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Treatment of Dementia with Lewy Bodies

Brendon P. Boot, MBBS, **Eric M. McDade, DO**, **Scott M. McGinnis, MD**, and **Bradley F. Boeve, MD**
Department of Neurology, Brigham and Women's Hospital (Boot, McGinnis), Boston, MA, University of Pittsburgh Medical Center (McDade), Pittsburgh, PA and Mayo Clinic (Boeve), Rochester, MN.

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INTRODUCTION

Patients with DLB have cytoplasmic neuronal accumulation of alpha-synuclein, a feature that it shares with other synucleinopathies such as Parkinson's disease (PD). PD dementia (PDD) is primarily distinguished from DLB by the presence of motor symptoms for more than a year prior to cognitive decline [1]. DLB accounts for 5–25 % of dementia [2-6]. A meta-analysis of epidemiological studies suggests a lower prevalence (3.8–4.5 % of diagnoses), and an incidence of 0.57–1.4 cases / 1000 person-years [7]. These are underestimates: the diagnostic criteria have low sensitivity (12–32 %) but high specificity (>95 %)[8], suggesting that many DLB diagnoses are “missed”[9].

Establish the diagnosis

The diagnostic symptoms and signs for DLB (Table 1)[1] are of value only when present early in the disease. This is because the same features arise late in other dementia syndromes [8]. Despite the poor sensitivity in multi-center data [8], diagnostic accuracy can be achieved. When visual hallucinations, parkinsonism, and REM sleep behavior disorder (RBD) are used to define disease, sensitivity is 83 %, and specificity 85 % for autopsy confirmed cases [10]. The sleep disorder indicates synucleinopathy in 94 % of autopsies

Correspondence: Dr. Brendon Boot Dept. Neurology Brigham and Women's Hospital 221 Longwood Ave Boston, MA 02115 Phone: (617) 732-8060 Fax: (617) 738-9122 bboot@partners.org.

Conflict of Interest

Brendon P. Boot has served as an investigator for clinical trials sponsored by Pfizer, Janssen Pharmaceutica, and Bristol-Myers Squibb.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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[11]. Fluctuations in cognition are also a diagnostic feature, but they are defined loosely in routine clinical practice and easily over-diagnosed, as most patients respond in the affirmative to a question about variation in cognitive function. The Mayo Fluctuations Scale codifies the salient elements: significant daytime drowsiness and lethargy, daytime sleep >2 hours, staring into space for long periods, and episodes of disorganized or tangential speech [12].

Parieto-occipital cerebral hypometabolism, preserved posterior cingulate metabolism, and the absence of medial-temporal and parietal atrophy all help to establish the diagnosis [1, 13]. Ioflupane (123I, also known as FP-CIT) single-photon emission computed tomography (SPECT), fluorodopa positron emission tomography (PET) and [11C]dihydrotetrabenazine (DTBZ) positron emission tomography accurately identify the nigral degeneration seen in the synucleinopathies. It is particularly helpful in differentiating the synucleinopathies from other degenerative diseases (and especially Alzheimer's disease) [1, 14, 15]. MIBG cardiac scintigraphy has the same role [16, 17]. Given the frequency of DLB and Alzheimer's disease co-pathology [18–21], amyloid positron emission tomography is not useful in differential diagnosis. The same issue complicates spinal fluid amyloid-beta and tau analysis [18–21].

Multifaceted treatment is needed in this complex disease

DLB is a complex disease with a wide variety of sequelae that each need consideration for treatment [22, 23]. Many symptoms go unreported because they are non-specific, and patients incorrectly assume that “physical” and “psychological” symptoms are unrelated to DLB. Treating symptoms with the assumption that they are caused by synucleinopathy is often effective and efficient. For example, a trial of levodopa at bedtime may resolve nocturnal cramps without the discomfort and expense of spinal MRI and electromyography. Given the limitations of current practice models, it is helpful to schedule frequent follow-up visits in the first 3-6 months, with each visit addressing a specific component of the multisystem involvement.

Cease and avoid treatments likely to exacerbate symptoms

Many commonly used medications can produce severe side effects in patients with DLB, notably medications with anticholinergic or antidopaminergic actions. Substantial improvement in quality of life can be achieved by ceasing these treatments.

There are no studies to guide decisions to withdraw therapy in end-stage DLB, and very few treatment trials are specific to DLB, therefore the following draws heavily from the non-DLB evidence base.

TREATMENT

Treatment of Cognitive Features

Memory and Attention

Cholinesterase Inhibitors

- The cholinesterase inhibiters (ChEi) rivastigmine and donepezil have class I evidence for efficacy in DLB [24–28]. Patients with DLB often have a greater treatment response to these medications compared to Alzheimer's disease patients [26, 29], reflecting the profound reduction in cholinergic function with relative neuronal preservation seen in DLB [30].
- A Cochrane review [28] of DLB trials concluded that significant improvements in delusions, hallucinations, apathy and anxiety occur with ChEi treatment.

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- A recent Cochrane review [31] of DLB [24], PDD and PD Mild Cognitive Impairment studies [32–34] (total N=1236) concluded that ChEi's improved:
    - **a.** Cognition [standardized mean difference (SMD) −0.34, p< 0.00001].
    - **b.** Mini-Mental State Examination in PDD (Weighted Mean Difference 1.09, p=0.0008) but not DLB.
    - **c.** Behavior: (SMD -0.20, p=0.01).
    - **d.** Activities of daily living (SMD -0.20, p=0.03), and
    - **e.** Mortality [odds ratio (OR) 0.28, p=0.03], despite an increase in adverse events (OR 1.64, p=0.0003) and dropouts (OR 1.94, p=0.0006).
- Theoretically, ChEi's can exacerbate parkinsonism, however this is rare in practice. They do increase tremor (OR 2.71, p=0.002) [24], but this is rarely bothersome enough to warrant discontinuation, and global PD severity scores are unaffected (p=0.71) [24].
- Nausea and vomiting are common side effects during initiation of ChEi treatment; they frequently abate with time. The 5HT-3 receptor antagonists (e.g., ondansetron, granisetron) are appropriate short-term remedies, but antiemetics that block dopamine (e.g., prochlorperazine and metaclopramide), and anticholinergic and antihistamine nausea treatments are best avoided in DLB.
- Forewarn patients that ChEi treatment may induce vivid dreaming. This can be minimized by avoiding nocte dosing; for the twice daily preparations, morning and early afternoon doses are preferable.
- Fluctuations are difficult to manage because they have multiple contributing causes [12].

