as modifiable risk factors for neurodegeneration

Although traditionally thought to cause only transient and reversible impairment, exposure to anticholinergic medications has recently been linked to an elevated risk of AD. In 2015, a prospective cohort study of more than 3400 adults showed that higher cumulative anticholinergic use is associated with increased risk of both all-cause dementia (adjusted hazard ratio aHR, 1.65) and AD (aHR, 1.94) [5]. The most commonly used anticholinergic medications in this study were bladder antimuscarinics, tricyclic antidepressants, and first-generation antihistamines. A subsequent case-control study of nearly 300,000 older adults published in June 2019 showed a nearly 50% increased odds of dementia with exposure equivalent to 3 years' daily use of a single, strong anticholinergic medication [6].

Similarly, obstructive sleep apnea (OSA) has long been recognized as an important cause of cognitive impairment, but there has been recent attention on the potential role of sleep disturbance in AD pathogenesis. Prospective

Table 1. Reversible dementia syndromes

Metabolic and endocrine
Vitamin B12 deficiency
Vitamin B1 (thiamine) deficiency
Hypo-/hyperthyroidism
Hypo-/hyperparathyroidism
Hepatic failure
Renal failure
Hypoglycemia
Wilson's disease
Inflammatory
Systemic lupus erythematosus
Neurosarcoidosis
Hashimoto encephalopathy
CNS vasculitis (primary and secondary)
Paraneoplastic
Infectious
Neurosyphilis
HIV encephalitis/HIV-associated neurocognitive disorder (HAND)
HSV encephalitis
Neuroborreliosis
Whipple's disease
Cognitoxins
Medications: anticholinergics, benzodiazepines, opiates
Alcohol
Heavy metals
Neurosurgical
Normal pressure hydrocephalus
Intracranial tumors
Intracranial bleeds (e.g., subdural hematoma)
Others
Transient epileptic amnesia
Non-convulsive status epilepticus
Vascular corticobasal syndrome caused by carotid artery occlusion
Sleep apnea
Depression
Anxiety

cohort studies of incident dementia have shown that people with sleep complaints in middle age have an increased risk of developing AD, and meta-analyses have confirmed the potential role for sleep disorders as predictors of AD development [7]. At least two recent studies have shown that sleep disruption increases soluble amyloid-β (Aβ) in CSF, suggesting a potential mechanism [8, 9]. The link between OSA and AD is further supported by treatment trials. A large randomized controlled trial (RCT) showed a mild but significant

improvement of executive function in patients with both AD and OSA treated with continuous positive airway pressure (CPAP) for 6 months [10]. A smaller RCT showed that CPAP treatment improved verbal learning, memory, and executive functions in mild to moderate AD subjects with OSA [11]. A 3-year pilot study revealed that AD patients with OSA who were treated with CPAP showed significantly slower decline than the non-CPAP group [12].

Midlife hypertension has also been associated with an increased risk for all-cause dementia and AD. A 2020 systematic review and meta-analysis showed that midlife hypertension conferred a 1.19- to 1.55-fold increased risk of cognitive dysfunction, and treatment with antihypertensives reduced dementia risk by 21% [13].

There is an expanding body of literature on the association between depression and AD. It is commonly known that depression often accompanies AD, even in individuals with no prior history of depression. Several studies have shown that depression symptoms associate with changes in AD biomarkers [14–17]. A 2019 longitudinal study showed that worsening depression symptoms significantly associated with cognitive decline over 2 to 7 years in patients who were cognitively unimpaired but amyloid positive by positron emission tomography (PET) at baseline. The authors of this study proposed a model by which cortical amyloid might underlie both depression and cognitive decline in early AD. However, a causal association was not demonstrated, so it remains unclear whether treatment of depression symptoms might improve cognitive impairment due to amyloid burden [18].

