

Treatment Approach to a Patient with Lewy Body Dementia

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Introduction

An estimated 5.5 million Americans that are 65 and older are living with dementia. ⁽³⁴⁾ Despite this number, many believe that dementia remains under-diagnosed due to the time constraints of the primary care visit. ⁽³⁵⁾ In addition, this number may be higher due to evidence that missed diagnoses of dementia are more common among minorities. ^(29,34) According to data for Medicare beneficiaries age 65 and older, Alzheimer's or other types of dementias were diagnosed in 6.9% of Caucasians, 9.4% of African-Americans, and 11.5% of Hispanics. ^(29, 34) With more than five million people living with dementia, healthcare providers are likely to encounter patients with dementia in all settings and specialties.

Because adults 65 and older are projected to make up a greater portion of the United States population, the cost of caring for patients with dementia is an important public health concern. ⁽¹⁵⁾ Medicare and Medicaid are estimated to cover \$175 billion of the total health care and long term care costs for patients with dementia by the end of 2017. ⁽³⁵⁾ The majority of the 68% of healthcare costs spent on dementia patients in the United States come from frequent hospitalizations and placement in skilled nursing facilities. ⁽³⁵⁾ This makes long-term care for patients with dementia one of the largest expenses in the healthcare budget. Looking ahead, it is projected that expenses related to caring for a patient with dementia will increase by more than 300% by the year 2050. ⁽³⁵⁾

Dementia is a decline in memory and executive function significant enough to affect a person's ability to perform activities of daily living independently. ⁽³²⁾ Dementia can result from reversible metabolic conditions such as thyroid dysfunction, vitamin deficiencies, and infectious diseases. ⁽³⁰⁾ These conditions should be ruled out with laboratory testing before exploring neurodegenerative causes. ⁽³⁰⁾ In addition to eliminating metabolic, psychiatric, and other neurological conditions, a detailed cognitive assessment must be completed.

Types of dementia are differentiated based on risk factors, neurobehavioral assessment, and brain imaging, but a definitive diagnosis is impossible without a post-mortem examination of the brain. ^(16,32) In addition, patient responses to medications are sometimes helpful in differentiating among the types of dementia. ⁽¹⁵⁾ In actuality, having a combination of more than one type of dementia is common. ⁽¹⁵⁾

Alzheimer's disease (AD) is the leading cause of dementia in older people in the United States. ⁽¹⁶⁾ AD accounts for 4.7 million of the 5.5 million people in the United States living with some form of dementia. ⁽³⁴⁾ One in ten people age 65 and older have AD. ⁽³⁴⁾ The greatest risk factors include age, family history, and the presence of apolipoprotein E (APOE). ⁽³²⁾ Studies show that patients with mild cognitive impairment are at a greater risk for AD. Research showed that 10-15% of individuals with mild cognitive impairment progressed to AD. ⁽¹⁶⁾ AD is differentiated from other types of dementia because of its gradual progression of cognitive decline. ⁽¹⁶⁾ The initial presenting symptom is difficulty recalling new information. ⁽¹⁶⁾ For example, the patient may repeatedly ask the same question. Later in the progression of AD, the patient will experience additional memory loss and decline in language, visuospatial, and executive

function. ⁽¹⁶⁾ The MRI shows diffuse atrophy of the brain. ⁽³⁰⁾ Post-mortem histology reveals amyloid protein and neurofibrillary tangles diffused throughout the brain. ⁽³⁰⁾

Lewy Body Dementia (LBD) is second in prevalence to AD, accounting for nearly 1 million cases of dementia in the United States. ^(14, 34) It remains underdiagnosed due to its resemblance to more well-known diseases such as AD. ⁽¹¹⁾ Risk factors for LBD are Parkinson's disease (PD) and depression. ⁽³⁰⁾ The core features of LBD are problems with cognition and movement. ⁽¹⁶⁾ Features also include 1) recurrent visual hallucinations, 2) parkinsonism, 3) sleep disturbance, and 4) dysautonomia. ⁽³⁾ LBD is said to have a worse prognosis and shorter disease course than AD due to neuropsychiatric symptoms such as psychosis and depression. ⁽¹¹⁾ Staging of the disease is difficult due to ongoing fluctuations in attention and cognitive function. ⁽¹⁴⁾ MRI shows atrophy of the substantia nigra and brain stem with decreased perfusion. ⁽¹⁶⁾ Low dopamine transporter uptake in the basal ganglia is seen on PET/SPECT. ⁽³⁰⁾ Post-mortem histology reveals lewy body protein. ⁽³⁰⁾

