New evidence on the management of Lewy body dementia

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Dementia with Lewy bodies and Parkinson's disease dementia, jointly known as Lewy body dementia, are common neurodegenerative conditions. Patients with Lewy body dementia present with a wide range of cognitive, neuropsychiatric, sleep, motor, and autonomic symptoms. Presentation varies between patients and can vary over time within an individual. Treatments can address one symptom but worsen another, which makes disease management difficult. Symptoms are often managed in isolation and by different specialists, which makes high-quality care difficult to accomplish. Clinical trials and meta-analyses now provide an evidence base for the treatment of cognitive, neuropsychiatric, and motor symptoms in patients with Lewy body dementia. Furthermore, consensus opinion from experts supports the application of treatments for related conditions, such as Parkinson's disease, for the management of common symptoms (eg, autonomic dysfunction) in patients with Lewy body dementia. However, evidence gaps remain and future clinical trials need to focus on the treatment of symptoms specific to patients with Lewy body dementia.

Introduction

Lewy body dementia comprises both dementia with Lewy bodies and Parkinson's disease dementia, and is the second most common cause of neurodegenerative dementia.[1–3] Dementia with Lewy bodies accounts for 4–8% of patients with dementia in clinic-based studies,[1,2] and dementia is a common (up to 80%) outcome for people with Parkinson's disease.[4] Consensus clinical diagnostic criteria have been proposed for both dementia with Lewy bodies[3] and Parkinson's disease dementia,[5] but the association between the two disorders remains to be clarified; the two diseases are likely to represent different points along a Lewy body disease continuum with pathological and genetic overlap.[6,7] The two diseases are demarcated clinically from one another by the so-called 1-year rule, based on the temporal onset of motor relative to cognitive symptoms (ie, in Parkinson's disease dementia the motor symptoms precede the onset of dementia by at least one year).[3]

Dementia with Lewy bodies and Parkinson's disease dementia are complex and heterogeneous disorders; patients present with a wide range of cognitive, neuropsychiatric, sleep, motor, and autonomic symptoms.[3,5] Although clinical guidelines outline some treatment options for patients with dementia with Lewy bodies and those with Parkinson's disease dementia,[8–10] no comprehensive guide to the management of patients with Lewy body dementia exists. Lewy body dementia management has particular challenges: symptoms differ between patients and, even within a patient, can be expressed variably over time; natural fluctuations in symptoms are an inherent part of the disease and frequently treatment of one symptom can worsen another. Furthermore, an individual patient's symptoms are often managed by different specialists, leading to uncoordinated and suboptimal care.[11,12] With the inclusion of dementia with Lewy bodies and Parkinson's disease dementia in the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) and WHO's 11th International Classification of Diseases (ICD-11) and the development of diagnostic toolkits for use in both types of dementia to improve case detection,[13] a clear need exists for an inclusive, standardised management approach to improve care and outcomes of patients with Lewy body dementia.

Since 2000, the number of clinical trials in Lewy body dementia has gradually increased. Consequently, it is now possible to conduct robust systematic and meta-analytic reviews to inform management practise. A number of these reviews and meta-analyses have been published since 2015[14–18] and there is new evidence for the treatment for symptoms, such as parkinsonism[19] and daytime somnolence.[20] However, some gaps in our knowledge remain. For example, few studies have focused on how to manage autonomic and sleep symptoms in Lewy body dementia. These non-motor symptoms are evident in advanced Parkinson's disease and therefore drawing upon the wider evidence base, for example in Parkinson's disease, to inform best practice in Lewy body dementia is appropriate.

In this Review, we present expert opinion developed from a Delphi consensus process (appendix p 4), drawing upon expert clinical experience and data from related disorders, such as Alzheimer's disease and Parkinson's disease, to address these gaps in the management of Lewy body dementia. We bring together the evidence base in Lewy body dementia and these expert opinions to form a comprehensive management approach. We cover the management of key domains of cognitive impairment, neuropsychiatric, and motor symptoms before moving on to the treatment of autonomic and sleep symptoms, which has often been neglected in previous reviews. Additionally, we identify key evidence gaps and areas for future consideration, including suggestions of treatment trials for specific symptoms in patients with Lewy body dementia.

Cognitive impairment

Attention, executive, and visuoperceptual functions are disproportionately affected in patients with Lewy body dementia compared with naming and memory abilities,[3] with variations in cognitive function (cognitive fluctuation), a key feature and a core diagnostic symptom of dementia with Lewy bodies.[3] Systematic reviews and meta-analyses[14,15] found that the cholinesterase inhibitors donepezil and rivastigmine were similarly effective at

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improving cognition for patients with dementia with Lewy bodies and those with Parkinson's disease dementia. Additionally, both drugs had positive effects on the completion of activities of daily living and reduced caregiver burden. One meta-analysis of two trials[15] suggested that rivastigmine was also associated with reduced mortality in patients with Lewy body dementia, although this effect disappeared with a trial sequential analysis (which provides better control of type I and type II errors than the traditional meta-analysis). Both donepezil and rivastigmine are recommended as first-line treatments for dementia with Lewy bodies by the UK National Institute for Health and Care Excellence;[10] donepezil is licensed for the treatment of dementia with Lewy bodies in Japan and rivastigmine is licensed for use in Parkinson's disease dementia in the USA and the UK. Evidence of the efficacy of a third cholinesterase inhibitor, galantamine, in patients with Lewy body dementia is sparse as only open-label trials support its use.[14,15]

The choice of cholinesterase inhibitors is influenced by the ease of administration, side-effect profile, presence of comorbidities, dose titration regime, cost, caregiver preference, and previous clinical experience.[21] Rivastigmine has been associated with more adverse events than donepezil in patients with Parkinson's disease dementia and those with dementia with Lewy bodies.[14,15] However, rivastigmine has a transdermal patch formulation that appears to have fewer gastrointestinal side-effects than oral rivastigmine in patients with Parkinson's disease dementia.[22] An open-label, uncontrolled study of seven patients with Lewy body dementia showed the benefit of high-dose (15 mg donepezil daily) cholinesterase inhibitors,[23] but this benefit resulted in increased side-effects.