Lastly, a recent article published in July 2020 in the Journal of the American Medical Association summarized evidence for neurotropic viruses such as herpesviruses causing chronic inflammation that may contribute to AD pathogenesis [19, 20]. Multiple epidemiological studies have reported an association between herpes simplex virus type 1 (HSV-1) infection and AD [21]. In vitro studies have demonstrated that HSV-1 infection of neuronal and glial cells impairs autophagy, which leads to an accumulation of Aβ and tau that appears reducible with acyclovir treatment [21]. Whether treatment with acyclovir might have any impact on preventing or even reversing AD pathology in vivo remains unknown.

Highlighting some reversible dementia syndromes

Sleep dysfunction, depression, and exposure to toxic medications are common contributors to dementia and should be assessed in all patients. Consideration of rarer entities is appropriate in a subset of patients. The following are rare but treatable dementia syndromes worth noting.

Vitamin B12 (cobalamin) deficiency

Although vitamin B12 deficiency is relatively common in the elderly, and the AAN recommends screening for vitamin B12 deficiency in all dementia cases, it is an uncommon cause of dementia. One meta-analysis attributes only 1% of all potentially reversible dementia to vitamin B12 deficiency [2]. The question of reversibility remains controversial, but correction of deficiency may improve mild cognitive impairment, especially verbal fluency [22]. Risk factors for

vitamin B12 deficiency include age greater than 75 years and history of gastrointestinal surgery or gastrointestinal disease such as Crohn's, Whipple's, and celiac. Other neurologic manifestations include acroparasthesia, loss of position, and vibratory sense and optic neuropathy.

Autoimmune dementia

Cognitive impairment caused by autoantibodies directed against CNS targets is typically associated with other neurologic features such as new-onset seizures, but cognitive symptoms can occur in isolation, especially early in disease course. Cognitive dysfunction tends to develop over days to weeks with a fluctuating or rapidly progressive course. An autoimmune etiology should be considered in the presence of a subacute evolution, younger age of onset, presence of seizures or focal findings, or precedent viral prodrome or immunologic challenge. Cerebrospinal fluid (CSF) typically shows a pleocytosis, and magnetic resonance imaging (MRI) may show T2/fluid-attenuated inversion recovery (FLAIR)-hyperintensities with or without gadolinium enhancement. Positron emission tomography (PET) may be useful in detecting hypermetabolism associated with an autoimmune lesion [23]. Autoantibody detection in the serum or CSF confirms the diagnosis but is not always possible. First-line treatments include intravenous methylprednisolone, intravenous immunoglobulin (IVIg), and plasma exchange (PLEX) [22]. Recent comprehensive reviews are available [24].

Hashimoto encephalopathy

Hashimoto encephalopathy—also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis—is a rare syndrome whose pathophysiology is poorly understood. Patients are predominantly female with highest incidence in the fifth and sixth decades of life. Clinical presentation is variable but often involves confusion and behavioral changes. Seizures, ataxia, and myoclonus may also be present. Symptoms may be episodic or progressive, and there are case reports of HE presenting as a subacute dementia with insidious onset [23]. The majority of patients are euthyroid at presentation but have abnormal elevations of either antithyroglobulin or anti-thyroid peroxidase (anti-TPO) antibodies. Most patients respond to treatment with corticosteroids, although sometimes immunosuppressive medications are needed.

Neurosyphilis: general paresis (or dementia paralytica)

Neurosyphilis results from CNS infection by the spirochete *Treponema pallidum* and can occur at any time after the initial infection, although it does not cause dementia until the tertiary stage of infection, which is typically at least 10 years from initial infection. Despite the widespread use of penicillin, the global prevalence of syphilis continues to rise, making recognition of neurosyphilis vital. HIV is often a co-infection with syphilis. General paresis typically presents with psychosis, stuttering speech, depression, and at times, delusions of grandeur [24]. Other common neurologic signs include dysarthria, intention tremors of the face and tongue, facial and appendicular hypotonia, and pupillary abnormalities. Without treatment, general paresis is a progressive, dementing illness that leads to death within a few years.

