

Dementia, bizarre creatures, and a white knight to the rescue

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Ms. L, age 78, experiences visual and tactile hallucinations of bizarre creatures in her home that are related to dementia with Lewy bodies. How would you treat her?

CASE Strange creatures

Ms. L, age 78, is admitted to the inpatient unit for treatment of psychosis and behavioral changes. In the months before this admission, she had visited the emergency room several times for recurrent falls. CT scans of the head show no acute changes; brain and spinal MRI reveal evidence of chronic white matter disease and degenerative changes of the spine. Medical workup is unremarkable and includes evaluation for syncope and ambulation impairments related to degenerative disease of the hip joints.

Ms. L and her family are instructed to follow-up with her primary care physician and a neurologist for neuromuscular workup.

She next presents to her primary care physician, describing hallucinations of strangers walking around her house. Over a few weeks, hallucinations expand to include a fixed hallucination of creatures that she describes as having qualities of insects and plants, “piling up” around her. She describes tactile hallucinations of these creatures crawling on her skin, and she tracks their movements around her. She complains of vivid visual hallucinations of these creatures spinning webs across the room and she says she keeps the lights on at night. Ms. L becomes anxious and depressed, and her insomnia becomes worse.

She is referred for outpatient psychiatric evaluation and treatment.

Ms. L’s family notes lapses of short-term memory, disorganization, and difficulty with tasks such as cooking because she has trouble following steps. These deficits come and go, with periods when she is functional and others during which she experiences considerable confusion. The family is uncertain when these signs and symptoms first appeared, but are clear that these deficits are having an impact on her day-to-day life. She can conduct activities of daily living, but with increasing difficulty—and only with help from her husband for tasks that require complex order and movement.

Over several months, Ms. L’s gait stability decreases and she begins to rely on a walker to keep from falling. On the Montreal Cognitive Assessment screening for cognitive dysfunction, she scores 19 out of 30 (normal range >25). This suggests cognitive impairment greater than expected for her age, compared with normal controls, and, when coupled with her functional impairment, raises the possibility of a diagnosis of dementia with Lewy bodies (DLB).

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Disclosures

The authors report no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.

Which would you prescribe first to address**Ms. L's hallucinations?**

- a) donepezil
- b) memantine
- c) quetiapine
- d) low-dose clozapine

The authors' observations

Limited literature exists of placebo-controlled, large-scale studies on DLB treatment. Cholinesterase inhibitors have shown some symptomatic benefit, including for hallucinations.¹⁻³ Memantine, an *N*-methyl-D-aspartate receptor blocker, shows mixed results.⁴ Many studies explore the use of neuroleptics for treating hallucinations in psychosis in Parkinson's disease and Parkinson's disease dementia (PDD) but, in DLB, the literature primarily consists of case reports.² Much of DLB treatment is inferred and intermixed with studies on PDD.^{5,6}

Low-dose clozapine has become a standard treatment for psychosis in Parkinson's disease based on the findings of several trials.⁶ Despite its side-effect profile, clozapine has been shown to ameliorate hallucinations in PDD without exacerbating parkinsonian symptoms,^{7,8} and is the only medication with proven efficacy in PDD.² The French Clozapine Parkinson Study Group demonstrated relief of psychotic symptoms of Parkinson's disease with clozapine, 6.25 mg/d.⁹ The Clozapine Study Group found complete resolution of hallucinations in some patients within 1 day of initiating clozapine. Among patients in this study who did not see immediate benefit, most showed significant improvement of psychotic symptoms in 1 or 2 weeks.¹⁰

TREATMENT Few options

Ms. L's psychiatrist and primary care physician start her on a series of medications. Donepezil is initiated for suspected dementia. We begin a trial of quetiapine to address the hallucinations, but the drug makes her movement symptoms

worse. Risperidone also is tried but, again, the drugs make movement symptoms, particularly gait instability, tremor, and rigidity worse without alleviating the hallucinations. Neuroleptics seem to exacerbate confusion. Because of worsening depressive symptoms and our concern over possible pseudodementia, we try several selective serotonin reuptake inhibitors (SSRIs) and mirtazapine. Antidepressants have little effect on her depressive symptoms and do not improve hallucinations or insomnia.

Ms. L's signs and symptoms become worse over the next few months, with more severe hallucinations, agitation, insomnia, and gait instability. Her agitation over the hallucinations increases and she begins pouring bleach around herself in bed and spraying her house with toxic bug spray. Ms. L's family brings her to the hospital after they observe her scratching the hallucinatory creatures off of her skin with a razor blade and trying to pry them out of her mouth with a piece of metal.

In the hospital, medical and neurologic workups rule out organic causes for her symptoms and signs. MRI is consistent with imaging from 6 months earlier. Focal neurologic signs are absent. Blood work is within normal limits, failing to reveal any pathology that would suggest a cause for her symptoms and signs, such as syphilis, vitamin deficiency, and Lyme disease.