An absence of improvement should not be a reason for the discontinuation of cholinesterase inhibitors because patients with Lewy body dementia are less likely to deteriorate globally while taking them.[14] No randomised controlled trials have assessed cholinesterase inhibitor withdrawal, although an open-label trial of 19 patients with Lewy body dementia found that sudden withdrawal could be associated with deterioration in both cognitive function and neuropsychiatric symptoms.[24]

Clinical trials of the NDMA receptor antagonist memantine showed that it was well tolerated in patients with Lewy body dementia, but evidence for its efficacy remains mixed.[14,15] Two 24-week, double-blind, randomised controlled trials of memantine in Lewy body dementia have been conducted.[25,26] The first trial, by Aarsland and colleagues,[25] reported significant improvements in their primary outcome (Alzheimer's disease cooperative study Clinical Global Impression of Change [ADCS-CGIC] scores [a measure based on observation by a clinical assessor of change in the patient's cognitive, functional, and behavioural performance]) in both patients with Parkinson's disease dementia and dementia with Lewy bodies (34 patients in active group *vs* 38 in placebo group), with the effect possibly greater in the Parkinson's disease dementia group. The second, larger study, by Emre and colleagues,[26] showed significant improvements in ADCS-CGIC scores only in the dementia with Lewy body group (34 patients in active group *vs* 41 in placebo group) and not the Parkinson's disease dementia group (62 patients in active group *vs* 58 in placebo group). Further lack of consistency between these trials was also evident for other outcomes: Emre and colleagues[26] reported substantial benefits in terms of neuropsychiatric symptoms in dementia with Lewy bodies only with memantine, whereas Aarsland and colleagues[25] reported a statistically significant, 1·9 point, improvement in MMSE scores in the active group compared with placebo. Data from 51 patients (21 with dementia with Lewy bodies and 30 with Parkinson's disease dementia) taken from the study by Aarsland and colleagues[25] found that the improvement in ADCS-CGIC score was related to improvements in attention, a cognitive domain which is often profoundly impaired in Lewy body dementia.[27] Another post-hoc analysis from this trial of memantine[25] reported improvements in patient quality of life as a whole,[28] and a 22-week randomised control trial of 25 patients with Parkinson's disease dementia who received memantine noted a reduction in caregiver burden and improvements in individually set goals.[29] A 36-month, open-label, follow-up study of 42 patients from one of the centres in one of the memantine trials[25] suggested that a positive response to memantine compared with placebo was associated with improved survival in patients with Lewy body dementia, but the small sample size in this study could have introduced bias and confounders that might not have been adequately controlled for.[30]

In summary, robust evidence exists for the efficacy of rivastigmine and donepezil in the treatment of cognitive symptoms in patients with Lewy body dementia,[14,15] but high-quality randomised controlled studies of galantamine are needed to draw conclusions about this agent. Memantine could have some benefits, but further studies with larger numbers of patients with dementia with Lewy bodies and Parkinson's disease dementia are needed to determine whether there is an improvement with this drug in either dementia with Lewy bodies or Parkinson's disease dementia and, if so, which specific symptoms are improved. Whether memantine should be used as a monotherapy or whether it should be combined with cholinesterase inhibitors is also unclear, as only one of the two trials of memantine allowed concomitant cholinesterase inhibitors use.[25]

Dosing and drug side-effects are important to consider when selecting the cholinesterase inhibitors or memantine for patients with Lewy body dementia (table 1).

Neuropsychiatric symptoms

Patients with Lewy body dementia present with a variety of neuropsychiatric symptoms, including visual hallucinations and hallucinations in other sensory modalities,

	Dosing	Adverse effects	Comment
Donepezil	5 mg once daily for 4–6 weeks, increased to 10 mg daily if tolerated	Overall cholinesterase inhibitors are well tolerated; adverse effects include: gastrointestinal symptoms, postural hypotension, urinary frequency, drooling, watering eyes, runny nose, and worsening of extrapyramidal motor symptoms, particularly fine tremor; these effects only occurs in a few patients, particularly those with more advanced disease; given the high incidence of autonomic dysfunction (eg, orthostatic hypotension, syncope or presyncope, or cardiac dysrhythmia or conduction disturbances), examination for these must be done before treatment; if the patient has a history of these signs and symptoms, cardiac issues, or autonomic dysfunction, an electrocardiogram might be appropriate and specialist cardiology advice might need to be sought, particularly if a pacemaker is required	Double-blind randomised control trial evidence in both patients with dementia with Lewy bodies and those with Parkinson's disease dementia support the use of donepezil; meta-analyses suggest a similar effectiveness to rivastigmine[14,15]
Rivastigmine (oral)	1·5 mg twice daily for 4 weeks, increased to 3 mg twice daily. Dose can be increased up to 6 mg twice daily if tolerated	Similar to donepezil	Double-blind randomised control trial evidence in both patients with dementia with Lewy bodies and those with Parkinson's disease dementia support the use of rivastigmine;[14,15] rivastigmine might be associated with more adverse effects than donepezil[14,15]
Rivastigmine patch	4·6 mg/24 h for 4 weeks, increased to 13·3 mg/24 h if tolerated	Similar to donepezil	Might have advantages in patients with swallowing difficulties; those who have gastrointestinal side-effects in response to oral agents; those that have compliance issues; or if the patient has a history of a variable response to oral dosing
Galantamine	8 mg/day increased to the initial maintenance dose of 16 mg/day after a minimum of 4–6 weeks; if tolerated after 4 weeks at 16 mg/day, a further dose increase to 24 mg/day of galantamine can be attempted	Similar to donepezil	Open-label trial data only, but galantamine might have positive effects on cognition and neuropsychiatric symptoms[14]
Memantine	Dosing of memantine should be increased gradually (typically by 5 mg per week) to 20 mg once daily (some patients might prefer divided dosing) over 4 weeks according to tolerance	Side-effects of memantine include gastrointestinal symptoms, confusion, somnolence, hypertension, and dizziness; be cautious when prescribing memantine to individuals with a history of seizures or poor renal function; memantine might enhance the effects of dopaminergics, such as selegiline, and can be toxic when given with, for example, amantadine	In clinical trials memantine was superior to placebo on Global Impression of Change scores, but not on cognitive function or other outcomes, with inconsistent findings reported between patients with dementia with Lewy bodies and those with Parkinson's disease dementia[14,17]