Whipple's disease

Whipple's disease is a rare systemic disease caused by infection with gram positive bacillus *Tropheryma whippeli*. It can cause a progressive cognitive dysfunction mimicking neurodegenerative disease [25] and should be suspected in patients who present with arthralgias, weight loss, diarrhea, and abdominal pain. Other neurologic findings include supranuclear opthalmoplegia, pendular nystagmus, and myoclonus. Although considered a very specific finding, the pathognomonic oculomasticatory myorhythmia is not always present. Labs may suggest malabsorption with low albumin and vitamin deficiencies. Acute phase reactants may be elevated. MRI brain may be normal or show a range of abnormalities including a focal mass lesion; multifocal lesions involving the mesial temporal lobe, midbrain, hypothalamus, and thalamus; periventricular diffuse leukopathy; diffuse cortical atrophy; or pachymeningitis [26]. Diagnosis is made by *T. whipplei* testing of small intestine tissue (for patients with gastrointestinal symptoms), and CNS involvement is confirmed by testing of CSF. Treatment is intravenous antibiotics.

Normal pressure hydrocephalus

The classic clinical triad in NPH involves gait disturbance as the earliest and most common symptom followed by cognitive impairment then urinary urgency and frequency. Although the pathophysiology is not fully understood, the disorder is thought to be caused by impairment in CSF flow, perturbations in CSF biochemistry, and cerebrovascular compromise. Radiologic evaluation includes objective assessment of ventricular size, such as with the Evans index (ratio of the largest width of the frontal horns and the widest measure of the inner table of the skull at that level) and DESH (disproportionately enlarged subarachnoid space hydrocephalus). The diagnosis is often raised by radiologists, and—because all three clinical elements may not be present in early disease—the absence of gait or bladder changes should not exclude the diagnosis if radiological findings are supportive. If NPH is suspected, a large-volume lumbar puncture is performed with formal evaluation of cognition and gait pre- and post-procedure to evaluate whether a patient might be responsive to shunting [27].

Subdural hematoma

Elderly individuals with brain atrophy are at increased risk for developing subdural hematoma (SDH) following even minor head trauma. A history of heavy alcohol use and the use of antithrombotics or anticoagulants further increases risk. Clinical presentation is variable and may include headaches, decreased level of consciousness, and seizures or focal findings. However, subacute or chronic SDH may present as an insidious cognitive impairment. Computed tomography (CT) of the head is generally sensitive; however, small SDHs less than 3 mm in thickness or small, bilateral SDH may be missed. MRI is more sensitive for the detection of SDH. Small hematomas can be managed conservatively with surveillance imaging; however, neurosurgical treatment is recommended for larger hematomas or hematomas that are causing a neurologic deficit [28].

Transient epileptic amnesia and nonconvulsive status epilepticus

Epileptic causes of cognitive dysfunction are often underdiagnosed, especially if there are no overt signs of seizure activity. Transient epileptic amnesia (TEA) is a subtype of temporal lobe epilepsy involving the bilateral mesial temporal lobes. Seizures manifest as recurrent episodes of isolated memory loss. Memory impairment can be anterograde, retrograde, or both. Episodes generally last less than 1 h and often occur upon waking with partial or complete amnesia for the event. Two-thirds of patients have other seizure types including olfactory hallucinations. Additionally, TEA is associated with two forms of interictal memory impairment including loss of newly acquired memories over days to weeks and autobiographical amnesia. Routine electroencephalogram (EEG) either is normal or shows nonspecific slowing in two-thirds of patients. MRI may show mild atrophy in bilateral hippocampi. Given the diagnostic challenge, it may be reasonable to empirically trial anti-epileptic drugs (AEDs) if clinical suspicion is strong despite normal EEG. Seizures typically respond well to treatment with antiepileptic drugs, but the interictal memory impairment may be irreversible [29].

Non-convulsive status epilepticus (NCSE) may also present as an acute dementia with fluctuating cognitive dysfunction and behavioral disturbance. It is often associated with subtle facial or limb twitches, head or eye deviation, automatisms, speech arrest, or autonomic changes, but may present as isolated cognitive impairment [26]. There has been increasing awareness of NCSE in the critical care and emergency department settings after studies have shown that EEG detects NCSE in nearly 10% of comatose patients who have no overt signs of seizure [30]. Its prevalence has not been well-studied in the ambulatory setting.