LBD is further broken down into the subsets of Dementia with Lewy Bodies (DLB) and Parkinson Disease Dementia (PDD). The main differentiator between the diagnosis of DLB and PDD is the timing of the onset of symptoms. For simplicity of diagnosis, providers use the 1 year rule. ⁽²⁵⁾ If cognitive symptoms begin one year prior to or concurrently with parkinsonian symptoms the patient is diagnosed with DLB. If the patient had a diagnosis of Parkinson's disease for at least one year prior to the onset of cognitive symptoms they are diagnosed with PDD. Regardless of the subset of LBD, these patients display parkinsonian features in addition to a decline in cognition. Post-mortem examination reveals lewy bodies in the brains of patients with both DLB

and PDD. ⁽³⁰⁾ LBD is often misdiagnosed as AD and often takes post-mortem histology to diagnose. LBD can be distinguished from AD in that memory loss tends to be mild in comparison to the pronounced amnesic disturbance of AD. ⁽²⁵⁾ In AD, pathologic and imaging studies show significant atrophy of the hippocampus in AD, while patients with LBD the hippocampus remains largely intact. Parkinsonian symptoms of LBD are often more associated with rigidity and bradykinesia than tremor. ⁽²⁵⁾ Patients with LBD experience more balance instability and gait difficulty in comparison to patients with AD. ⁽²⁵⁾

Although LBD and AD share many of the same symptoms, their etiologies differ as does their approach to treatment. Therefore, it is important for the clinician to be able to assess for differences between the two. LBD has earlier detrimental effects on quality of life in comparison to AD. ⁽³⁾ The approach to therapy should be targeted and an intervention should be initiated as early as possible. There is no cure for either at this time, therefore the mainstay of therapy is symptom management. The goal of treatment is to improve quality of life, maintain as much independence as possible, and minimize adverse reactions to medications.

⁽¹⁴⁾ Among available medications, cholinesterase inhibitors have shown some benefit in cognitive functioning for AD, but less for LBD. Even within the subset of LBD, DLB patients respond better to cholinesterase inhibitors compared to PDD patients. ⁽²⁶⁾ This is likely because the pathology of DLB is more similar to AD than PDD. ⁽²⁵⁾ In contrast, treatment with levodopa is more effective in treating parkinsonian symptoms in patients with PDD compared to LBD. This is likely due to PDD being more similar to Parkinson's disease pathology than DLB. ⁽²⁵⁾ Research

continues to investigate appropriate therapies for both AD and LBD. Unfortunately, LBD lags behind most other neurological disorders in research, treatment, and awareness. ⁽¹⁴⁾

Pathophysiology

The exact cause of LBD and AD are unknown. ⁽¹⁶⁾ Both are neurodegenerative diseases that contain an intracellular deposition of abnormal proteins. The mechanisms of nerve cell destruction include disruption of tissue architecture, alteration of cell metabolism, and initiation of apoptosis. ⁽¹⁶⁾ These disruptions cause oxidative stress and damage of cell components, resulting in brain inflammation. ⁽¹⁶⁾ Neurotransmitter abnormalities cause the gradual loss of connections between neurons and eventual neuronal death. ⁽¹³⁾ Symptoms of cell death may include loss of motor control, cognitive deterioration, and autonomic nervous system dysfunction. Both LBD and AD contain a non-specific pathological change of atrophy and enlarged ventricles.