Class Effects

Contraindications: none. Use with caution in patients with cardiac conduction disorders, severe asthma or obstructive pulmonary disease, peptic ulcer disease, or bladder outflow obstruction.

Main drug interactions: antipsychotics, increased extrapyramidal side effects; beta-blockers, increased bradycardia

Main side effects: gastrointestinal (GI) distress (10 % of patients: nausea, vomiting, anorexia, weight loss, diarrhea), dizziness, insomnia, vivid dreams, muscle cramps, tremor, weakness, diaphoresis, bradycardia, syncope, falls.

- Side effects frequently abate after several weeks.

Rivastigmine

Standard dosage: oral 1.5 mg twice daily to 6 mg twice daily, transdermal 4.6–13.5 mg / 24 h.

Contraindications: see class effects.

Main side effects: tolerated by 75 % of DLB subjects; see class effects.

Special points: Start at 1.5 mg twice daily, increase by 1.5 mg for both doses every 2 to 4 weeks; maximum dose 6 mg twice daily.

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- Best taken with food.

- Transdermal: 4.6 mg/24 h patch, increase to 9.5 mg/24h after 1 month; maximum 13.5 mg/24 h.

Cost (median adjusted wholesale price; U.S. retail markup is typically 20–50 % above wholesale): 1.5 mg, 3 mg, 4.5 mg, 6 mg (60 capsules): $255; 4.6 mg transdermal, 9.5 mg transdermal (30 patches): $356

Donepezil

Standard dosage: oral 10 mg once daily

Contraindications: see class effects

Main side effects: see class effects

Special points: Start at 5 mg daily, increase to 10 mg daily at 4 weeks; may increase further in increments of 5 mg.

- Some patients may respond to higher doses given in twice daily dosing (10 mg in AM and 5 mg in PM). We use multiples of the generic tablets, rather than the expensive 23 mg tablets, although insurers will often refuse to cover more than 10 mg daily dosing.

- Patients with vivid dreams may benefit from AM dosing, whereas patients with GI sensitivity may benefit from PM dosing.

Cost: 5 mg, 10 mg (30 tablets): $260

Galantamine

Standard dosage: oral 4 mg twice daily to 12 mg twice daily; extended-release 8 mg daily to 24 mg daily

Contraindications: see class effects

Main drug interactions: see class effects

Main side effects: see class effects

Special points: Start at 4 mg twice daily, increase in 4 mg increments for both doses over 2 to 4 weeks; maximum dose 12 mg twice daily or 24 mg daily for extended-release formulation.

Cost: immediate-release 4 mg, 8 mg, 12 mg (60 tablets): $191; extended-release 8 mg, 16 mg, 24 mg (30 capsules): $191.

N-methyl-D-aspartic acid receptor antagonists

- Memantine produced small and significant improvements in global clinical impression scores in DLB / PDD cohorts [35, 36]. However, these findings were not consistent over the duration of the study in one trial [35], and sub-group analysis of the other suggested that the overall results were due to improvements in the PDD patients only [36].

Memantine

Standard dosage: oral 5 mg daily to 10 mg twice daily; extended-release 7 mg daily to 28 mg daily

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Contraindications: none. Use with caution in patients with severe hepatic impairment or renal impairment.

Main drug interactions: Memantine may increase serum concentrations of buproprion and trihexyphenidyl. Trimethoprim and memantine mutually increase serum drug levels, possibly increasing risk of confusion and myoclonus due to the latter. Sodium bicarbonate and carbonic anhydrase inhibitors decrease the excretion of memantine.

Main side effects: GI side effects (constipation, nausea, vomiting), dizziness, confusion, headache, hallucinations, aggression, pain, hypertension, and heart failure.

Special points: Start at 5 mg daily, increase in 5 mg increments after one or more weeks to 10 mg twice daily.

- May decrease seizure threshold

Cost: 5 mg, 10 mg (60 tablets): $319; extended-release 7 mg, 14 mg, 21 mg, 28 mg (30 capsules): $303

Treatment of Neuropsychiatric Features

- These features are often difficult to diagnose and treat: advanced dementia limits a patient's ability to describe neuropsychiatric symptoms [37], and widespread neuronal loss means that there are few targets for drug action.
- Treat infections, electrolyte disturbances, other medical conditions and social stressors, all of which are triggers for neuropsychiatric symptoms.
- Impulse dyscontrol and abnormal repetitive behaviors related to levodopa or dopamine agonist treatment may respond to amantadine [class II][38].

Anxiety and Depression

- Prodromal anxiety (27 % of cases) and depression (59 %) often predate DLB by many years [39]. Patients may find solace in the knowledge that their long fight with anxiety or depression has a pathological basis.
- There are no studies of antidepressants in DLB. Those in Alzheimer's disease show variable results [40]. Citalopram and mirtazapine were ineffective in a large, recent Alzheimer's disease trial [41].
- Studies in PD have not yielded sufficient evidence on which to base treatment recommendations [42–44]. Tricyclic antidepressants (TCAs) have the most consistent evidence for efficacy [44], but their anticholinergic properties exacerbate cognitive dysfunction, orthostatic hypotension, and constipation [45] in DLB patients—many of whom have significant cholinergic dysfunction [30]. Results in randomized controlled trials, open-label studies and case series, albeit mixed, suggest potentially favorable results with SSRIs or SNRIs [class III–IV] [44, 46]. Motor function should be monitored closely with these therapies [44, 46].
- There is insufficient evidence to determine whether monoamine oxidase inhibitors (an MAOi) slow the symptomatic progression of DLB; concomitant use with selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) increases the risk of serotonin syndrome, a potentially life-threatening condition.

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- Patients with treatment-refractory depression may benefit from transcranial magnetic stimulation or electroconvulsive therapy [47, 48], although the latter can cause confusion and exacerbate dyskinesia [48].

Antidepressant medications: SSRIs, SNRIs, bupropion: Selected SSRIs, SNRIs and bupropion are prescribed frequently for depression and/or anxiety in DLB. General principles of starting at a low dose, increasing the dose gradually, and monitoring closely for side effects should be followed.