Ms. L's symptoms were consistent with consensus guideline criteria for a clinical diagnosis of DLB (**Table 1, page 40**).¹¹⁻¹⁸

She is started on low-dose quetiapine, which she tolerates poorly with worsening confusion, rigidity, tremor, and gait instability. Because other agents failed, Ms. L's providers and family decide on a trial of clozapine.

Within 24 hours after the first dose of clozapine, 25 mg, sleep improves, the tactile component of hallucinations diminish, and she begins to spend increasing periods of time "observing the creatures" rather than fighting with them.

Over the next few days, Ms. L's attitude towards the creatures changes. Now, as she sits observing them intently, the hallucinations evolve: rather than tormenting her and causing distress, the plant-creatures burst apart and a miniature

Clinical Point

Cholinesterase inhibitors have shown some symptomatic benefit for dementia with Lewy bodies, including for hallucinations



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Clinical Point

In DLB, the aim is to alleviate the agitation and suffering from the psychotic symptoms without exacerbating other motor and cognitive symptoms

Table 1

Diagnostic criteria for dementia with Lewy bodies

Central feature: <ul style="list-style-type: none"> • Progressive cognitive, executive, and attentional decline that impact normal functioning • Memory impairment is evident as disease progresses but may not be present early in diagnosis
Core features: <ul style="list-style-type: none"> • Cognitive and attentional fluctuation • Visual hallucinations of a complex and recurrent nature • Parkinsonian features (present in the absence of other known etiology of parkinsonism)
Supportive features: <ul style="list-style-type: none"> • Neuroleptic sensitivity • Rapid eye movement behavior disorder • Gait instability, recurrent falls, syncopal episodes • Other psychiatric symptoms such as delusions, depression, agitation, aggression, auditory/tactile/olfactory hallucinations
Features that make diagnosis less likely: <ul style="list-style-type: none"> • History (or diagnosis during workup) of other neurologic or medical conditions known to effect cognition that could offer alternative explanation of symptoms
A probable clinical diagnosis (sensitivity: >80%, specificity 50%) is made with: <ul style="list-style-type: none"> • Dementia with 2+ core features; Dementia with 1 core feature and 1+ suggestive features
A possible clinical diagnosis can be made with: <ul style="list-style-type: none"> • Dementia with 1+ core feature; Dementia with 1+ suggestive features
Source: References 11-18

knight on horseback charges out. The rest of the creatures then gather into a rank and file and the knight leads them to the nearest exit.

Clozapine is titrated to 50 mg/d, which she tolerates well without exacerbation of cognitive symptoms or movement disorder. The only notable adverse effect at the time of her discharge is sialorrhea.

What precautions would you take when treating Ms. L with an antipsychotic?

- start low and go slow
- monitor her heart rate and blood pressure
- readminister the Montreal Cognitive Assessment
- all of the above

The authors' observations

Ideally, in psychosis, antipsychotics eliminate positive symptoms such as hallucinations and delusions. In DLB, the aim is to alleviate the agitation and suffering brought on by the psychotic symptoms without ex-

acerbating other motor and cognitive symptoms. The hallucinations are obstinate, and it is a well-known quality of this disorder that patients are exceptionally susceptible to a range of antipsychotic side effects including cognitive impairment, fatigue, neuroleptic malignant syndrome, and parkinsonism.¹⁹

Treatment in DLB requires trial and error, and medications with fewer associated risks should be administered first. Patients with DLB treated with neuroleptics have an increased risk of death compared with those who are not treated.¹⁹ Moreover, prescribing information for clozapine includes a black-box warning that the drug:

- is not approved for dementia-related psychosis and
- is associated with an increased risk of death in elderly patients with these conditions, similar to what is seen with other neuroleptics.²⁰

Despite these well-known concerns, it remains difficult for clinicians *not* to try to treat the distress caused by these symptoms.

We chose clozapine for Ms. L because:

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Table 2

Recommendations for treating patients with dementia with Lewy bodies

Diagnostic accuracy is important, when possible

- DLB patients respond very different to standard medications than patients with diseases that share many of the same characteristics
- If not suspected, by the time medication is given you may find out quickly (and dangerously) that the patient, in fact, has DLB

Approach pharmacological treatment with exquisite care

- Medication sensitivity is common and the side effect burdens are high

Family and patient concerns are paramount and should guide treatment

- The family and patient must be part of the discussion to determine the symptoms that are most life-affecting
- Autonomic instability, motor symptoms, REM sleep disorder, cognitive effects, behavioral symptoms and non-cognitive neuropsychiatric effects can all be part of this illness to a widely varying degree from one patient to another
- Medications and non-pharmacological management must be tailored to the patient and his or her needs

Avoid first-generation, strongly D2-specific neuroleptics (eg, haloperidol)

- They increase risk of death markedly and cause substantial extrapyramidal, anticholinergic and other side effects

Start low, go slow

- This is the case with all medical management in this condition, however it is especially essential in the use of neuroleptics
- Work closely with patient and family to understand the side effects that they may be having so that medication effects and underlying symptoms can be monitored

- other neuroleptics failed
- acetylcholinesterase inhibitors did not alleviate Ms. L's psychosis and associated behavioral disturbance
- there is substantial evidence that the drug can be effective in Parkinson's disease with psychosis.