Table 1: **Cholinesterase inhibitors and memantine for the treatment of cognitive and neuropsychiatric symptoms in patients with Lewy body dementia**

systematised delusions, apathy, aggression, anxiety, and depression.[31] Symptoms might not always need treatment (eg, hallucinations can be regarded neutrally or as being comforting or pleasurable, with little or no effect on psychosocial function).[3,32] Including collateral information from the care-giver or an informant in the clinical assessment of patients is essential to diagnosis and management because patients frequently lack insight or awareness of the extent of their neuropsychiatric symptoms. Rating scales can provide a useful framework for assessing the severity and frequency of symptoms and monitoring treatment response (eg, for visual hallucinations).[33] Scales can either be specific to a symptom or a composite; composite scales, such as the Neuropsychiatric Inventory,[34] aggregate several symptoms and are commonly used as measures in clinical trials in patients with Lewy body dementia.[25,26,35,36]

As for other types of dementias, non-pharmacological interventions (eg, musical therapy and environmental modifications) are usually advocated as a first-line treatment for neuropsychiatric symptoms;[10] however, the evidence base for this in patients with Lewy body dementia is weak, based only on case report and case series data.[17,18] In this context, the application of approaches shown to be effective in patients with Alzheimer's disease might also be helpful in patients with Lewy body dementia, but no specific consensus exists as to if, or how, they could be adapted.[18]

If symptoms are severe or distressing, or if non-pharmacological interventions do not succeed, then pharmacotherapy might be indicated.[10] Studies of donepezil and rivastigmine have found improvements in composite scores of neuropsychiatric symptoms in patients with Lewy body dementia;[15] however, evidence on whether a treatment leads to the improvement of a specific symptom is more challenging to obtain, because these are not commonly reported in studies. Scores that aggregate apathy, delusions, depression, and hallucinations have indicated a benefit to patients with dementia with Lewy bodies from donepezil, but not rivastigmine.[35,36] One systematic review[14] suggested that donepezil, but not rivastigmine, might reduce delusions, hallucinations, and cognitive fluctuations in patients with dementia with Lewy bodies. In patients with Parkinson's disease dementia,

donepezil does not appear to be beneficial for hallucinations, hostility, suspiciousness, or unusual thought content.[37] Despite the absence of consistent effects on specific neuropsychiatric symptoms, expert opinion from our Delphi consensus group and national guideline bodies[10] have endorsed the use of rivastigmine and donepezil for neuropsychiatric symptoms in patients with Lewy body dementia. Open-label trial data of galantamine provides preliminary evidence of improved cognitive fluctuation, sleep, and psychiatric symptoms in patients with dementia with Lewy bodies,[38] and an improvement in hallucinations, anxiety, apathy, and sleep symptoms in patients with Parkinson's disease dementia;[39] therefore, galantamine could be an alternative if other cholinesterase inhibitors are not tolerated. As noted previously, the reported efficacy of memantine on neuropsychiatric symptoms in patients with Lewy body dementia is mixed.[14,15]

If, despite cholinesterase inhibitor or memantine treatment, psychotic symptoms remain, an antipsychotic agent could be considered, although its use needs to be balanced against a scarcity of documented efficacy of these agents when assessed systematically[14] and the high-risk of severe sensitivity reactions that can occur in up to 50% of patients with Lewy body dementia, which can be life-threatening, as well as an enhanced mortality risk in the longer term.[40–42] If antipsychotics are prescribed in patients with Lewy body dementia, there needs to be a high degree of caution in their use.[43] No evidence supports the use of any antipsychotic drug in patients with Lewy body dementia. Quetiapine appears to have the fewest side-effects, but evidence for its efficacy in patients with Parkinson's disease[9] and those with Lewy body dementia is insufficient.[14] Clozapine, effective in patients with Parkinson's disease psychosis,[44] might also help in patients with Lewy body dementia, but no trials have been done with this drug in patients exclusively with Lewy body dementia. Pimavanserin is a new antipsychotic drug with specific inverse agonism for the 5-HT_{2A} receptor. It is available in the USA but not in Europe, and has shown antipsychotic effects in patients with Parkinson's disease psychosis;[45] its safety and efficacy have not been formally evaluated in patients with Lewy body dementia, although a phase 3 clinical trial of pimavanserin (NCT03325556) in patients with dementia related psychosis is ongoing that will include patients with Lewy body dementia.