Class effects: SSRIs

Contraindications: concomitant use with an MAOi, pimozide

Main drug interactions: drugs metabolized by various pathways of the hepatic cytochrome p450 system (CYP), especially CYP1A2, 2C19, 2D6, and 3A4 (includes some anticonvulsants, antipsychotics, benzodiazepines, stimulants, opioids, proton pump inhibitors, anti-arrhythmics, antibiotics, antifungals, antiretrovirals, numerous other medications); other serotonergic drugs (includes triptans, SNRIs, TCAs, trazodone, cyclobenzaprine, tramadol), nonsteroidal anti-inflammatory drugs, antiplatelet agents, anticoagulants, QTc interval-prolonging drugs, an MAOi

Main side effects: GI side effects (nausea, diarrhea), sleep side effects (somnolence or insomnia), dry mouth, increased sweating, dizziness, fatigue, headache, sexual dysfunction, tremor, apathy, QTc prolongation, SIADH

Special points:

- Allow 3–8 weeks for symptomatic improvement.

- Use the lowest effective dose.

- Do not discontinue suddenly.

Sertraline

Standard dosage: oral 25–200 mg daily

Contraindications: see class effects

Main drug interactions: see class effects; primarily metabolized by CYP2B6, less so by 2C19, 3A4, 2D6; inhibitor of CYP2D6, 3A4

Main side effects: see class effects

Special points: Start at 12.5 mg or 25 mg daily; may increase in increments of 12.5 mg or 25 mg over intervals of at least one week; maximum dose 200 mg daily.

- Has weak dopamine reuptake inhibition and sigma receptor actions, in addition to serotonin reuptake inhibition

Cost: 25 mg, 50 mg, 100 mg (30 tablets): $85

Citalopram

Standard dosage: oral 10–40 mg daily

Contraindications: see class effects

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Main drug interactions: see class effects; primarily metabolized by CYP2C19, 2D6 and 3A4

Main side effects: see class effects

Special points: Start at 10 or 20 mg daily; may increase in increments of 10 or 20 mg over intervals of at least one week; maximum dose 40 mg daily.

- Relatively selective for serotonin reuptake inhibition

Cost: 10 mg, 20 mg, 40 mg (100 tablets): $255

Escitalopram

Standard dosage: oral 5 mg daily to 20 mg daily

Contraindications: see class effects

Main drug interactions: see class effects; primarily metabolized by CYP2C19 and 3A4

Main side effects: see class effects

Special points: Start at 5 or 10 mg daily; may increase in increments of 5 or 10 mg over intervals of at least one week; maximum dose 20 mg daily.

- Relatively selective for serotonin reuptake inhibition

- Fewer drug interactions than other SSRIs

Cost: 5 mg, 10 mg, 20 mg (100 tablets): $450

Venlafaxine (SNRI)

Standard dosage: oral 37.5–225 mg/day in two to three divided doses or with single extended-release preparation

Contraindications: concomitant use with an MAOi

Main drug interactions: CYP2D6 or 3A4 inhibitors; other serotonergic drugs (see SSRI class effects above), an MAOi

Main side effects: GI side effects (anorexia, nausea, constipation), sleep side effects (somnolence, insomnia, RBD), dry mouth, increased sweating, dizziness, fatigue, headache, nervousness

Special points: Start at 37.5 or 75 mg daily; may increase in increments of 37.5 mg over intervals of at least one week.

- See special points relevant to SSRI class effects above.

- Venlafaxine may provide slightly more activating properties, as well as improvement in executive cognitive problems compared to SSRIs.

- Venlafaxine can precipitate or aggravate REM sleep behavior disorder (RBD); therefore, avoid if dream enactment behavior is frequent and/or violent, and use with caution in all others.

Cost: 25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg (100 tablets): $194–232; extended-release 37.5 mg, 75 mg, 150 mg, 225 mg (30 tablets): $102–$239.

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Bupropion (dopamine-norepinephrine reuptake inhibitor)

Standard dosage: oral 100 mg daily to 450 mg daily in three to four divided doses (immediate-release), two divided doses (sustained-release), or single dose (extended-release)

Contraindications: concomitant use with an MAOi; seizure disorder

Main drug interactions: CYP2B6 inducers (some anticonvulsants, rifamycin antibiotics) or inhibitors, cyclosporine, MAOis

Main side effects: GI side effects (nausea), sleep side effects (insomnia), dry mouth, headache, anxiety, agitation, tremor, seizure

Special points: Start at 100 or 150 mg daily; may increase in increments of 50–150 mg; maximum daily dose 450 mg.

- See special points relevant to SSRI class effects above.

- Bupropion may provide slightly more activating properties, as well improvement in executive cognitive problems compared to SSRIs.

- When converting from one preparation to another, give the same daily dose if possible.

Cost: 75 mg (100 tablets): $79, 100 mg (100 tablets): $106; sustained-release 100 mg (60 tablets): $101, 200 mg (60 tablets): $226; extended-release 150 mg (30 tablets): $156, 300 mg (30 tablets): $143

Hallucinations and Delusions

- Sixty to seventy percent of patients experience hallucinations [22, 49]. They distinguish DLB from Alzheimer's only if present in the first years of illness [50]. They are often not bothersome to patients, who frequently retain insight into their non-veridicality, but patients and caregivers often argue over their veridicality if insight is lost. Education of caregivers in the use of distraction techniques to “change the subject” is anodyne in these situations.
- Regular vision correction and the use of bright lights in the evening and *no* lights at night may decrease their frequency.
- The first step in medication adjustment should be the stepwise, gradual reduction of medications that have the potential to exacerbate neuropsychiatric symptoms, in the following order: anticholinergic medications, amantadine, dopamine agonists, MAOis, COMT inhibitors, and levodopa/carbidopa. They should be decreased slowly to avoid the possibility of neuroleptic malignant syndrome [51].
- The second step is the introduction of or increase in ChEi therapy. This reduces hallucinations in >90 % of PDD patients [25].

Electing not to use neuroleptics is often the best course of action

- They rarely treat the hallucinations effectively [52–54].
- They increase risk of stroke, sudden cardiac death and overall mortality in dementia populations [55–57]. In a meta-analysis of 10–12 week trials (N=5110) of all-cause dementia, death occurred in 3.5 % of treated dementia subjects, and 2.3 % of controls, resulting in a number needed to harm of 100 (range 53–1000) and a number needed to treat of 4–12 [58]. Weighing against this, a recent observational study found that after controlling for important risk factors such as cardiovascular

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risk and severity of psychosis, antipsychotic use was not associated with premature death [59].