Amyloid plaques and neurofibrillary tangles are the hallmark finding in AD. ⁽¹⁶⁾ These plaques and tangles disrupt the normal function of the neuron. Neurofibrillary tangles contain tau protein. An important role of tau protein is to maintain the internal structure of the neuron. ⁽¹⁶⁾ Excess phosphorylation of tau protein cause a disruption in the internal formation of the nerve cells causing tangle formation. ⁽¹⁶⁾

The hallmark pathologic finding in LBD is the lewy body. ⁽³⁰⁾ Autopsied brains of LBD patients reflect pallor of the substantia nigra, cerebral atrophy, and ventricular enlargement. ⁽³⁰⁾ Lewy body neuronal inclusions consist of alpha-synuclein, ubiquitin alpha B-crystallin, and

phosphorylated neurofilament protein. ⁽¹³⁾ Tau proteins can also be present. ⁽¹³⁾ These neuronal inclusions displace other cell components, causing a disruption in normal cell function. ⁽¹⁶⁾ This disruption is reflected in the neurocognitive symptoms seen in LBD.

There are minor pathology differences between the two subsets of LBD. For example a primary structural component in the subset DLB, is that alpha-synuclein protein is found in pre-synaptic terminals. ⁽¹³⁾ The pre-synaptic terminal releases neurotransmitters from synaptic vesicles and is essential in relaying signals between neurons and overall cognition. ⁽¹³⁾ In PDD, a subset of LBD, neuron loss is most prominent in the substantia nigra, brainstem, and brain cortical cells. ⁽³⁰⁾ The degeneration of these dopaminergic cells cause parkinsonian symptoms of bradykinesia, rigidity, and tremor. ⁽³⁰⁾ In DLB, lewy body cells are diffusely spread out in the brain in contrast to being concentrated in the substantia nigra in PDD. ⁽¹¹⁾

In both LBD and AD, damage to neurotransmitters negatively affect cognitive performance.

Abnormal proteins create blockages and destroy the normal function of key neurotransmitters acetylcholine, dopamine, and glutamate. A decrease in cholinergic activity in both LBD and AD causes increased acetylcholinesterase activity which negatively affects cognitive function. ⁽²²⁾ A greater depletion of cholinergic markers is responsible for the earlier onset of hallucinations and cognitive fluctuations in LBD. ⁽¹⁴⁾ An important neurochemical difference between LBD and AD is dopaminergic metabolism, which is greatly affected in LBD. ⁽¹⁴⁾ The lack of dopamine causes problems with movement. Dopamine also regulates emotion, pleasure, and reward centers. ⁽¹⁴⁾ In addition, overstimulation of NMDA-glutamate receptors causes an influx of calcium-inducing excitotoxicity. The ultimate result is glutamate receptor damage and cell

death. ⁽²²⁾ Increased influx of calcium into neurons is known to play an early role in the formation of glutamate-induced excitotoxicity that occurs in many neurodegenerative diseases. ⁽²⁷⁾ Glutamate receptors are essential for synaptic plasticity which is vital for memory formation, neural communication, and learning. ⁽²²⁾

Clinical Presentation

LBD and AD share core features of dementia such as a decline in memory from the previous level of function. ⁽¹⁴⁾ 1) Parkinsonism, 2) rapid eye movement sleep disorder (RBD), 3) hallucinations, 4) delusions, and 5) fluctuations in attention are specific to LBD and not evident in most cases of AD. ⁽¹⁴⁾

Parkinsonian features include bradykinesia, stiffness, tremor, and facial masking. ⁽¹⁴⁾ Symptoms of spontaneous parkinsonism are reported in 25-50% of patients with DLB at the time of diagnosis. ⁽¹⁴⁾

Rapid eye movement disorder (RBD) is a condition in which the patient physically acts out their dreams. ⁽¹⁸⁾ Bed partners describe the patient screaming and flailing their arms and legs while sleeping. ⁽¹¹⁾ Partners also report having to awaken the patient promptly or move out of the way to avoid injury. ⁽³⁰⁾ Evidence supports the idea that this is often an early sign and predictor of LBD. ^(11, 18) One study showed that, 40-65% of patients with RBD will develop a neurodegenerative disorder, most often a synucleinopathy which includes LBD. ⁽¹⁸⁾ Studies show that RBD can precede LBD by up to ten years. ⁽¹¹⁾

Neuropsychiatric symptoms occur early in LBD. ⁽¹⁴⁾ Visual hallucinations are common and may or may not be distressing to the patient. ⁽¹¹⁾ Patients often see family members, children, or

objects. The incidence increases in the evening or with poor lighting. ⁽¹⁴⁾ In addition, delusions may occur. Typical delusions include accusations of infidelity, theft, and misidentification. ⁽¹⁴⁾ Visual hallucinations and delusions occur in 60-70% of patients with LBD. ⁽¹⁴⁾ Auditory hallucinations are rare.