Depression occurs in about a third of patients with Lewy body dementia[46,47] and is often accompanied by anxiety. Pharmacological treatments for depression and anxiety in patients with Lewy body dementia have not been adequately evaluated. A small randomised controlled trial comparing citalopram, a selective serotonin reuptake inhibitor, with risperidone in 14 patients with dementia with Lewy bodies did not show efficacy and found high overall burden of side-effects.[48] More studies with antidepressants have been conducted in Parkinson's disease.[9] A randomised control trial of paroxetine (n=42), venlafaxine (n=34), or placebo (n=39) for the treatment of depression in patients with Parkinson's disease, reviewed by Sepp and colleagues,[9] found a reduction in depressive symptoms for both drugs. However, other studies are less conclusive and provide mixed results for selective serotonin-reuptake inhibitors and tricyclics.[9] Therefore, it is difficult to conclude which drugs are best to use in the treatment of depression in patients with dementia with Lewy bodies or Parkinson's disease dementia and there are concerns that antidepressants might affect sleep and worsen REM sleep behaviour disorder symptoms.[49]

Electroceutical approaches are increasingly being investigated in patients with Lewy body dementia, but many of these techniques are primarily research based rather than being used clinically. Statistically significant reduction in depression scores after repetitive transcranial magnetic stimulation was shown in one case series of six patients with dementia with Lewy bodies.[50] By contrast, two randomised sham-controlled trials of transcranial direct current stimulation in patients with Lewy body dementia have not shown statistically significant improvements in cognition (42 patients)[51] or hallucinations (36 patients).[52] A study of six patients with Parkinson's disease dementia[53] reported that deep brain stimulation of the nucleus basalis of Meynert improved neuropsychiatric inventory scores compared with sham stimulation, but findings remain tentative and numbers small on which to base any firm conclusions.

Even electroconvulsive therapy, an established clinical treatment has surprisingly little evidence in Lewy body dementia although a comprehensive review[18] in this area noted a reduction in depressive symptoms with electroconvulsive therapy across four uncontrolled studies, in a total of 22 patients.

In summary, a number of case studies have examined the non-pharmacological management of neuropsychiatric symptoms in patients with Lewy body dementia; future studies are needed to address this gap. Cholinesterase inhibitors might help, but further studies focusing on which particular symptom domains are most likely to improve are needed. The effect of memantine on neuropsychiatric symptoms needs to be confirmed in large randomised controlled studies. Studies of pimavanserin in patients with Lewy body dementia for psychosis and trials of antidepressants for depression have not yet been done and should be a future priority.

Motor symptoms

Up to 85% of patients with dementia with Lewy bodies experience motor difficulties,[3] although resting tremor is less prevalent than in those with Parkinson's disease.[54] By contrast, parkinsonism in patients with Parkinson's disease dementia can be moderate-to-severe and patients have often been exposed to long-term and high-dose antiparkinsonian medications with commensurate side-effects, including motor fluctuations and psychosis.[55,56] Thus, the management of motor symptoms can differ markedly between patients with dementia with Lewy

	Dosing	Adverse effects	Comment
Parkinson's disease dementia			
Simplification of antiparkinsonian treatment regime	Withdraw one at a time in the order: (1) anticholinergic drugs, (2) amantadine, (3) selegiline, (4) dopamine agonists, and (5) catechol-O-methyltransferase inhibitors	Reduction in antiparkinsonian medications can lead to the worsening of motor symptoms	Despite the poor correlation between dopaminergic drug exposure and psychosis,[55] a stepwise withdrawal approach might be useful, especially if psychosis is present[57]
Dementia with Lewy bodies			
Levodopa monotherapy	Either co-careldopa or co-beneldopa can be used; start with a low dose and increase slowly; commonly, dementia with Lewy bodies initiation doses (50 mg levodopa equivalent dose, for example co-careldopa 12·5 mg/50 mg, taken one to three times daily) are lower than in patients with Parkinson's disease	Psychosis, postural hypotension, sedation, nausea, and vomiting	Up to a third of patients might experience improvement; however, a third of these patients might also experience psychotic symptoms (eg, hallucinations or delusions)[58,59]
Zonisamide	25–50 mg once a day as an adjunct to levodopa	Side-effects include weight loss and decreased appetite	Evidence for use in patients with dementia with Lewy bodies comes from one phase 2 randomised control trial[19]

Table 2: **Pharmacological interventions for motor symptoms in patients with Parkinson's disease dementia and those with dementia with Lewy bodies**

bodies and those with Parkinson's disease dementia (table 2).

To date, no double-blind randomised controlled trials have investigated levodopa therapy in patients with dementia with Lewy bodies, or whether changing to a levodopa monotherapy regimen in patients with Parkinson's disease dementia is beneficial. However, open-label studies suggest that both acute and chronic levodopa monotherapy can improve motor function and reduce tremor in patients with dementia with Lewy bodies and patients with Parkinson's disease dementia.[58,59] Motor function appears to improve more in patients with Parkinson's disease dementia (65–70%) than in those with dementia with Lewy bodies (32–50%).[14] Approximately one in three patients with dementia with Lewy bodies treated with levodopa will experience psychotic symptoms.[59] A meta-analysis of four double-blind randomised controlled trials, which recruited a total of 1068 patients with Parkinson's disease across these four studies,[60] and a phase 2 trial of 158 patients with dementia with Lewy bodies have reported a statistically significant improvement in motor function compared with patients receiving placebo with zonisamide, an antiepileptic agent, when used as adjunctive treatment to levodopa.[19]

In terms of non-pharmacological approaches, deep brain stimulation is an effective treatment for motor symptoms in patients with Parkinson's disease that are medication refractory, display significant on–off fluctuations, tremor, or dyskinesias.[61] However, pre-existing cognitive impairment is a contraindication for deep brain stimulation because stimulation impairs cognitive function and exacerbates any pre-existing cognitive impairment.[62]

Falls

Falls are common in patients with Lewy body dementia and are associated with substantial morbidity and mortality.[63,64] Contributors to fall risk in patients with Lewy body dementia are commonly multifactorial, including parkinsonism, dysautonomia, and frailty.[64] The use of physiotherapy has a robust evidence base in patients with Parkinson's disease and can help to improve balance, power, flexibility, and enhance mobility—all factors that can decrease the risk of falls and improve functional independence.[64,65] Hypothetically, cognitive impairment could influence engagement with therapy in Lewy body dementia. Unfortunately, no evidence exists for the use of physical therapy in Lewy body dementia and such studies are needed.