- The outcomes for antipsychotic treatment are sometimes worse in DLB: 30–50 % of patients experience sensitivity reactions, including increased parkinsonism and severe rigidity, dysautonomia, confusion and prolonged periods of decreased responsiveness [1, 60–62]. These may be fatal [60, 62], may occur after a single dose, and after most antipsychotics (e.g., olanzapine 58 %, clozapine 11 %, thioridazine 6 %) [60, 63, 64].
- Despite these concerns, antipsychotic medications are used more frequently in DLB than in Alzheimer's [65], presumably when quality of life is so severely affected that safety concerns are considered of less significance.

A programmed trial of cessation should accompany all prescriptions

- In a pivotal trial of demented patients already on neuroleptics, 3-year survival doubled in those randomized to cease treatment (59 % versus 30 %; hazard ratio 0.58, 95 % CI 0.35-0.95) [66].

Choice of Antipsychotic

- Limited data exist for DLB. Meta-analyses of all-cause dementia patients (N>5000) mostly aged in their 80s and in nursing facilities suggest that aripiprazole and risperidone are effective, olanzapine ineffective, and the evidence for quetiapine is mixed [53]. Differences in treatment versus placebo were only marginal in their clinical significance, but 25–30 % improvements were also seen in the placebo groups (hence the value of programmed treatment cessation).
- In treatment of PD- and PDD-associated psychosis, clozapine is effective, and olanzapine ineffective [44]. The evidence for quetiapine is again mixed, but most of the trials were underpowered [44]. In head-to-head trials, quetiapine and clozapine were equally effective [class I][51, 67].
- The difference in side effect profile between typical and atypical antipsychotics is less marked in the elderly [63].
- There are important caveats to consider when interpreting any clinical trial data involving medications for problematic neuropsychiatric features in dementia. In addition to the problems of underpowered trials and low doses used in some of the studies, one must recognize the reality of patients and particularly caregivers opting for participation in trials: these largely involve subjects who have relatively mild hallucinations, delusions, agitation, etc. In other words, many patients and caregivers facing significant challenges relating to hallucinations, delusions, agitation, etc., are not as likely to participate in trials involving a placebo arm, as they are seeking a medication—proven effective or not—to improve quality of life. Therefore, by default, the published data likely pertains more to those with milder neuropsychiatric morbidity, and may not be representative of the full (and more severe) spectrum of features associated with DLB.
- In DLB, avoid:
  - Typical antipsychotics (e.g., haloperidol)
  - Atypical antipsychotics with strong D2 receptor antagonism (e.g., olanzapine and risperidone) [68, 69]
  - Injectable antipsychotics

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- Despite the mixed evidence, the Lewy Body Dementia Association's Scientific Advisory Committee suggests using quetiapine [68–70] or clozapine (second-line) [71–75] when other treatments have failed and quality of life dictates the use of treatments with potential morbidity/mortality. In our experience, many patients eventually reach this juncture. Clozapine should be used only when ChEi and quetiapine have failed, because of the risk of agranulocytosis associated with its use.
- Due to the potential QTc interval prolongation associated with the atypical neuroleptics, many clinicians will perform an electrocardiogram at baseline to ensure QTc is normal, and periodically thereafter as the medication is adjusted to ensure that worrisome QTc prolongation does not occur. If it does occur, the dose is lowered until the QTc interval normalizes, or the medication is discontinued altogether.

Quetiapine

Standard dosage: 25–50 mg nocte

Contraindications: see above

Main drug interactions: CYP3A4 inducers (carbamazepine, phenytoin, rifampin, St. John's wort) require increased (up to 6-fold) doses of quetiapine. CYP3A4 inhibitors (ritonavir, indinavir, ketoconazole, itraconazole) require lower doses.

Main side effects: sedation, headache, confusion, agitation, hypotension, dizziness, fatigue, dry mouth, extrapyramidal symptoms, insomnia, tardive dyskinesia, restless legs syndrome, urinary retention, raised cholesterol/triglycerides/prolactin, weight gain, QTc prolongation

Special points: Start at 12.5 mg or 25 mg nocte; may increase in increments of 12.5–25 mg over intervals of at least 3 days; usual maximum 100 mg mane / 400 mg nocte; further increases are possible, but they should be done with caution.

- Sedative side effects may help to treat DLB-related sleep disorders, however they may also exacerbate daytime sleepiness.

- Quetiapine has the lowest risk of neuroleptic malignant syndrome; monitor if used with an SSRI or SNRI.

- Patients should obtain ophthalmological evaluations biannually, as quetiapine may cause cataracts.

Cost: 25 mg, 50 mg, 100 mg (30 tablets): $218

Clozapine

Standard dosage: 6.25–50 mg nocte

Contraindications: myeloproliferative disorders, uncontrolled epilepsy, paralytic ileus, agranulocytosis, granulocytopenia, use of medications known to induce myelosuppression (e.g., carbamazepine)

Main drug interactions: ChEIs increase extrapyramidal symptoms, carbamazepine increases agranulocytosis risk, CYP2D6 substrates (e.g., SSRI antidepressants) decrease clozapine metabolism

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Main side effects: agranulocytosis (1–2 %), eosinophilia, QTc prolongation, cardiomyopathy, myocarditis, hypotension, syncope, hepatotoxicity, agitation, headache, parkinsonism, confusion, akinesia, anorexia, diarrhea, urinary retention/incontinence

Special points: Start at 6.25 mg nocte, increase in increments of 6.25–12.5 mg over intervals of at least 3 days; maximum dose 50 mg three times daily.

- Potentially fatal agranulocytosis requires routine blood monitoring throughout treatment; use only when other treatments fail.

- Taper other antipsychotics prior to commencing.

Cost: 25 mg (100 tablets): $132; 50 mg (100 tablets): $165

Non-Pharmacologic Interventions

- Very few studies specifically deal with DLB; the following section relates to the available evidence in all-cause dementia.
- Having a reference folder for caregivers can be very helpful [55].