Vascular corticobasal syndrome caused by carotid occlusion

There have been a few case reports of corticobasal syndrome (CBS) caused by internal carotid artery (ICA) occlusion. These patients demonstrated classic features of CBS including cognitive dysfunction, unilateral limb-kinetic apraxia, and extrapyramidal symptoms. MRI showed asymmetric atrophy mimicking the characteristic appearance of CBS due to neurodegenerative cause. However, vessel imaging revealed ipsilateral ICA occlusion [28, 31]. The incidence of CBS due to large vessel occlusion is unknown, and it remains unclear whether vessel imaging should be obtained in all patients who present with the clinical and radiographic features of CBS. Additional case series have shown that ICA occlusive disease can also lead to diverse presentations of cognitive impairment including a frontal dysexecutive syndrome with left frontotemporal atrophy mimicking behavioral variant frontotemporal dementia [32].

Diagnostic evaluation

Assessment of the dementia patient should begin with a detailed history with special attention to acuity of onset, precipitating factors, high-risk behaviors, and medical comorbidities (see Figs. 1 and 2). A thorough medication reconciliation is critical and should include discussion of over-the-counter medications and supplements with special attention to anticholinergics and benzodiazepines. All patients should be screened for depression, sleep dysfunction, and

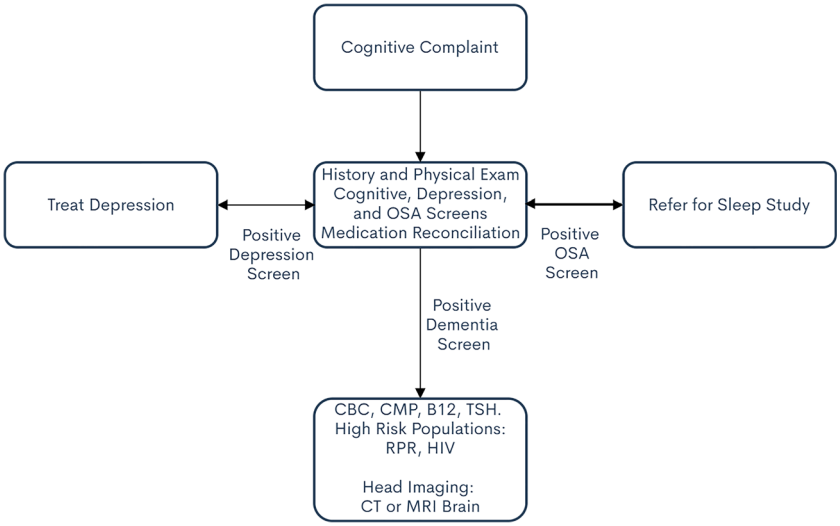

Fig. 1. Diagnostic algorithm for identifying and treating dementia. PHQ-2, Patient Health Questionnaire 2; PHQ-9, Patient Health Questionnaire 9; OSA, obstructive sleep apnea; PSG, polysomnography; MoCA, Montreal Cognitive Assessment; NPH, normal pressure hydrocephalus; NCSE, non-convulsive status epilepticus.

excessive alcohol consumption. The Patient Health Questionnaire 2 consists of two questions and has been validated as a screen for depression in this population [33]. Questions about sleep should specifically address whether there are any symptoms concerning for OSA such as snoring, apneic events, trouble waking in the morning, or excessive daytime somnolence. In patients who report these symptoms and in patients with physical attributes that place them