Autonomic dysfunction

There are a wide range of autonomic signs and symptoms in patients with Lewy body dementia and these are associated with more rapid disease progression and shorter survival.[66] Despite the prominence and effect of these symptoms, no evidence base is yet established for their treatment; as a result, opinion on best management is largely drawn upon from the more established evidence base in patients with Parkinson's disease.[8,67,68]

Orthostatic hypotension

Non-pharmacological approaches are not evidence based but our Delphi panel recommended advising the patient to stand slowly, raising the head of the bed for those with morning orthostatic hypotension, increasing fluid intake and for some, the use of compression hosiery, and increased salt intake, when appropriate. Pharmacologically, fludrocortisone, a drug with significant mineralocorticoid effects, and midodrine, whose active metabolite, desglymidodrine, is a α1-receptor agonist with vasopressive effects, have both been suggested for the treatment of orthostatic hypotension in patients with Parkinson's disease on the basis of a small number of trials (table 3).[8,9,69] No trials with these drugs have been specifically conducted in Lewy body dementia; however,

	Dosing	Adverse effects	Comment
Midodrine	A 2·5–10 mg dose taken up to three times daily; avoid evening doses of midodrine; last dose should be taken at least 4 h before bed; monitor hepatic and renal function	Risk of supine hypertension	Several trials of patients with orthostatic hypotension (which have included patients with Parkinson's disease) with some suggestion of efficacy[9]
Fludrocortisone	50–300 µg/day; titrate slowly and monitor electrolytes	Electrolyte disturbances, hypertension (especially supine), and oedema	A crossover clinical trial in 17 patients with Parkinson's disease showed statistically significant subjective benefits with fludrocortisone compared to a range of non-pharmacological interventions[70]
Droxidopa	100–600 mg three times daily	Risk of supine hypertension, worsening heart disease or heart failure, and arrhythmias	A phase 3 trial of 162 patients with Parkinson's disease with orthostatic hypotension reported subjective improvements in symptoms and a mean standing systolic blood pressure increase of 11·2 mm Hg *vs* 3·9 mm Hg compared with placebo;[71] however, an interim analysis of a double-blind randomised controlled trial in patients with Parkinson's disease did not show subjective benefits of droxidopa compared with placebo with regard to orthostatic hypotension symptoms,[72] although a revised primary outcome in the full trial, which specifically focused on feelings of dizziness, light headedness, and feeling faint, suggested short-term benefits[73]

Table 3: **Potential pharmacological interventions for orthostatic hypotension in patients with Lewy body dementia**

consensus from our Delphi panel supported the use of these agents in Lewy body dementia. Both agents require specific monitoring of supine blood pressure. Electrolytes should also be monitored in patients taking fludrocortisone, as should hepatic and renal function in patients taking midodrine. Droxidopa (a prodrug that converts to norepinephrine) is licensed for the treatment of orthostatic hypotension in patients with Parkinson's disease in some countries, including the USA and Japan. Although no data for droxidopa exist in patients with Lewy body dementia, given its low side-effect profile,[71] the use of droxidopa in these patients could be a viable treatment option if licensed or available (table 3). The importance of treating orthostatic hypotension in patients with Lewy body dementia is highlighted by the link between orthostatic hypotension and attention-executive impairments in patients with Parkinson's disease, which raises the possibility that treatment of the low blood pressure might have benefits beyond the hypotension itself, but randomised controlled trials are needed to assess this effect.[74]

Gastrointestinal dysfunction

The full extent of the alimentary tract can be affected in patients with Lewy body dementia with symptoms ranging from sialorrhoea to dysphagia, gastroparesis, and constipation.[75–77] When reviewed,[77] the prevalence of excessive drooling in patients with Parkinson's disease has been reported to range from 10% to 81% of patients in case controlled studies. In part, the wide variation might reflect differences in how drooling was assessed, cohort ascertainment, and the lack of established diagnostic criteria.[78] Excessive drooling can have substantial negative effects on the quality of life and social and emotional function of the patient. Drooling has been linked to inefficient swallowing, which leads to high prevalence of aspiration (>80%) in patients with Lewy body dementia.[78] A randomised controlled trial of 132 patients with Parkinson's disease dementia with dysphagia investigated the effects of the interventions that prevent aspiration. Fewer patients using honey-thickened fluids aspirated compared with those receiving nectar-thickened liquids or completing chin-down posturing, as evidenced by videofluoroscopy.[79] Another observational study reported objective improvements in swallowing function after the consumption of carbonated liquids in 48 patients with Lewy body dementia referred for videofluoroscopy.[78] Whether such interventions have clinically meaningful effects (eg, prevention of aspiration pneumonia) remains to be resolved. A randomised, double-blind, placebo-controlled, crossover trial of glycopyrrolate (1 mg two or three times a day) in 23 patients with Parkinson's disease reported that nine (39·1%) patients had a clinically meaningful improvement in sialorrhoea over a 4-week period;[80] however, the efficacy of this agent in patients with Lewy body dementia is not known. Botulium toxin injection into the salivary glands appears effective and safe in patients with Parkinson's disease,[77] and consensus opinion suggests that it would be similarly effective in patients with Lewy body dementia, although repeated injections are often needed.

Gastric emptying is slow in patients with Parkinson's disease, but this process might be even slower in patients with dementia with Lewy bodies,[81] and slow emptying correlates with severity of motor impairment.[82] Impairments in gastric motility can lead to fullness, reflux and excess eructation, and, importantly, affect drug absorption. Management includes the avoidance of high fat foods, drinking during meals, walking after meals, and an awareness that dopaminergic medications can exacerbate gastroparesis.[68,75] Domperidone, a peripheral dopamine blocker, might have efficacy in the treatment of gastroparesis in patients with Parkinson's disease,[68,83] but it is associated with cardiotoxicity and the risk of QT prolongation.