Agitation and Behavioral Disturbance

- Educate caregivers about the possibility of behavioral problems at the time of diagnosis. These problems frequently escalate if they remain untreated, so preventative treatment (such as environmental and behavioral modification techniques) and early recognition are essential.
- Identify and remove triggers for behaviors, e.g.: pain, fear, hallucinations, delusions or specific environmental triggers.
- Pain is a common trigger in patients who cannot communicate their needs, and many sources of pain have no signs. Empiric therapy with simple analgesia (e.g., acetaminophen) is often an effective first-line therapy [76].
- Non-pharmacological interventions that increase social interaction, remove triggers and offer comfort are effective [77–79]. For example, dementia patients in U.K. nursing facilities have less than two minutes of social interaction in a 6-hour period, and simple measures that increase this interaction reduce agitation considerably [80].
- Individualized counseling and training of caregivers has an effect size of 0.34 in reduction of agitation, comparable to pharmacologic treatments [78].
- Most episodes of behavioral disturbance in nursing facilities are self-limited; watchful waiting is often appropriate [80].
- Benzodiazepines may paradoxically exacerbate neuropsychiatric symptoms.
- Phase II trials are underway for alpha-2 agonists, and 5HT6 receptor antagonists, for the treatment of neuropsychiatric symptoms in dementia.

Cholinesterase inhibitors

- See treatment of cognitive dysfunction.

Selective serotonin reuptake inhibitors

- See treatment of anxiety and depression.

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Mood stabilizers

- Mood stabilizers have not been studied extensively in DLB.
- Carbamazepine, but not valproate, moderated behavioral disturbance in Alzheimer's trials [81].
- Preliminary observations suggest that valproate may be effective for medication-induced impulse control disorders in patients with Parkinson's disease [82].

Carbamazepine

Standard dosage: 200–800 mg twice daily

Contraindications: bone marrow suppression; concomitant use of an MAOi; concomitant use of nonnucleoside reverse transcriptase inhibitors; hypersensitivity to tricyclic compounds

Main drug interactions: medications associated with CYP1A2, 2B6, 2C, 3A4 pathways, of which carbamazepine is an inducer

Main side effects: dizziness, drowsiness, tremor, nausea, hyponatremia, rash, diplopia, blurred vision, confusion, change in blood pressure, myelosuppression, hepatitis

Special points: Start at 200 mg twice daily; may increase in increments of 200 mg over intervals of at least one week; maximum dose 800 mg twice daily.

- Patients should be monitored for hyponatremia, agranulocytosis, pancreatitis, liver dysfunction and drug reaction with eosinophilia and systemic symptoms (DRESS).

- Patients' CBCs and basic metabolic profiles should be monitored every 2 weeks when starting treatment, then every 3 months once a stable dose has been established.

Cost: 200 mg (100 tablets): $41; extended-release 200 mg (100 tablets): $139.94, 400 mg (100 tablets): $280; extended-release 100 mg, 200 mg, 300 mg (120 capsules): $215

Divalproex sodium

Standard dosage: 250–1000 mg daily, administered once daily (extended-release) or twice daily (delayed-release)

Contraindications: liver disease, urea cycle disorders

Main drug interactions: medications associated with CYP2C9/10, 2C19 pathways (includes lacosamide); lamotrigine, serotonergic agents

Main side effects: somnolence, dizziness, alopecia, changes in weight, abdominal pain, GI side effects (diarrhea, loss of appetite, nausea, vomiting), fatigue, ataxia, headache, tremor, diplopia, confusion

Special points: Start at 125 mg or 250 mg twice daily, or extended-release 250 mg once daily; may increase dose in increments of 250 mg; maximum dose 500 mg twice daily.

- Monitor liver function tests, platelet counts and coagulation tests.

- Check serum ammonia level in patients who develop lethargy, vomiting, change in mental status, or hypothermia.

- Monitor fluid and nutritional intake, motor and cognitive functions.

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Cost: 125 mg (100 tablets): $90, 250 mg (100 tablets): $176, 500 mg (100 tablets): $325; extended-release 250 mg (100 tablets): $258, 500 mg (100 tablets): $453

N-methyl-D-aspartic acid receptor antagonists

- A small, randomized, controlled trial of memantine in patients with DLB / PDD identified an improvement in neuropsychiatric symptoms in the DLB group [35]. Discontinuation rates were similar between the treatment and placebo groups.

Memantine

- See treatment of cognitive dysfunction.

Treatment of Motor Dysfunction

- Minimize parkinsonism due to antipsychotic medications, nausea treatments (e.g., prochlorperazine, metoclopramide), and anticholinergic tremor medications (e.g., trihexyphenidyl, benztropine) [83].
- Nocturnal parkinsonism with inadequate nocturnal levodopa may disrupt sleep, alter sleep architecture, allow painful muscular cramps, and place subjects at risk of falls upon waking.
- L-dopa replacement is less effective in DLB than for PD [84, 85]. It is more likely to induce psychosis in DLB patients [84, 85], though this tends to occur only with high doses. In cases where neuropsychiatric features predominate, it is wise to accept minor parkinsonism rather than risk treatments that worsen these symptoms.
- Late in the disease, when maximal treatment of neuropsychiatric symptoms with ChEis +/− antipsychotic medication fails to control the side effects of dopaminergic therapy, a choice is forced between directing therapy toward the motor or neuropsychiatric features. Patients and caregivers find it easier to accept this dilemma if they are educated about it early in the treatment process. Neuropsychiatric features usually limit treatment well before dopa-induced dyskinesias arise, but we educate patients about these nevertheless.
- Oral dopamine agonists frequently cause hallucinations, impulse dyscontrol and abnormal repetitive behaviors [64]; they should be avoided in this population. There is insufficient evidence to determine if transdermal formulations (e.g., rotigotine transdermal patch) are effective and/or well-tolerated. These behavioral problems occur less frequently with levodopa. Mixed evidence suggests that amantadine may reduce their severity, but may also induce postural hypotension, confusion, insomnia and hallucinations.[44]

Carbidopa / Levodopa

Standard dosage: 25/100 mg, 1–3 tablets three times daily

Contraindications: concomitant use with an MAOi; narrow-angle glaucoma; current diagnosis of melanoma

Main drug interactions: antipsychotics, iron supplements

Main side effects: nausea, vomiting, anorexia, lightheadedness, hypotension, confusion, hallucinations, dyskinesia, axonal polyneuropathy

Special points: Start with a half-tablet three times daily, increase inhalf-tablet increments for all doses weekly, maximum dose 3 tablets every 6 hours.

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- Use the minimal dose required, review regularly and slowly increase as necessary.

- Carbidopa/levodopa competes with protein for absorption: take 1 hour before, or 2 hours after a meal; if nausea develops, take with protein-poor snacks (e.g., soda crackers).