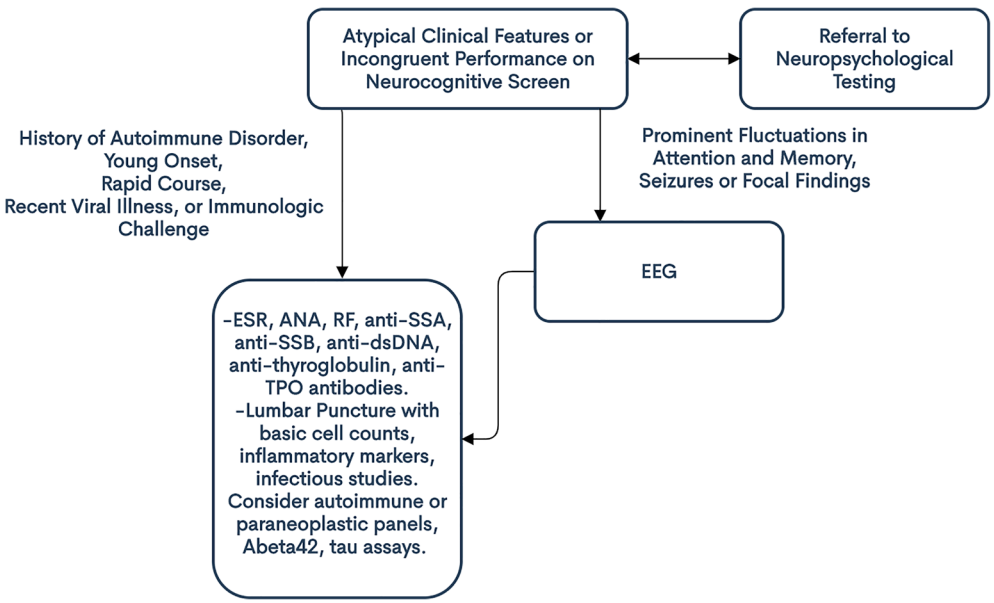

Fig. 2. Recommended investigations for dementia with atypical features. ESR, erythrocyte sedimentation rate; ANA, antinuclear antibodies; RF, rheumatoid factor; Anti-SSA/SSB, Anti-Sjögren's syndrome A and B; Anti-dsDNA, anti-double stranded DNA; Anti-TPO, anti-thyroid peroxidase; ABeta42, amyloid beta 42; EEG, electroencephalogram.

at high risk for sleep apnea (increased neck circumference, retrognathia, and body mass index greater than 35 kg/m^2), a referral for sleep consultation and polysomnography should be made.

General physical examination should focus on any signs of toxic, metabolic, or endocrine disease, such as skin, hair, or nail changes. A detailed neurologic examination should make note of any focal findings, gait abnormalities, parkinsonism, or eye movement abnormalities. Brief cognitive assessments such as the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA) should be administered to objectively establish cognitive impairment and approximate severity. A referral for more detailed neuropsychological testing is often warranted to characterize the severity and pattern of impairment.

All patients with dementia should undergo structural neuroimaging with either CT or preferably MRI. Gadolinium should be added if there are any signs or symptoms suggestive of an infectious or inflammatory etiology, or if the patient has a history of malignancy. Vessel imaging should be considered in cases of asymmetric brain atrophy in order to evaluate for ipsilateral vaso-occlusive disease.

The standard serum evaluation includes complete blood count (CBC), comprehensive metabolic panel (CMP), thyroid function tests, and vitamin B12. Further serum evaluation should be targeted to clinical history and examination findings. Patients with a history of high-risk behaviors (including multiple sexual partners, men who have sex with men and intravenous drug use) or with any history of immunosuppression should be screened for HIV and syphilis. Patients who have been diagnosed with or suspected to have an autoimmune disorder should undergo further testing with erythrocyte sedimentation rate (ESR), anti-nuclear antibody (ANA), rheumatoid factor (RF), anti-SSA, anti-SSB, and anti-dsDNA. Patients who present as a subacute or rapidly progressive dementia should be tested for anti-thyroglobulin and anti-TPO. Serum and urine heavy metal should be ordered in patients with a history of workplace or recreational exposure.