Constipation is one of the most common symptoms in patients with Lewy body dementia,[84] with prolonged colon transit time and pelvic floor dyssynergia as plausible

Figure: **Current challenges and future opportunities for improving care and outcomes of patients with Lewy body dementia**

causes.[75,76] Constipation can also be exacerbated by opiates and anticholinergics,[84,85] poor fluid intake, reduced fibre intake, and sedentary behaviour. Polyethylene glycol (also known as macrogrol) and psyllium increase bowel frequency in patients with Parkinson's disease,[86,87] and experts advocate dietary modification, increased fluid intake, and suppositories as treatments for constipation in patients with Lewy body dementia. Stronger laxatives, suppositories, or enemas might be needed in severely affected patients.[68] Lubiprostone, a bicyclic fatty acid that activates type-2 chloride channels in the gut and enhances intestinal secretions, has been shown to have short-term benefits in patients with Parkinson's disease.[84,88]

Although randomised controlled trial evidence supports the use of thickened liquids to reduce aspiration in patients with Lewy body dementia, further studies of interventions to help other symptoms, such as constipation, are needed. Until then, the evidence base for Parkinson's disease can be used to inform management of gastrointestinal symptoms in patients with Lewy body dementia.

Urinary symptoms

Urinary symptoms in patients with Lewy body dementia are very common and include urgency, frequency, and incontinence.[89] Despite being common, no trials for patients with Lewy body dementia have been conducted; thus, treatment recommendations are based on data from Parkinson's disease studies. A double-blind randomised placebo-controlled trial of solifenacin over 12 weeks in 23 patients with Parkinson's disease and urinary frequency, incontinence, or nocturia reported a statistically significant reduction in urinary incontience over a 24 h period.[90] However, antimuscarinics (such as solifenacin) have a high risk of adverse effects, including cognitive side-effects,[91] which might be a contraindication for their use in patients with Lewy body dementia. An alternative drug without cognitive side-effects is the β_3-adrenoceptor

	NCT number	Study design	Proposed mechanism of action	Main outcomes	Comment
Intepirdine (RVT-101)	NCT02669433, NCT02910102, and NCT02928445	Double-blind, randomised, placebo-controlled study of RVT-101 in patients with dementia with Lewy bodies (NCT02669433) and a double-blind randomised placebo-controlled study of gait impairment in patients with either Alzheimer's disease, dementia with Lewy bodies, or Parkinson's disease (NCT02910102); additionally, there was a planned 6 month extension study with RVT-101 in patients with dementia with Lewy body (NCT02928445)	Serotonin 6 receptor antagonist that causes the release of acetylcholine and other neurotransmitters	Primary outcome for first study (NCT02669433) was Unified Parkinson's Disease Rating Scale-Part III and, for the second study (NCT02910102), quantitative gait function; secondary outcomes included cognitive and Clinician's Interview-Based Impression of Change score Plus Caregiver Input (NCT02669433) and safety outcomes (NCT02910102)	NCT02669433, NCT02910102, and NCT02928445 were terminated in 2018. The results indicated a lack of efficacy on all outcomes for NCT02669433. No formal results have been posted for NCT02910102 and NCT02928445
Nelotanserin	NCT02640729, NCT02708186, and NCT02871427	Double-blind, randomised, placebo-controlled cross-over study in patients with Lewy body dementia with visual hallucinations (NCT02640729) and a double-blind, randomised, placebo-controlled parallel-arm study in patients with dementia with Lewy bodies or Parkinson's disease dementia who have REM sleep behaviour disorder (NCT02708186); additionally, an open-label study was planned in patients with Lewy body dementia with frequent visual hallucinations or REM Sleep Behavior Disorder (NCT02871427)	Serotonin receptor subtype 5-HT_{2A} inverse agonist	Visual hallucinations and safety data as well as motor function in first trial (NCT02640729), and REM sleep behaviour disorder symptoms in the second (NCT02708186)	No formal results from these trials have been posted or published but further development of this drug has been discontinued
SYN120	NCT02258152	Double-blind randomised placebo-controlled study in patients with Parkinson's disease dementia	Dual HT_{2A} with a dual 5-HT_6 or 5-HT_5 antagonist	Primary outcomes were attention measures	Results posted (May 2019) to clinicaltrials.gov indicated a lack of statistical difference on primary outcomes between active and placebo arms
LY3154207	NCT03305809	Double-blind randomised placebo-controlled study in patients with Parkinson's disease dementia	Enhancer of dopamine receptor D1	Attention measures (primary) and cognitive, neuropsychiatric outcomes, sleep, motor, and functional measures (secondary)	Recruiting
E2027	NCT03467152	Double-blind randomised placebo-controlled study of patients with dementia with Lewy Bodies	A selective phosphodiesterase 9 inhibitor that might maintain cyclic GMP concentration in the brain	Cognitive measures and Global Impression of Change scores with wide range of secondary outcomes including, for example, neuropsychiatric, cognitive fluctuations, global impression of change, and safety data	Recruiting
Ambroxol	NCT02914366	Double-blind randomised placebo-controlled parallel study in patients with Parkinson's disease dementia	Raises the concentrations of the enzyme β-glucocerebrosidase, which might lead to reduced concentrations of α-synuclein	Cognitive measures and Global Impression of Change scores with wide range of secondary outcomes including, for example, motor performance measures, cerebrospinal fluid concentrations of α-synuclein, tau, phospho-tau and β amyloid 42 and structural magnetic resonance biomarkers (ventricular volumes and hippocampal atrophy)	Recruiting

(Table 4 continues on next page)

agonist mirabegron (25–50 mg once per day); a retrospective cohort study, which considered 50 patients with Parkinson's disease between 2012 and 2017, suggested that this agent was well tolerated in patients with Parkinson's disease and offered benefit.[92] A wide range of medications are available to treat urinary symptoms, such as over active bladder, frequency, and nocturia. Trials specific to Lewy body dementia patients are needed given the major effect of these symptoms have on patient quality of life.

