

TREATMENT OF LEWY BODY DEMENTIA

The importance of early treatment is supported by recent data suggesting that patients with Lewy body dementia (LBD), which includes dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), might respond better to cholinesterase inhibitors than patients with Alzheimer's disease (AD). In addition, an early diagnosis of DLB will help treating physicians know which medications to avoid or use cautiously, especially the antipsychotics (aka neuroleptics).

IMPORTANT NOTE: It is estimated that a high percentage of DLB patients exhibit worsening parkinsonism, sedation, immobility, or even neuroleptic malignant syndrome (NMS) after exposure to antipsychotics. NMS is a rare, life-threatening medical emergency characterized by fever, generalized rigidity and breakdown of muscle tissue that can cause renal failure and death. The heightened risk of NMS in DLB mandates that **typical or traditional antipsychotics (such as haloperidol, fluphenazine or thioridazine) should be avoided**. Atypical antipsychotics have been available for treating mental illness for 25 years and may be safer to use in patients with DLB, but only with extreme caution. Patients with PDD appear to have a lower risk of an adverse reaction to an antipsychotics, but all patients with LBD should be carefully managed with any antipsychotic drug.

Goals of Care

Comprehensive, palliative management of LBD should begin at diagnosis to promote the best quality of life for the person with LBD and the family and caregivers. An early, wide-ranging discussion of symptoms and goals of treatment will proactively inform both the provider and the primary family caregiver about important future decisions.

The goals of care may change as the illness progresses due to emerging or evolving issues of safety, caregiver burden, or comorbid illness. An ongoing dialogue between the health care providers, patient and family about management, especially in regard to later, end-of life decisions, should occur regularly throughout the course of the illness.

First line medications

Cognitive Impairment and Fluctuations

Acetylcholinesterase inhibitors (AChEIs): AChEI's are the current standard of care for treating cognitive and psychiatric symptoms of LBD. Three have been approved by the FDA for treatment of AD--donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne). Rivastigmine is the only one of the three approved for treating LBD, specifically PDD. The other two are used "off label." There is no compelling evidence that any one of the three is superior to the other two in treating LBD.

AChEIs are generally well-tolerated by patients with LBD, but not always. For example, in a study of rivastigmine in PDD, approximately 10% of patients experienced worsening of tremor, but it was not usually clinically significant. Health care providers and patients/caregivers must always be on guard for the development of adverse effects of any drug.

Memantine (Namenda) is another drug (with a different pharmacological mechanism of action) approved for AD but not LBD and is also used off label as an add-on therapy to AChEIs, typically in patients with more severe dementia. Only a few studies of memantine have been done in LBD, with mixed results.

Parkinsonism

Levodopa is a most potent and the safest drug for treating Parkinson's disease (PD); most patients with LBD will show at least modest improvement in motor function, without side effects as long as the dosing is kept at the lowest, most effective level. However, all patients with LBD are vulnerable to the development of medication-induced behavioral or psychotic symptoms. Not everyone with LBD requires anti-parkinson treatment. In fact, some patients may go years before showing signs of parkinsonism. Given the potential for adverse effects, health care providers should use levodopa in this setting only when symptoms are truly bothersome and should start with a low dose and slow up-titration.

Dopamine agonists are less effective than levodopa and are more likely to cause more side effects, especially drug-induced psychosis even at low doses. Dopamine agonists also cause excessive daytime sleepiness and swelling of the legs. Other PD medications such as amantadine, COMT inhibitors, MAO inhibitors and anticholinergics, likewise, can induce psychosis and exacerbate cognitive impairment and should be avoided. Furthermore, the cognitive impairment in LBD is a contraindication to deep brain stimulation, even when the Parkinson signs and symptoms suggest that the patient is a good candidate.

Behavioral Changes

The overarching goal of managing psychotic and behavioral disturbances in LBD is to improve outcome without compromising safety of the patient and others. If hallucinations (usually visual) are not frightening to the patient, even if they are considered bothersome by the family, treatment with a drug may not be needed, especially if the patient understands that the hallucinations are not real. On the other hand, delusions (a false belief held with strong conviction despite evidence to the contrary), are often socially disruptive and in most cases should be treated, most productively by a mental health professional.

The first line intervention should be non-pharmacologic measures including evaluation for acute physical ailments that may be provoking behavioral disturbances (e.g., fecal impaction, pain, decubitus ulcers, urinary tract infection and other febrile illnesses). Medications that can potentially cause agitation, especially those with anticholinergic properties, including amantadine and certain antidepressants, should be reviewed for need and stopped if possible.

Although little evidence exists to guide specific pharmacotherapy for hallucinations and behavioral symptoms in LBD, the following background literature review should be helpful.

AChEI for behavioral symptoms

Deficits in the brain's supply of the neurotransmitter acetylcholine probably contribute to cognitive impairment and psychosis in LBD. Visual hallucinations may predict a favorable response to treatment with an AChEI. By comparison, a meta-analysis of 6 large trials in AD, which also causes depletion of acetylcholine in the brain, showed a small but significant benefit of AChEI treatment in decreasing neuropsychiatric symptoms. Moreover, AChEI may selectively ameliorate psychosis and anxiety compared with other psychiatric symptoms. .

A few published reports have shown behavioral improvement in patients with LBD treated with the AChEI rivastigmine. In a large multicenter trial, rivastigmine resulted in improvement by 30% from baseline in psychiatric symptoms. In a recent case-control study of rivastigmine in patients with a clinical diagnosis of AD, treatment was associated with improvement in total behavioral scores, hallucinations and sleep disturbance compared to controls. There were lower rates of apathy, anxiety, delusions and hallucinations in the treatment group compared to controls.