- Carbidopa/levodopa interferes with vitamin metabolism, supplement with:

  ○ Folic acid, 2.5 mg

  ○ Vitamin B12, 2 mg

  ○ Vitamin B6, 25 mg (warn patients that >100 mg is neurotoxic).

- To prevent osteoporosis, if patient has no history of calcium-containing renal stones:

  ○ Vitamin D: 1,000 U daily

  ○ Calcium: 1200 mg (1500 mg for postmenopausal women or men with osteoporosis)

Cost: 25/100 mg (100 tablets): $80

Treatment of Autonomic Dysfunction

Constipation

- This is an uncomfortable, under-recognized and poorly treated feature of synucleinopathy: 80–89 % of PD patients report constipation and/or diarrhea, and 16 % have been hospitalized for bowel obstruction [86, 87]. Although most cases of constipation are secondary to decreased colonic transit and gastrointestinal dysmotility, anorectal dysfunction (dyssenergy) may contribute significantly in a small set of subjects. Gastrointestinal specialist involvement is important in cases of refractory symptoms.
- A high-fiber diet combined with adequate hydration, regular exercise and stool softeners is often effective and should be the first step in treatment.
- When pharmacological interventions are needed, osmotic agents are preferred over prokinetic agents: they have fewer side effects with long-term use.
- Psyllium [class I][88] and *polyethylene glycol* [class I] are effective [89].
- Alternatives include methylcellulose, docusate, magnesium hydroxide, and misoprostol [51].
- A recent double-blind, 4-week study found significant improvement with the use of the chloride channel activating agent lubiprostone [90].

Psyllium

Standard dosage: 5.1 g twice daily (mixed with 8 ounces of water)

Contraindications: bowel obstruction

Main drug interactions: TCAs

Main side effects: gastrointestinal obstruction, nausea, bloating, and diarrhea

Special points:

- Psyllium may cause gastrointestinal obstruction if not taken with adequate fluid.

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- Common trade names include Metamucil, Reguloid, and Konsyl.

Cost: Price varies by product; Konsyl Oral powder 28.3 %, 538 g: $9

Polyethylene Glycol (Macrogol)

Standard dosage: 17g (powder dissolved in 4–8 ounces of water, juice, coffee or tea) daily.

Contraindications: bowel obstruction

Main drug interactions: none

Main side effects: bloating, cramping, diarrhea, and nausea

Special points:

- Close monitoring for electrolyte abnormalities is required when used continuously for more than 1–2 weeks.

- Common trade names include SoftLax, Miralax, Glycoprep, and Movicol.

Cost: 238 g: $12

Lubiprostone

Standard dosage: 24 mcg twice daily

Contraindications: bowel obstruction

Main drug interactions: none

Main side effects: nausea, diarrhea, flatulence; headache, and edema

Special points: Start at 8 mcg twice daily.

- If significant nausea is encountered with 24 mcg twice daily, decrease to 24 mcg daily.

Cost: 8 mcg, 24 mcg (60 capsules) $313

Postural Hypotension

- Postural hypotension is common [61, 91, 92], and may become prominent late in the disease.
- It is essential to consider this syndrome in patients who describe non-specific weakness, fatigue, intolerance of physical activity, dizziness, confusion, postural symptoms or syncope.
- Avoid vasodilator medications.
- Decrease the dose or discontinue antihypertensive medications.
- Fragment meals, avoid low sodium and carbohydrate rich meals, and increase salt (>8g) and water (2–2.5 L/day) intake [44].
- Consider salt tablets (swallow with liquids at meals).
- Thigh-high compression stockings and abdominal binders are effective (when tolerated).
- Primary fall prevention programs by physical and occupational therapists are essential; a single fall can be devastating in this frail population. Physical counter-

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maneuvers to ward off hypotension, such as squatting or leg-crossing with tension in the buttock and leg muscles, need to be used only in patients with good balance.

- Educate patients about the need to sit on the side of the bed when arising, and of the risks of postural hypotension before and after using the toilet.
- Fludrocortisone is life-changing in subjects with debilitating symptoms [Class II] [93]; perform 24-hour blood pressure monitoring intermittently to detect malignant supine hypertension. A simple remedy for this is to raise the head of the bed, either by purchasing an expensive motor-driven bed, or by placing bricks under the head of the existing one (a cheaper option).
- Midodrine may be added second-line, however there are no data to suggest one treatment over another [51].

Fludrocortisone

Standard dosage: oral 0.1 mg every other day to 1 mg daily

Contraindications: supine systolic hypertension >180 mmHg; hypersensitivity to corticosteroids; congestive heart failure, systemic fungal infections.

Main drug interactions: bupropion (may lower seizure threshold)

Main side effects: peripheral edema, hypertension, depression, delirium, psychosis, anxiety, bruising, rash, hyperpigmentation, hyperglycemia, hypokalemia, hypokalemic alkalosis, and osteoporosis

Special points:

- Increases risk of immunosuppression.
- Monitor electrolytes regularly.
- Monitor closely in those with diabetes or psychiatric symptoms.

Cost: 0.1 mg (100 tablets): $79

Midodrine

Standard dosage: 10 mg three times daily.

Contraindications: significant heart disease; severe urinary retention.

Main drug interactions: TCAs, MAOis, ergot derivative medications; sympathomimetic agents.

Main side effects: supine hypertension, piloerection, pruritus, dysuria or urinary retention, paresthesias.

Special points: Start at 2.5 mg or 5 mg twice daily or three times daily, increase in increments of 2.5 mg over intervals of at least 5 days; maximum dose 10 mg three times daily.

- Monitor both supine and standing BP; decrease dose if >180 mmHg systolic supine.
- Monitor for supine headache.

Cost: 5 mg (100 tablets): $242

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Indomethacin

Standard dosage: 25–200 mg daily in two to four divided doses

Contraindications: bleeding disorder; anticoagulants

Main drug interactions: NSAIDS, ACE inhibitors, lithium, SSRIs, methotrexate, loop diuretics, cyclosporine

Main side effects: dizziness, headache, fatigue, and dyspepsia

Special points:

- Begin at low dose and titrate to achieve desired effect.
- Increases risk of cardiac events and gastrointestinal bleeding.