Fluctuations in attention and concentration are also very common. ⁽²⁵⁾ The patient displays 1) excessive daytime drowsiness, 2) daytime sleep more than two hours, 3) staring in space for long periods, and 4) episodes of disorganized sleep. ⁽¹⁴⁾ Three out of four of these features are seen in 63% of patients with LBD compared to 12% with AD. ⁽¹⁴⁾

Dysautonomia is a non-specific symptom that many patients with LDB encounter. The most common sign of dysautonomia is orthostatic hypotension, a significant decrease in blood pressure when the patient goes from the sitting to standing position. ⁽¹⁴⁾ The patient often reports feeling dizzy upon standing. ⁽³⁰⁾ One early sign of autonomic dysfunction in men can be the inability to maintain an erection. ⁽¹⁶⁾ Other autonomic changes are variable. They include the following 1) urinary, 2) vision, 3) digestion, and 4) sweat gland abnormalities. ⁽¹⁶⁾

Memory difficulties appear to be fairly mild in LBD compared to AD. They often do not occur until later in the course of the disease. ⁽¹³⁾ AD has a gradual progression of cognitive decline including symptoms of difficulty remembering recent conversations and learning new information. ⁽³⁶⁾ In comparison, 57% of LBD patient caregivers report a presenting symptom of memory problems, compared to almost 100% of AD caregivers. ⁽¹⁴⁾

Diagnostic Evaluation

A comprehensive dementia evaluation should include 1) detailed cognitive testing, 2) laboratory panels for treatable causes, 3) a neurologic exam, and 4) brain imaging. ⁽¹⁴⁾ The goal of these tests is to rule out psychological or neurological disorders that could be the cause of the cognitive decline seen in patients with dementia.

Key Features

Key Differences Between Lewy Body Dementia and Alzheimer's Disease	
Lewy Body Dementia	Alzheimer's Disease
<ul style="list-style-type: none">○ Visual hallucinations○ Parkinsonian Symptoms○ Fluctuating cognition	<ul style="list-style-type: none">○ Short-term memory loss○ Difficulty learning new information○ Insidious cognitive decline

Key Differences Between Subsets of Lewy Body Dementia	
Dementia with Lewy Bodies	Parkinson's Disease Dementia
<ul style="list-style-type: none">○ Cognitive symptoms must precede the onset of parkinsonian features by at least 1 year.○ More similarities with AD pathology.	<ul style="list-style-type: none">○ Prior diagnosis of Parkinson's disease must precede the onset of dementia by at least 1 year.○ More similarities with Parkinson's disease pathology.

Neurological Assessment

Many primary care offices perform annual cognitive screening for older adults. In addition, depression screening via the PHQ-9 should be performed to rule out pseudo-dementia or a mental illness. ⁽³²⁾ The Mini-Mental State Exam (MMSE) and Montreal Cognitive Assessment (MoCA) are two tests used for dementia screening. ^(31, 32) Over the years, the MMSE has become less popular and is often replaced by the MoCA for dementia screening. ⁽³²⁾

The MoCA is more difficult and sensitive, thus making it easier to discover mild cognitive impairment. In contrast, the MMSE is less challenging and has a greater focus on vocabulary. Because of this, the MMSE may mask cognitive deficits in highly educated individuals. ⁽³²⁾ The MMSE is often used to monitor trends in cognitive function for patients with a more profound cognitive deficit. Regardless of the test, the MMSE and MoCA require knowledge of the patient's baseline and a systematic approach to achieve valid results. ⁽³³⁾

A baseline level of function is obtained through a detailed timeline of onset of symptoms and cognitive decline provided by a caregiver or family member. Events of concern such as automobile accidents, getting lost, and inability to manage finances warrant more detailed neurocognitive testing and diagnostic evaluation. ⁽³³⁾