There is controversy regarding use of clozapine in DLB. In one case series, clozapine trigger extreme neuroleptic reactions in some patients, similar to what occurs with other second-generation antipsychotics.²¹ Another case series provides examples of the drug's efficacy in treating hallucinations and delusions with minimal adverse effects.²²

It is important to emphasize that Ms. L's hallucinations did not go away; rather, they changed to a more benign presentation that she could manage and, occasionally, found pleasant. Ultimately, her agitation—the primary target of treatment—improved markedly with the arrival of the knight in shining armor.

Treatment recommendations

If neuropsychiatric symptoms in DLB are the primary concern of the patient and family, we recommend the following:

- Begin treatment with a cholinesterase inhibitor. The best evidence exists for rivastigmine and donepezil. These drugs have a low risk of side effects, which are primarily gastrointestinal effects with some reports of worsening extrapyramidal symptoms.²³⁻²⁵
 - If the patient obtains minimal benefit or develops a significant adverse effect from cholinesterase inhibitors, consider memantine. Its efficacy is under examination and results are mixed; it can be used in combination with cholinesterase inhibitors.²⁶⁻²⁸
 - If psychotic symptoms are upsetting and refractory to other therapies, consider antipsychotics. Avoid first-generation antipsychotics. The American Psychiatric Association recommends aripiprazole or quetiapine initially, although there is little evidence comparing neuroleptics in DLB.²⁹

Clinical Point

If neuropsychiatric symptoms are a primary concern, start with a cholinesterase inhibitor; rivastigmine and donepezil have the best evidence

continued

Clinical Point

SSRIs and other antidepressants have not been shown to improve neuropsychiatric symptoms, and often are poorly tolerated

See this article at

CurrentPsychiatry.com

for an algorithm for treating dementia with Lewy bodies

Related Resources

- Bishnoi RJ, Grossberg GT, Manepalli J. Differentiating Alzheimer's disease from dementia with Lewy bodies. *Current Psychiatry*. 2012;11(11):22-27.
- McKeith I, Emre M. Management of Parkinson's disease dementia and dementia with Lewy bodies. In: Emre M, ed. *Cognitive impairment and dementia in Parkinson's disease*. Oxford, United Kingdom: Oxford University Press; 2010:245-256.

Drug Brand Names

Aripiprazole • Abilify	Mirtazapine • Remeron
Clozapine • Clozaril	Olanzapine • Zyprexa
Donepezil • Aricept	Quetiapine • Seroquel
Haloperidol • Haldol	Risperidone • Risperdal
Memantine • Namenda	Rivastigmine • Exelon

Because of its risks, reserve clozapine for refractory cases. An exception might be made for patients sensitive to extrapyramidal effects, in whom clozapine could be considered earlier.

There are no formal neuroleptic dosing guidelines beyond a general urging towards minimalism. Mosimann and McKeith³⁰ recommend clozapine, 12.5 mg/d; olanzapine, 2.5 mg/d; risperidone, 0.25 mg/d; or quetiapine, 12.5 mg/d. Such dosages might be effective while producing only minimal side effects.^{9,31}

SSRIs and other antidepressants have not been shown to improve neuropsychiatric symptoms, and often are poorly tolerated.³²

One study found efficacy with electroconvulsive therapy and transcranial magnetic stimulation in treatment-resistant patients.³³

In addition to these treatments, nonpharmaceutical interventions should be employed from the earliest stages of diagnosis and treatment (*Table 2, page 45*). See this article at CurrentPsychiatry.com for an algo-

rithm for treating DLB. These include educational and behavioral interventions, social support, psychological interventions, and environmental therapies and modifications.

OUTCOME New friends

The creatures return from time to time, Ms. L reports, but are no longer upsetting because the white knight (a sort of mental *deus ex machina*) leads the once-terrifying things away. She describes the hallucination as a kind of zoological observation, refers to the creatures that once horrified her as “her friends,” and chuckles as she observes their natural history. This new, far more benign hallucination becomes a mainstay of her symptoms, and she is discharged to the care of her husband and family.

Soon after her discharge, her hallucinations resolved completely, but returned briefly when Ms. L resumed smoking cigarettes because smoking is known to lower clozapine serum levels.³⁴

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Bottom Line

Consider a low dosage of a neuroleptic when a patient suffers significant distress and behavioral disturbance related to psychotic symptoms in dementia with Lewy bodies and those problems are not relieved by other agents. Low-dose clozapine is an option for refractory psychotic symptoms or in patients with severe extrapyramidal sensitivity. Start low, and go slow.

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Clinical Point

Employ educational and behavioral interventions, social support, and environmental therapies for patients with DLB

Figure

Decision tree for treating dementia with Lewy bodies