Behavioral Medications to AVOID

- **Typical antipsychotics** (neuroleptics) should always be avoided in the management of patients with LBD, especially DLB, who risk severe worsening of all symptoms, and, as mentioned above, may develop potentially fatal NMS
- **Atypical antipsychotics, especially those with high D2 receptor antagonism** (such as olanzapine and risperidone), should also be avoided due to the risk of severe neuroleptic sensitivity reactions, neuroleptic malignant syndrome, worsening parkinsonism, somnolence and orthostatic hypotension. Quetiapine and clozapine are two from this class of drugs that have been shown to be well tolerated in low doses for treatment of psychosis (see below).
- **Benzodiazepines** should not be first-line agents given their risk of sedation and paradoxical agitation.

Atypical Antipsychotics

If long term treatment with AChEIs is ineffective, or more acute symptom control of behavior is required, it may be difficult to avoid a cautious trial of an atypical antipsychotic. When medications are needed to modify behaviors, they should be used for the shortest duration possible.

Quetiapine and clozapine are preferred when psychosis warrants drug treatment. Clozapine has been demonstrated to be effective for PD psychosis in several randomized clinical trials. However, due to the small but serious risk of the potentially fatal adverse effect of agranulocytosis (severe depression of white blood cells) and the corresponding need for weekly blood monitoring to prevent such a reaction, clozapine is not the drug of first choice. Quetiapine is a safe alternative atypical antipsychotic in PDD and DLB, typically in the dose range of 6.25 mg to 50 mg a day, although higher doses may be used if tolerated and necessary. As with any drug in this setting the low slow approach is required.

Black box warning: The FDA's 'black box warning' indicates both typical and atypical antipsychotics are associated with an increased risk of mortality and morbidity in elderly patients with dementia. However, if used carefully according to the guidelines mentioned above, the risk of mortality is extremely low. Physicians should discuss the risks and benefits of these types of medications, so that patients with LBD and caregivers can weigh the impact of the symptoms against the potential risks associated with these medications.

Non-pharmacological Methods to Managing Behavioral Changes

Refer to LBDA's publication *Understanding Behavioral Changes in Dementia*, which can be downloaded at <http://www.lbda.org/content/understanding-behavioral-changes-dementia>.

Emergency Room Treatment of Psychosis

Refer to LBDA's publication, *Emergency Room Treatment of Psychosis*, which can be downloaded at www.lbda.org/go/er.

REM Sleep Behavior Disorder and Insomnia

Clonazepam has been the mainstay of medical therapy for REM sleep behavior disorder (RBD). Melatonin is a safe, over-the-counter natural substance that may also offer benefit either as monotherapy without risk or in conjunction with clonazepam.

For insomnia, treatment can be attempted with low doses of benzodiazepines (such as clonazepam), specific sedative-hypnotic agents (such as zolpidem), or antidepressants (such as trazodone or mirtazapine). These medications have not been extensively studied in LBD, and worsening confusion and daytime sedation is a potential side effect of sedative-hypnotics, such as zolpidem.

Autonomic Dysfunction

Orthostatic hypotension (drop in blood pressure) is a common manifestation of LBD, often presenting as lightheadedness or fainting, mainly when standing. Initial management consists of simple measures such as arising slowly from a reclining or seated position, leg elevation when sitting, elastic stockings, increasing salt and fluid intake, and if possible avoiding medications that are known to exacerbate orthostasis. If simple measures fail, medications such as midodrine, fludrocortisone or the newly-approved droxidopa can be used.

Medications with anticholinergic activity, such as oxybutynin, tolterodine tartrate, bethanechol chloride, and propantheline, can be used to treat urinary urgency, frequency and urge incontinence. They should be used cautiously however, given their risk of exacerbating cognitive problems because of their anticholinergic properties.

Constipation can usually be treated by exercise and modifications of the daily diet to include foods with high fiber content (fruits and vegetables) and bran cereal. Laxatives, stool softeners and mechanical disimpaction may be needed.

Erectile dysfunction (ED), loss of libido and impotence in LBD is likely multifactorial. While autonomic dysfunction is a possible cause, other factors often contribute, such as depression, poor bed mobility, pain and co-morbid illnesses. Treatment can be complex, requiring a urologic and/or psychiatric consultation. Medications for ED include three inhibitors of phosphodiesterase-5 (sildenafil [Viagra], tadalafil [Cialis], and vardenafil [Levitra]), the natural substance yohimbine, or the intracavernosal injectables phentolamine and prostaglandin E. If immobility in bed is a major problem, a bedtime dose of levodopa is worth a try. If mood disturbances are associated with sexual dysfunction, psychotherapy or a trial of an antidepressant can be considered, although antidepressants often cause ED.

Other Drugs to Avoid

- Anticholinergics, as already mentioned several times above, may worsen cognitive impairment, confusion, and hallucinations.
- Benzodiazepines are best avoided unless specifically indicated (e.g. clonazepam for RBD), given their risk of sedation, increasing risk of falls, worsening cognition, and potentially paradoxical agitation.
- Inhaled anesthetics should be avoided when possible to minimize delirium and a decrease in functional ability.
- OTC sleep agents such as Tylenol or Advil PM and bladder-control medications may cause agitation. Many of these drugs contain diphenhydramine (Benadryl), an antihistamine with anticholinergic effects.

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