Detailed cognitive assessments are the most important tool in the diagnosis of dementia and should assess performance in at the following cognitive domains: 1) memory, 2) language, 3) attention, 4) executive function, and, 5) visuospatial ability. ⁽³³⁾

Compared to AD, LBD patients show a greater deficit when performing visuospatial tasks such as drawing a clock. ⁽¹⁴⁾ In contrast, AD patients perform worse on language function tests

compared to LDB patients. ⁽¹⁴⁾ Verbal Fluency is often assessed by having the patient name animals and then list words that start with a particular letter. The patient is given one minute to complete each category of this language function test. Periodic cognitive evaluations are important to track cognitive decline or improvement.

A thorough neurological exam including assessment of 1) cranial nerves 2) strength, 3) reflexes, 4) sensation, and 5) gait should be completed in addition to cognitive testing. ⁽³⁰⁾

Imaging

MRI scans showing progressive atrophy and white matter lesion progression, are seen in many dementia subtypes. ⁽³⁰⁾ The MRI of an AD patient displays a diffuse atrophy of the brain. ⁽³⁶⁾ The MRI of a patient with LBD shows atrophy of the substantia nigra and brain stem. ⁽¹⁶⁾ PET/SPECT scan shows low dopamine transporter uptake in the basal ganglia and decreased perfusion. ⁽³⁰⁾

Pharmacologic Treatment

Cholinesterase inhibitors remain the most often used therapy in the treatment of AD and LBD. ⁽¹⁰⁾ The available cholinesterase inhibitors on the market have similar efficacy in AD and include donepezil, rivastigmine, and galantamine. ⁽¹⁵⁾ Currently this class of medications are approved by the FDA for treatment of AD. ⁽⁴⁾ Treatment results include improvements in overall cognition and behavior. ⁽⁹⁾ Cholinesterase inhibitors prevent the breakdown of acetylcholine, a key neurotransmitter in cognition. ⁽⁹⁾ Because less acetylcholine is broken down, more of it is available at the cholinergic synapse to send and process signals in the brain. ^(2,9) With cholinesterase inhibitors, preventing the breakdown of acetylcholine can be accomplished through various mechanisms of action.

Research shows that, cholinesterase inhibitors are most effective when initiated within the first year of diagnosis. ⁽²⁹⁾ Studies reflect an extended ability to self-perform activities of daily living thus, delaying skilled nursing facility placement usually by months. ⁽⁴⁾ Benefits wane over a period of 1-2 years. ⁽¹⁵⁾ This is likely explained by disease progression, making even less acetylcholine available for memory and learning. ⁽¹¹⁾ Cholinesterase inhibitor side effects include gastrointestinal complaints such as 1) nausea, 2) vomiting, 3) diarrhea, and 4) constipation. ⁽⁴⁾ Patients taking cholinesterase inhibitors at night may report leg cramps, insomnia, or vivid dreams. ⁽⁴⁾ This side effect can be minimized by instructing the patient to take the dose in the morning. ⁽⁴⁾ The effectiveness of cholinesterase inhibitors is often dose dependent. ⁽⁴⁾ Doses are often titrated to the maximum tolerable dose based on individual side effect profiles. ⁽⁴⁾

Although cholinesterase inhibitors increase acetylcholine concentration in the brain, the mechanism of action differs within the class of medications. For example, donepezil selectively inhibits acetylcholinesterase via a mechanism of action that is not completely understood. ⁽⁹⁾ We do know that donepezil binds and reversibly inactivates cholinesterases, therefore inhibiting hydrolysis of acetylcholine. ⁽⁹⁾ Rivastigmine inhibits acetylcholine in a less specific way. It inhibits both butyrylcholinesterase and acetylcholinesterase. ⁽¹⁵⁾ Galantamine uses a dual mode of action. It is a reversible competitive inhibitor of acetylcholinesterase and an allosteric modulator of nicotinic acetylcholine receptors. ⁽¹⁵⁾ In addition to making more cholinesterase available, allosteric modulation plays an important role in increasing the nicotinic receptor response to acetylcholine. ⁽¹⁵⁾