Excess sweating

Hyperhidrosis is reported by two-thirds of patients with Parkinson's disease;[93] it is associated with disease severity and might be linked with fluctuations in motor symptom severity,[94,95] but how common hyperhidrosis is in patients with Lewy body dementia is not known. It has substantial social and emotional effects and might occur with other autonomic disturbances.[93] No treatment trials have been done, but the consensus from our Delphi panel group is that patients might benefit from the use of loose fitting clothing, cotton bedding for night sweats, antiperspirants, and avoidance of triggers, including alcohol, spicy foods, and rooms with a high ambient temperature, to control symptoms. For those with dyskinesias and hyperhidrosis, reducing dopaminergic medication should be considered.[93,95]

Sleep disturbances

Sleep disturbances in patients with Lewy body dementia can be severe and include insomnia, sleep fragmentation,

	NCT number	Study design	Proposed mechanism of action	Main outcomes	Comment
(Continued from previous page)					
Deep brain stimulation	NCT01340001 and NCT02263937	Pilot studies assessing stimulation of the nucleus basalis of Meynert in patients with dementia with Lewy bodies	Enhance cholinergic output of the nucleus basalis of Meynert	Various cognitive and neuropsychiatric outcomes	Completed: awaiting results
HTL0018318	NCT03592862	Double-blind randomised placebo-controlled trial of patients with dementia with Lewy bodies	Muscarinic M1 agonist	Primary outcome was to assess safety and secondary outcomes included measures of cognition and psychosis	Trial suspended pending investigation of an unexpected animal toxicology finding (development of tumours)
Ramelteon	NCT00745030 and NCT00907595	Double blind, randomised placebo-controlled pilot studies for REM sleep behaviour disorder which included patients with dementia with Lewy body	Selective agonist of melatonin receptors (MT1 and MT2)	Primary outcomes included sleep efficiency and other sleep parameters with a wide range of secondary outcomes (motor, cognitive, and functional etc)	Trials terminated due to low participant enrolment and recruitment
Pimavanserin	NCT03325556	Double-blind randomised placebo-controlled trial for the treatment of hallucinations and delusions associated with dementia related psychosis; it will include patients with dementia with Lewy bodies or Parkinson's disease dementia	Selective 5-HT_{2A} inverse agonist	Time to relapse in double blind period or discontinuation for any reason	Recruiting
Bosutinib	NCT03888222	Double blind randomised placebo-controlled study in dementia with Lewy bodies	Tyrosine kinase inhibitor targeting c-Abelson and Src tyrosine kinases. In models of neurodegeneration, it reduces alpha-synuclein, tau, and amyloid β	Primary outcome is safety with secondary outcomes including cerebrospinal fluid markers of, for example, bosutinib levels, cell death, tau, phosphorylated tau, amyloid β, and inflammation	Recruiting

REM=rapid eye movement.

Table 4: **Examples of clinical trials assessing treatment interventions in patients with Lewy body dementia**

rapid eye movement (REM) sleep behaviour disorder, motor-related sleep disturbances, restless legs syndrome, periodic limb movements, obstructive sleep apnoea, and excessive daytime sleepiness.[3] Most of the evidence base for the management of these symptoms comes from studies done in patients with Parkinson's disease and those with idiopathic REM sleep behaviour disorder rather than from studies of patients with Lewy body dementia. Management begins with education on good sleep hygiene and avoidance of any drugs that can affect sleep or alertness.[8]

For insomnia, a meta-analysis of melatonin from nine randomised controlled trials in patients with different neurodegenerative diseases, including patients with Parkinson's disease, found improvements in subjective sleep quality and the drug appears to be well tolerated.[96,97] Non-benzodiazepines (Z-drugs), such as eszopiclone, zopiclone, and zolpidem, have not been trialled in patients with Lewy body dementia, but the consensus opinion from experts is that they could be considered for short-term treatment of insomnia if sleep apnoea is not evident, with the caveat that they might have negative effects on cognition, daytime sleepiness, and increase the risk of fractures and falls.[98] If sleep disturbances occur secondary to nocturnal parkinsonism, long-acting levodopa preparations might be useful.[99] Randomised controlled studies have shown that dopaminergic medications, such as ropinirole, pramipexole, and rotigotine, have efficacy in treating idiopathic restless legs syndrome,[100] but have not been trialled in patients with Lewy body dementia. A network meta-analysis of 35 studies, which collectively included 7333 participants, found that gabapentin and pregabalin were statistically superior to placebo and as effective as dopaminergic drugs, such as rotigotine, for the treatment of restless legs syndrome.[100] However, all of the drugs need to be used with caution in patients with Lewy body dementia given their cognitive side-effects.

Obstructive sleep apnoea might occur in up to a third of patients with Lewy body dementia[101] and is often unrecognised. Patients might experience excessive daytime somnolence, worsening cognitive function, unrefreshing sleep, and early morning headaches.[102] Pauses in breathing during sleep and regular snoring raise the suspicion of this particular sleep symptom. A number of associated risk factors exist, including being overweight, male sex, smoker, use of sedatives, alcohol use, reflux, and anatomical considerations (eg, collar size >43 cm [>17"]),[103] which should be assessed for in every patient.