Cost: 25 mg (100 tablets): $38

Genito-urinary Symptoms

- Urinary frequency, urgency and incontinence are common problems in DLB. There is scant data in DLB patients [94, 95], but they occur in 57–83 % of PD patients, and hesitancy or reduced urinary stream occurs in 17–27 % [96].
- Oral trospium or transdermal oxybutynin are effective treatments of detrusor instability. Trospium is less likely than oxybutynin to cross the blood–brain barrier based on its polarity. Alternatives include tolterodine, flavoxate, propiverine, prazosin and desmopressin [44].
- Avoid the anticholinergic treatments such as trihexyphenidyl and oral oxybutynin, which may cause confusion [22, 97–99].
- Other conditions [51]:
  - Prostatism: tamsulosin.
  - Urinary retention: bethanechol chloride 25–75 mg/day.
  - Nocturnal polyuria: intranasal desmopressin 10–40 mcg/night.

Trospium chloride

Standard dosage: 20–60 mg daily in two doses or single dose of extended-release.

Contraindications: gastric retention, uncontrolled narrow-angle glaucoma, and urinary retention

Main drug interactions: oral potassium, metformin, vancomycin, tenofovir, procainamide, pancuronium, morphine, and cisapride

Main side effects: dizziness, blurred vision, impaired heat regulation, constipation, xerostomia, headache, and angioedema

Special points:

- Take on an empty stomach or at least 1 hour prior to meals.
- Patients should be educated about angioedema.

Cost: 20 mg (60 tablets): $170

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Erectile / Sexual dysfunction

- The phosphodiesterase-5 inhibitors sildenafil, vardenafil and tadalafil are effective. The former has class I evidence for efficacy in PD subjects [22, 100, 101].
- Sexual partners should be involved with administration.
- Requests for prescription by patients should prompt review because dopamine agonists and, to a lesser extent, levodopa can induce hypersexuality [96, 102].

Sildenafil

Standard dosage: 25–100 mg once daily 1 hour prior to sexual activity

Contraindications: nitrates; HIV protease inhibitors or elvitegravir/cobicistat/tenofovir/emtricitabine

Main drug interactions: macrolide antibiotics, -azole antifungals, alpha-1 adrenergic antagonists, nefazodone, dihydrocodeine, dabrafenib, primidone, cannabis, bosentan, etravirine, nebivolol, rifapentine, ciprofloxacin, deferasirox, ranolazine, crizotinib, and amiodarone.

Main side effects: flushing, dyspepsia, and headache.

Special points:

- May cause angina, dizziness and nausea in patients with cardiovascular risk factors.
- Warn patients to seek treatment for priapism, or sudden loss of hearing or vision.
- Should not be taken more than once per day.

Cost: 50 mg (30 tablets): $960

Treatment of Sleep Dysfunction

Excessive Daytime Sleepiness

- This is common and debilitating. There are multiple causes other than degenerative changes of the arousal system. Obtain a sleep history, including sleep disordered breathing and nocturia due to dysautonomia or prostatism, and consider overnight oximetry or polysomnography.
- Ensure restorative sleep with a fixed sleep hygiene regime, including an afternoon nap if necessary.
- Minimize sedating medications, and/or switch them to evening dosing.
- Prescribe caffeinated drinks from the morning until early afternoon, but avoid caffeine if the patient has Periodic Leg Movement Disorder of Sleep, or Restless Leg Syndrome [103].
- Stimulant medications such as methylphenidate and dextroamphetamine can be effective, but the evidence is mixed [44]. They have the potential for abuse, can induce psychosis and should be avoided in patients with cardiac risk factors [44]. While worsening of neuropsychiatric features may occur, clinical experience suggests that this is uncommon.
- Modafinil and armodafinil have more benign risk profiles, although they are rarely covered by insurance unless obstructive sleep apnea is confirmed on polysomnography. Two of three randomized controlled trials in PD showed

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improvements in daytime sleepiness [44, 104]; it remains to be seen whether DLB patients would benefit.

- In a small open-label study involving 20 DLB patients, armodafinil was well-tolerated in almost all, and clinical improvement occurred in 90 % [105].
- Other physicians may need to be appraised of the reasons for combination of stimulants and sedatives in some patients (e.g., the presence of REM sleep behavior and excessive daytime sleepiness), and optimal management usually requires iterative treatment to arrive at a regime suitable for the individual.

Methylphenidate

Standard dosage: oral 5–60 mg daily in two doses or single dose of extended-release

Contraindications: glaucoma, concomitant use of an MAOi, marked agitation or anxiety, and Tourette's syndrome.

Main drug interactions: MAOis, bupropion, tricyclic antidepressants, SSRIs, carbamazepine, phenytoin, phenobarbital, primidone, tyrosine, dicumarol, warfarin

Main side effects: weight loss, nausea, vomiting, insomnia, blurred vision, dizziness, tics, labile affect, and nasal congestion.

Special points: Start at 5 mg daily in the morning, increase to 5 mg twice daily after one week with second dose around noon; may increase daily dose in increments of 5–10 mg over intervals of one week.

- Perform an electrocardiogram at initiation and dose increases; monitor pulse and blood pressure.

Cost: 5 mg (100 tablets): $73, 10 mg (100 tablets): $104, 20 mg (100 tablets): $150; extended-release 20 mg (100 tablets): $197

Modafinil

Standard dosage: 100–400 mg daily in single dose or two doses

Contraindications: hypersensitivity

Main drug interactions: CYP2C19 substrates (modafinil is a strong inhibitor), CYP1A2 substrates, CYP3A4 inducers or inhibitors (modafinil is a substrate)

Main side effects: nausea, xerostomia, anorexia, dizziness, headaches, insomnia, and hypertension

Special points: Patients/caregivers should report chest pain, palpitations, agitation, anxiety, psychosis, mania, and depression

Cost: 100 mg (30 tablets): $662, 200 mg (30 tablets): $1000

Armodafinil

Standard dosage: 150–250 mg daily

Contraindications: hypersensitivity

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Main drug interactions: CYP2C19 substrates (armodafinil is a moderate inhibitor), CYP3A4 inducers or inhibitors (armodafinil is a substrate)

Main side effects: nausea, diarrhea, xerostomia, dizziness, headaches, and insomnia

Special points: Patients/caregivers should report palpitations, psychosis, mania, depression, and anxiety

Cost: 50 mg (30 tablets): $182, 150 mg, 250 mg (30 tablets): $550

REM Sleep Behavior Disorder (RBD)

- Non-pharmacological measures are prudent in every patient, measures such as removing sharp objects from around the bed [106], creating barriers with pillows and mattress, moving the mattress to the floor, and “cocooning” (sleeping in a tightly-closed sleeping bag), all decrease the significant risk of serious harm in severe cases [class I][103]. Sleeping partners can be incorporated into dreams as would-be attackers and seriously harmed. They should be warned to move out of reach of dream enactments, or sleep in a separate bed until treatment is effective [103].
- Customized bed alarms that detect vigorous movement and play soothing messages from caregivers significantly decrease sleep related injury [class II][106].
- Melatonin is well-tolerated and often effective for RBD [Class I][107]. In PD patients, it also improves sleep quality, but does not affect daytime sleepiness [Class I][108, 109].
- Add clonazepam as second-line therapy, but use with care as it may exacerbate obstructive sleep apnea, a condition that can mimic RBD. It is effective at doses low enough to be well-tolerated [class IV]; communicate this to other providers to prevent them from ceasing a medicine that is *prima facie* contraindicated in dementia.
- Small doses of levodopa/carbidopa at bedtime may be beneficial in selected patients [class IV].