Although not FDA approved for LBD treatment, cholinesterase inhibitors have shown to be beneficial for some patients with LBD. In a comparison study of LBD subsets, 30 DLB and 40 PPD patients were treated with donepezil. ⁽¹¹⁾ The patients showed an improvement in MMSE scores by a mean of 3.9 points in the DLB group and by 3.2 points in PDD by 20 weeks. ⁽¹¹⁾ For patients without immediate concerns regarding side effects and drug interactions, administration of 5 mg/day of donepezil is indicated, with an increase to 10 mg/day as tolerated. ^(2,9) In patients with LBD, response to therapy is maximal with a 10 mg dose as evidenced by reduced caregiver burden. ⁽⁴⁾ Unfortunately, with a higher dose, given that the patient with LBD often has autonomic dysfunction at baseline, the risk of hospitalization for bradycardia may double. ⁽¹⁶⁾

Another approach to enhancing cognition is the use of memantine, an NMDA (N-methyl D-aspartate) receptor antagonist. Memantine prevents glutamate toxicity which causes glutamate receptors to become less effective. This causes damage to the neuron by affecting signal transmission and interpretation to other areas of the body. ⁽¹⁰⁾ Memantine blocks the NMDA ion channel to reduce the influx of calcium. ⁽²⁷⁾ Increased influx of calcium into neurons play an early role in the formation of glutamate-induced excitotoxicity that occurs in many neurodegenerative diseases. ⁽²⁷⁾

Memantine is not beneficial in mild disease, but is often used in moderate to severe AD. It is especially useful for people who have a contraindication or intolerance to cholinesterase inhibitors. Memantine has been associated with a moderate decrease in cognitive deterioration. Like cholinesterase inhibitors, it is more efficacious in patients with AD in

comparison to LBD. Generally, patients with the LDB subset of DLB seem to benefit more from memantine than those with PDD. ⁽¹⁰⁾ In regards to the side effect profile, memantine is better tolerated than cholinesterase inhibitors. ⁽¹⁰⁾ The most common adverse effect of memantine is somnolence ⁽¹⁰⁾. The incidence of adverse effects were low with memantine and similar to placebo groups. ⁽¹⁰⁾ Memantine did not seem to have an effect on motor scores for patients with LDB. ⁽¹⁰⁾

Namzeric is the only FDA approved combination medication for moderate to severe stage AD. It is composed of donepezil and memantine. Studies indicate that a combination of a cholinesterase inhibitor with memantine produces a modest additive benefit. ⁽³⁷⁾ Namzeric increases acetylcholine concentration and regulates glutamate toxicity. Namzeric is most useful after each medication (donepezil, memantine) has been titrated to the highest tolerable level. Core motor features of LBD include rigidity, tremor, and bradykinesia. Levodopa is the first line treatment for the parkinsonian symptoms of LDB. In contrast to LDB, patients with AD do not experience movement disorder symptoms and do not require levodopa. In the brain, levodopa is converted to dopamine. Activation of central dopamine receptors improve movement in most cases of LBD. Responsiveness to levodopa is limited in LBD compared to Parkinson's disease. ⁽²⁶⁾ A significant improvement of symptoms was seen in 50% of PDD and a smaller proportion of DLB. ⁽²⁶⁾ Carbidopa is added to levodopa due to its inability to cross the blood brain barrier. Because of this inability, peripheral conversion of levodopa to dopamine is prevented. As a result, more levodopa is available in the brain for conversion to dopamine.

Treatment with levodopa should begin at a low dose with conservative titration to a therapeutic dose. Key possible side effects of levodopa are an exacerbation of neurobehavioral and motor symptoms. Neurobehavioral symptoms include disinhibition, hallucinations, and delusions. In addition, because of their motor symptoms, LBD patients are at an increased risk for falls. ⁽²⁶⁾ Levodopa treatment may reduce the occurrence of falls even in a patient that may not be achieving an optimal motor response. ⁽²⁶⁾ Dopamine deficiency increases as LBD progresses, making levodopa gradually less effective and titration essential for maintaining motor function.

Antipsychotics are not recommended for treatment of LBD. ⁽²⁵⁾ Prior to initiation of an antipsychotic, it is best to assess the patient for possible causes of delirium such as a urinary tract infection, pneumonia, or fecal impaction. This is key, because we know that, in advanced dementia, the patient is often unable to communicate their needs to the caregiver.