Lumbar puncture (LP) is indicated in patients with suspected NPH, in patients who have had rapid progression of symptoms, and in patients who have signs suggestive of infectious or inflammatory disease. In evaluating for NPH, at least 30 cc of cerebral spinal fluid (CSF) should be removed and quantitative measures of gait should be taken pre- and within 30 min post-procedure before CSF is replenished. Pre- and post-LP measures of cognition (such as digit span) may also be useful in determining whether a patient's cognitive deficits would respond to shunting. In all patients, CSF should be analyzed for basic cell counts and markers of inflammation and infection. Specific infectious studies should be chosen based on clinical history. Autoimmune and paraneoplastic antibody testing should be considered if there is suspicion for autoimmune encephalitis. Because AD is often in the differential diagnosis, sending CSF for ABeta42 and tau analysis may also be helpful.

An often-overlooked diagnostic tool in the workup of dementia is EEG. It should be obtained in patients who have prominent fluctuations in attention and memory or any other features suggestive of seizures (repetitive speech, rhythmic movements, tongue biting, etc.). EEG may also be useful in determining whether there are diffuse nonspecific electrical abnormalities suggestive of toxo-metabolic disease.

Diagnostic cerebral angiogram (DCA) may be useful to evaluate for vasculitis. Lastly, brain biopsy should be considered a last resort to evaluate for autoimmune or inflammatory disease, especially if the patient is young and otherwise healthy.

Treatment

Diet and lifestyle

- Medication reconciliation is perhaps the most impactful intervention for patients with dementia. The Beers Criteria provides helpful guidelines on which medications to avoid, especially anticholinergics, for elderly patients at risk of dementia [34].
- Encouraging a healthy lifestyle, including regular exercise and a Mediterranean diet may decrease the risk of dementia. Smoking cessation may also be helpful [35]

Pharmacologic treatment

Mirabegron

Indication	treatment of overactive bladder (in lieu of anticholinergics)
Standard dosage	25 mg qday. Can increase to 50 mg qday
Contraindications	allergy to drug
Main drug interactions	digoxin
Main side effects	hypertension, nasopharyngitis, UTI, headache.
Special points	works by a different mechanism of action than anticholinergics for bladder control in overactive bladder (selectively stimulates beta-3 adrenergic receptors, relaxing bladder smooth muscle).
Cost/cost-effectiveness	expensive. Prescription plans are available.

Interventional procedures

High-volume lumbar puncture

Indication	suspected normal pressure hydrocephalus
Contraindications	any risk of herniation
Complications	infection, hemorrhage, severe focal neurologic deficit
Special points	Perform cognitive and gait examinations before and after procedure. If there is significant improvement, patient may benefit from shunting.
Cost/cost-effectiveness	relatively cost-effective.

Transcranial magnetic stimulation

Indication	this is a newer non-invasive procedure FDA-approved for treatment refractory depression
Contraindications	absolute: metal implants. Relative: epilepsy, brain lesion, or at risk for seizure.

Complications	seizure, worsened depression or suicidality.
Special Points	can be completed in 6 weeks with 30 treatments.
Cost/Cost-Effectiveness	covered by most insurances

Physical/speech therapy and exercise

- Speech therapy: a structured speech therapy program can be useful for patients with moderate to severe dementia. It is very cost-effective and may lead to improved quality of life [36]
- Exercise has been shown to improve ability to partake in activities of daily living but not benefit cognition directly, according to a recent Cochrane Review. Exercise is a very cost-effective intervention [32]

Emerging therapies

Botox injection for treatment of depression

Standard procedure	30 unit injection to glabellar region
Contraindications	hypersensitivity, local infection, not recommended in pregnancy.
Complications	headache
Special points	although safe and FDA approved for migraine, this emerging treatment is not yet approved for depression so remains off-label.
Cost/cost-effectiveness	botox is expensive and requires a health care provider to administer.

Conclusion

Although it is rare to encounter a fully reversible dementia syndrome, the opportunity for cure in these cases necessitates clinical awareness. The presence of certain atypical clinical features should trigger additional evaluation beyond routine screening. Even in patients who present with classical features of neurodegenerative disease, the clinician should evaluate for potentially reversible contributors, most notably, depression, OSA, and cognitoxins. Although neurodegenerative disease remains irreversible, there is substantial opportunity to improve outcome by addressing reversible factors.

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