Melatonin

Standard dosage: 3–12 mg nocte

Contraindications: autoimmune disease, lactose intolerance, hepatic impairment

Main drug interactions: CYP1A1 and CYP 1A2 inhibitors or inducers, decreased metabolism of melatonin: fluvoxamine, methoxsalen, cimetidine, estrogen.

Main side effects: morning drowsiness, headache, back pain, arthralgia, nasopharyngitis.

Special points: Start at 3 mg or 5 mg nocte; may increase in increments of 3–5 mg over intervals of at least 1 week.

- Use with caution in those with coagulopathy, anticoagulant, or antiplatelet therapy.
- May affect gonadotropin levels.

Cost: 5mg (30) $8.

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Clonazepam

Standard dosage: 0.25–0.5 mg nocte

Contraindications: hepatic impairment, untreated acute-angle glaucoma.

Main drug interactions: anti-epileptic medications

Main side effects: sedation and drowsiness (up to 50 % of patients when starting therapy) [102], confusion, and paradoxical agitation

Special points:

- Use with great caution in patients with obstructive sleep apnea; monitor response clinically +/− by overnight oximetry if using nasal CPAP.

- Use with caution in patients with chronic obstructive pulmonary disease or renal impairment.

- Increase by 0.25 mg weekly as needed, doses of 2 mg and higher are safe if tolerated.

- Abrupt cessation can cause withdrawal symptoms.

Cost: 0.5 mg (100 tablets): $75, 1 mg (100 tablets): $86, 2 mg (100 tablets): $118

Carbidopa/levodopa

Standard dosage: (for REM sleep behavior disorder) 25/100 or CR 25/100 one tab nocte, increase to two tabs nocte if needed after 1 week

- See further details in the Treatment of Motor Dysfunction section above.

Restless legs syndrome / periodic limb movement disorder

- Carbidopa/levodopa may be used in a manner similar to that for RBD.
- Gabapentin dosed once daily in the evening in doses of 300–1200 mg is another option for RLS (see details about gabapentin in the Treatment of Motor Dysfunction section above).

Diet and lifestyle

- Regular driving assessment should be conducted. Cognitive fluctuations may affect results.
- Home modifications adapted for those with limited vision remedy some visuospatial problems, the use of hand rails and shower chairs and removal of fall hazards such as loose rugs and sharp-edged furniture prevents injury.
- Support handicap privileges for those with severe impairment.
- We suggest patients join local support groups, the Lewy Body Dementia Association (LBDA.org), visit Alz.org and LBDA.org for DLB updates, and read “The 36-hour Day” [110].

Assistive devices

- Medical alert bracelets describing adverse reactions to neuroleptics and dopamine-antagonists (e.g., metaclopramide and prochlorperazine) can be life saving.
- Gait aids (e.g., canes, walkers, scooters) can be effective, particularly when patients are educated on their use by a physical therapist.

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Physical/speech therapy and exercise

- Home modification for fall prevention by physical and occupational therapists
- Occupational therapy for apraxia and visuospatial abilities by expert therapists
- Programmed, regular cognitive and social stimulation, and daily exercise (e.g. *T'ai chi ch'uan)*

Other treatments (centered on behavioral management)

Person-Centered Care

- An effective care model that strives to remedy unmet needs or invalidated experiences [111]

Prescribed social interaction, music, and tape recordings of loved-ones

- Shown to produce 25 % reductions in agitation, abnormal vocalizations, and improve quality of life [Class II] [77]

Therapeutic Massage

- Improves agitation scores [Class III] [112, 113]

Music Therapy

- Decreases anxiety more than aggression, but can worsen behavior [Class II] [114, 115]

Emerging therapies

- The presence of REM Sleep Behavior Disorder (RBD*)* and positive adjunct tests [116, 117] reliably predict synucleinopathy. Neuroprotection trials in DLB should focus on prodromal disease [118].
- Deep brain stimulation for mood and obsessive behavior treatment has variable results in PD, as does repetitive Transcranial Magnetic Stimulation for depression in PD, and cognition in Alzheimer's disease.

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OPINION STATEMENT

Dementia with Lewy bodies (DLB) is a multisystem disorder with diverse disease expression. A treatment regime restricted to the cognitive aspects of the disease does no favor to patients. Instead, patients should be educated to recognize the symptoms of this multisystem involvement. There are no treatments that slow the progression of disease, but symptomatic treatments can be effective. When thinking about treatment, we find it useful to divide the symptoms and signs into five categories: (a) cognitive features, (b) neuropsychiatric features, (c) motor dysfunction, (d) autonomic dysfunction, and (e) sleep dysfunction. Clinicians, funding bodies and industry are increasingly recognizing the importance of this common and debilitating disease.

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Table 1

Revised criteria for the clinical diagnosis of Dementia with Lewy bodies (DLB)

1. *Central feature*
Progressive cognitive decline, usually with deficits in attention, executive function, and visuospatial ability
2. *Core features*
Fluctuating cognition
Recurrent visual hallucinations
Parkinsonism
3. *Suggestive features*
REM sleep behavior disorder
Severe neuroleptic sensitivity
Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging
4. *Supportive features*
Repeated falls and syncope
Transient, unexplained loss of consciousness
Severe autonomic dysfunction
Hallucinations in other modalities
Systematized delusions
Depression
Relative preservation of medial temporal lobe structures on CT/MRI scan
Generalized low uptake on SPECT/PET perfusion scans, with reduced occipital activity
Abnormal (low uptake) MIBG myocardial scintigraphy