Antipsychotics should only be used when the patient is an immediate danger to themselves or others. If this is the case, a second generation antipsychotic such as quetiapine is preferred. ⁽²⁶⁾

This preference is due to the neuroleptic sensitivity of patients with LBD. Symptoms of neuroleptic syndrome include altered mental status, rigidity, and tremor. Antipsychotic medications are known to have stronger adverse effects in the geriatric population due to polypharmacy and pharmacokinetic changes due to advanced age. ⁽²²⁾ There is also a black box warning for increased mortality with long-term use of antipsychotics within the geriatric population. ⁽²²⁾ Before prescribing an antipsychotic, a trial of cholinesterase inhibitors and antidepressants should be initiated to manage psychiatric symptoms. ⁽²⁶⁾ Second generation antipsychotic medications, such as quetiapine also require frequent laboratory testing to

monitor blood glucose and cholesterol, because this class of medications can precipitate metabolic syndrome. ⁽²²⁾

Sleep disorders associated with LBD include insomnia and frequent nighttime awakenings. These are often treated with melatonin and clonazepam. ⁽³⁰⁾ Melatonin is first titrated to its maximum tolerated dose. If the therapeutic effect is not achieved, clonazepam may be added. The choice to initiate and increase clonazepam should be approached with caution as clonazepam is contraindicated in this age group.

Depression and anxiety is more common in LBD than in AD. Antidepressants are the most common treatment for anxiety and major depressive disorder. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are used as first line therapy for symptoms of depression in patients with LBD. ^(22, 25) Unfortunately, studies lack consistent evidence of efficacy for patients with LBD. ⁽²²⁾ Tricyclic antidepressants should be avoided due to their anticholinergic properties. ⁽²²⁾ Electro-convulsive therapy has shown some benefit for some patients with refractory depression. ⁽²⁵⁾

Caregiver Support and Communication Tools

Patients with dementia require assistance with activities of daily living. As a result, caregiving is essential for the daily function of the patient. Oftentimes, the caregiver spends more time with the patient than any other member of the healthcare team.

Counseling and caregiver support is essential to manage the daily stress of caregiving. Allowing the caregiver to express frustration and learn new coping skills may prevent caregiver burnout.

⁽³²⁾

Good dementia communication tools are important to help manage frustration between the patient and the caregiver. ⁽³²⁾ The caregiver can be encouraged to make eye contact before speaking, use simple language, and speak slowly in a low pitched voice. ⁽³²⁾ Also, the caregiver should break down instructions into small steps and present them one at a time along with temporarily backing off if the patient seems agitated or refuses. In addition to promoting adequate sleep and activity, nutrition is also important in order to optimize functional capabilities of the patient. ⁽³²⁾ Of these, physical activity such as exercise has been shown to be effective in both mood and cognition. ⁽²⁵⁾

Prevention

There are no medications or specific lifestyle recommendations to prevent LBD or AD.

Preventative measures that show the strongest evidence include a) blood pressure control, b) head injury prevention, c) staying physically, cognitively, and socially active, and d) the Mediterranean diet. ⁽³²⁾ People who are more physically active are less likely to be diagnosed with neurodegenerative diseases. ⁽¹⁶⁾

Conclusion

LBD is second in prevalence to AD and is often underdiagnosed. 1) Pathophysiology, 2) clinical features, 3) imaging, and 4) a thorough neurological assessment are helpful in differentiating LBD from AD. Distinguishing symptoms of LBD are 1) visual hallucinations, 2) delusions, 3) fluctuations in attention, and 4) RBD. In contrast, hallmark symptoms of AD include 1) insidious cognitive decline, 2) short-term memory difficulties, and 3) difficulty learning new information. Early screening and diagnosis is important to guide therapy. Because there is no