REM sleep behaviour disorder is a parasomnia manifested by recurrent dream enactment behaviour, which includes movements mimicking dream content, and is associated with an absence of normal REM sleep atonia. Between half and three-quarters of patients with Lewy body dementia have REM sleep behaviour disorder,[104,105] and it is a core symptom for the diagnosis of dementia with Lewy bodies.[3] It can precede the onset of Parkinson's disease and Lewy body dementia by many years to decades or can emerge during the dementia phase.[106,107] However, obstructive sleep apnoea, narcolepsy, and nocturnal arousal events coupled with confusion might mimic REM sleep behaviour disorder.[101,107] As a result, the origin of sleep disturbance in patients with Lewy body dementia

might require polysomnography.[3] A number of non-pharmacological strategies have been used anecdotally in patients with Lewy body dementia with REM sleep behaviour disorder, including lowering bed height or placing a mattress on the floor; removal of potentially dangerous objects in the bedroom, such as sharp or glass objects; or, if necessary, asking bed partners to sleep separately from the patient. Some medications can worsen REM sleep behaviour disorder (eg, antidepressants),[108] and retrospective case series in patients with idiopathic and secondary REM sleep behaviour disorder supported the use of clonazepam, although caution is needed when prescribing it to patients with Lewy body dementia who are more prone to gait disturbance, sleep apnoea, cognitive impairment, and are at high risk of falls.[109] Pramipexole has been assessed in observational studies as a potentially effective treatment for REM sleep behaviour disorder in patients with Parkinson's disease,[99] but it is associated with an increased risk of psychosis.[110] Melatonin (3–12 mg before bedtime) is well tolerated and has a clinical trial evidence base in the treatment of idiopathic REM sleep behaviour disorder.[109,111] Another treatment option is memantine, which decreased physical activity during sleep over 24 weeks in a randomised controlled study of 20 patients with Lewy body dementia, while the 22 patients in the placebo group worsened over the same period.[112]

Excessive daytime sleepiness is common in patients with Lewy body dementia,[113] and it can make daily function challenging for patients and carers. Management is difficult and primarily draws upon ensuring good sleep hygiene and assessing for other potential causes or factors that might exacerbate the sleepiness.[69] A single-arm, open label, pilot study investigating the treatment of 20 patients with dementia with Lewy bodies and hypersomnia with armodafinil reported improvements in sleepiness, neuropsychiatric symptoms, and carer quality of life.[20] An open label trial of methylphenidate for gait dysfunction in 17 patients with Parkinson's disease[114,115] reported improvements in excessive sleepiness as a secondary outcome; however, sleepiness has not been assessed as a primary efficacy outcome in patients with Parkinson's disease or Lewy body dementia in any clinical trials. Other treatments, such as atomoxetine, sodium oxybate, istradefylline, and caffeine have been investigated for sleepiness in patients with Parkinson's disease, but evidence to support their efficacy in this patient population or those with Lewy body dementia remains insufficient.[116] In patients with Lewy body dementia, memantine did not improve day time sleepiness in a small controlled trial of 42 patients.[112]

Extrapolating from the evidence base in patients with Parkinson's disease and related disorders, management of sleep problems in patients with Lewy body dementia includes attention to sleep hygiene and the avoidance of exacerbating factors. REM sleep behaviour disorder treatment can include clonazepam, melatonin, or potentially memantine. Management of obstructive sleep apnoea is best undertaken by specialist sleep services. Further studies of management strategies for specific sleep disturbances in patients with dementia with Lewy bodies, including REM sleep behaviour disorder and excessive daytime sleepiness, are needed.

Search strategy and selection criteria

We identified clinical trials and intervention studies for patients with Lewy body dementia through bibliographic databases, trials registers, and grey literature. Search terms for identification of these studies included (Lewy OR Park*or Parkinson) and dementia from Jan 1, 1990 to Feb 13, 2019. We prioritised articles published in the past five years. Older articles for citation were chosen for their historical value, importance, ease of access, and timeliness. At least two reviewers J-PT, IGM, JTO'B independently assessed search results for inclusion by title and abstract with papers reviewed in full if patients had a diagnosis of dementia with Lewy bodies, Parkinson's disease dementia, or Lewy body dementia (or were the caregivers of patients with these diagnoses) and were relevant. We also examined reference lists of relevant studies and previous systematic reviews. In addition, we also sought input from members of the Delphi expert consensus panel for any missing literature and relevant trials in patients with Alzheimer's disease and those with Parkinson's disease and papers pertinent to Lewy body dementia symptom cause and epidemiology.

Conclusions and future directions

In this Review, we have summarised the new evidence base for pharmacological and non-pharmacological management of Lewy body dementia. Treatment of any single symptom should not be done in isolation, as benefit in one domain might be gained at the cost of deterioration in another. A multispecialist or interdisciplinary approach is likely to produce the greatest therapeutic gains, although delivery of that might present practical and logistical challenges for health-care services.

Many aspects of Lewy body dementia care need further research (figure)[117] and a major unmet challenge is the paucity of evidence from high-quality, large-scale clinical trials in patients with Lewy body dementia. Given the heterogeneous nature of Lewy body dementia and the different constellations of symptoms with which patients can present, trial design and definition of outcome measures remain problematic and need to be prioritised and agreed upon with the regulatory bodies before large trials are embarked upon. We also need to improve our understanding of the underlying molecular mechanisms behind the disease and to identify novel targets for therapeutic intervention. Inclusion of Lewy body dementia in formal diagnostic classifications, such as DSM-5 and ICD-11, is a substantial step forward, which is expected to drive interest in developing therapeutics for these conditions (table 4). International strategic efforts, such as the European Dementia with Lewy Bodies Consortium

and the US-based Lewy Body Dementia Association Research Centres of Excellence network, are also providing important research infrastructure to support such work, and resources need to be directed into developing and strengthening these collaborative efforts. The scale of costs and unmet needs in patients with Lewy body dementia is high and the management is complex. However the potential benefits of properly managing Lewy body dementia and its wide array of symptoms are substantial.

Contributors

J-PT and IGM directed the Delphi process, with DW and BFB contributing as experts. J-PT produced the first draft of the manuscript, including the tables, with assistance from IGM and JTO'B. All authors contributed equally to revising and rerevising the manuscript, and all authors approved the final submission.

Declaration of interests

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For more on the **Lewy Body Dementia Association Research Centres of Excellence** see https://www.lbda.org/rcoecenters

For more on the **clinical guidelines** see https://research.ncl.ac.uk/diamondlewy/

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