disease modifying solution for LBD or AD at this time, treatment is geared to symptom management. Cholinesterase inhibitors are the first line treatment for management of cognitive symptoms and have proven beneficial, at least in the short term. Cholinesterase inhibitors show the greatest benefit for the first 1-2 years after initiation of therapy. Due to the decrease in the acetylcholine of the patient, this class of medications become less effective as the disease progresses. NMDA receptor antagonists have shown a benefit in cognition, but less substantial compared to cholinesterase inhibitors. Modest benefit has been shown with a combination medication that includes donepezil and memantine. Levodopa is used for parkinsonian symptoms such as bradykinesia, rigidity, and tremor seen in LDB. It is generally effective in LBD, but less so than in Parkinson's disease. Anti-psychotic medications should be avoided if possible due to neuroleptic sensitivity in patients with LDB. Polypharmacy and changes in pharmacokinetics due to aging put the geriatric population at an increased risk for adverse effects. Neurobehavioral symptoms such as hallucinations, delusions, and behavior problems may respond to a trial of a cholinesterase inhibitor and antidepressant. Depression and anxiety is more common in LDB than AD. SSRIs and SNRIs are first line treatment for these symptoms. Patients with LDB often experience symptoms of RBD, such as frequent nighttime awakenings and vivid dreams. These can be managed with melatonin and clonazepam. Early treatment of both LBD and AD has been shown to increase quality of life, delay admission to a skilled nursing or assisted living facility, and aid in prevention of caregiver burnout.

Direction of future research

LBD is second in prevalence to AD. In the last few years, LBD has become more readily recognized by the medical community. Although there is no breakthrough in the immediate future, clinicians continue to create and engage patients in clinical trials to continue to work towards a cure.

Addendum

Methods

PubMed Clinical Queries and EBSCOhost Research Databases interfaces were used. A narrow therapy filter was used with the terms “lewy body disease or lewy body dementia”, “systematic and lewy body disease”, and “differential diagnosis and lewy body disease”. Variations of the order of these key terms synonyms, and related terms were used as MESH terms. All full text, human, and articles from 2007-2017 were included in the search. From the EBSCOhost Research Databases interface the CINAHL Plus with Full Text database was used with search terms “Lewy bodies” and “Epidemiology AND Lewy body dementia AND United States”. Limiters to these search terms included “full text, exclude MEDLINE, human, PDF full text, language (English³)”. MEDLINE was excluded to avoid redundancy from the previous PubMed Clinical Queries search. Expanders included “find any of the search terms” and “apply related words”.

Systematic reviews were evaluated using GRADE Criteria and the Cochrane risk of bias tool. Randomized controlled trials included evaluate of risk of bias including double-blinded studies, similar patient population groups, reasonable follow-up time, and evaluation of patient drop-out rate.

Search Strategy (MESH terms)

Interface – Pub Med Clinical Queries

Therapy/Narrow[filter] AND ("lewy body disease"[MeSH Terms] OR ("lewy"[All Fields] AND "body"[All Fields] AND "disease"[All Fields]) OR "lewy body disease"[All Fields] OR ("lewy"[All Fields] AND "body"[All Fields] AND "dementia"[All Fields]) OR "lewy body dementia"[All Fields]) AND ("loattrfull text"[sb] AND "2007/07/11"[PDat] : "2017/07/07"[PDat] AND "humans"[MeSH Terms])

Evaluation of Resources for Quality

Systematic Reviews (15) - Clinical question and outcomes were outlined clearly to the reader. Two independent reviewers evaluated quality and risk of bias in included studies. Study inclusion and exclusion data was provided clearly in a flow chart. The search was incomplete, however a MEDLINE database search was completed. In addition, these additional references were identified by reading through the bibliographies of relevant articles. Search terms were provided in detail for both disease and treatment. The quality assessment of the review is moderate.

Randomized Controlled Trials (4, 10) – Both RCT's were randomized and double-blinded. The randomization list was put in two sealed envelopes. ⁽⁴⁾ The randomization list was computer generated. They both reported when and if the randomization code was broken. Caregiver supervised compliance with dosing instructions were assessed. ⁽⁴⁾ Conflicts of interest were disclosed such as funding and the roles that the sponsor played in certain parts of the study. They also discussed limitations such as small sample size which occurred in both RCT's. ⁽⁴⁾ Strengths included the study being an accurate representation of the target population. ⁽⁴⁾ Data was reported clearly compared using tables.

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