New evidence on the management of Lewy body dementia

Dr John-Paul Taylor PhD; Professor Ian Grant McKeith, FMedSci; Professor David Burn FMedSci, Professor Brad Boeve, M.D.; Professor Daniel Weintraub, M.D.; Ms Claire Bamford, MSc; Professor Louise Allan PhD; Professor Alan Jeffrey Thomas; Professor John Tiernan O’Brien FMedSci

1. Institute of Neuroscience, Biomedical Research Building, Campus for Ageing and Vitality, Newcastle University, Newcastle upon Tyne NE4 5PL, UK
2. Department of Neurology, Mayo Clinic, Rochester, MN, USA
3. Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA.
4. Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, PA.
5. Parkinson’s Disease and Mental Illness Research, Education and Clinical Centers (PADRECC and MIRECC), Philadelphia Veterans Affairs Medical Center, Philadelphia, PA
6. Institute of Health and Society, Biomedical Research Building, Campus for Ageing and Vitality, Newcastle University, Newcastle upon Tyne NE4 5PL, UK
7. University of Exeter Medical School, South Cloisters Building, St Luke’s Campus, Heavitree Road, Exeter, Devon EX1 2LU
8. Department of Psychiatry, University of Cambridge School of Clinical Medicine, Box 189, Level E4 Cambridge Biomedical Campus, Cambridge CB2 0SP, UK

* Corresponding author
Abstract
Dementia with Lewy bodies and Parkinson’s disease dementia, jointly known as Lewy body dementia (LBD), are common neurodegenerative conditions. Patients with LBD present with a wide range of cognitive, neuropsychiatric, sleep, motor, and autonomic symptoms. The expression of these varies between individual patients, and over time. Treatments may benefit one symptom, but at the expense of worsening another, making management difficult. Often symptoms are managed in isolation and by different specialists, which undermines high quality care.

Clinical trials and meta-analyses now provide an improved evidence base for the treatment of cognitive, neuropsychiatric and motor symptoms in LBD, in addition to which expert consensus opinion supports the application of treatments from related conditions such as Parkinson’s disease (PD) for the management of, for example, autonomic symptoms. There remain however clear evidence gaps and there is a high need for future clinical trials focused on specific symptoms in LBD.

Introduction
Lewy body dementia (LBD), a term which comprises both dementia with Lewy bodies (DLB) and Parkinson’s disease dementia (PDD), represents the second most common cause of neurodegenerative dementia.\(^1\)-\(^3\) DLB accounts for 4.2–7.5% of cases of dementia in clinic-based studies\(^1\),\(^2\), and PDD is a frequent outcome for patients with PD, with up to 80% of patients affected in the long term.\(^4\) Consensus clinical diagnostic criteria have been proposed for both DLB\(^3\) and PDD,\(^5\) and the relationship between the two disorders remains to be clarified. They likely represent different points along a Lewy body disease continuum with pathological and genetic overlap\(^6\),\(^7\) and currently are demarcated clinically from one another using the “one-year rule”, based on the temporal onset of motor relative to cognitive symptoms.\(^3\)

DLB and PDD are complex and heterogeneous disorders; patients present with a wide range of cognitive, neuropsychiatric, sleep, motor and autonomic symptoms.\(^3\),\(^5\) There have been guidelines outlining some treatment options for DLB and PDD (e.g.\(^8\)-\(^10\)), but there is no comprehensive guide to management. Treatment of LBD has particular challenges. Symptoms are expressed variably between patients and 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 DLB and PDD in DSM-5 and ICD-11 and the development
of diagnostic toolkits to improve case detection there is a clear need for an inclusive, and standardised, management approach for LBD to improve care and outcomes.

Up to now, the evidence base for treatments in LBD has been limited. However, additional trials now allow for robust systematic and meta-analytic reviews of the evidence, and there is new evidence, for example, for the treatment for symptoms such as parkinsonism and daytime somnolence. Thus a review focussed on the clinical management of LBD is timely and appropriate.

There remain some gaps, for example, there are few data focussed on how to manage autonomic and sleep symptoms in LBD. These non-motor symptoms are evident in advanced PD and therefore drawing upon the wider evidence base in PD to inform best practice in LBD is appropriate. Similarly there is more interventional trial data in AD for cognitive and neuropsychiatric symptoms. In this review, to address these gaps, we include independent opinion developed from a Delphi consensus process (described in detail in Appendix) drawing upon expert clinical experience and data from related disorders such as AD and PD. We focus on the progress made in bringing these elements together to provide a basis for a comprehensive management approach to LBD and present our management review in a problem orientated format, covering the key symptom domains of cognitive impairment, neuropsychiatric symptoms, motor features before moving to autonomic and sleep symptoms, which have often been neglected previously and identify key evidence gaps and areas for future consideration including suggestions of future treatment trials for specific symptoms.

**Cognitive Impairment**

Attention, executive and visuo-perceptual abilities are disproportionately affected in LBD compared to naming and memory, with variations in cognitive function (cognitive fluctuation) a key feature and a core symptom for DLB diagnosis. Systematic reviews and meta-analyses found that the cholinesterase inhibitors (ChEI) donepezil (6 trials in both and 2 in) and rivastigmine (5 trials in and 2 in) were similarly effective in both DLB and PDD for improving cognition. Positive impacts on activities of daily living and caregiver burden were also found. One meta-analysis suggested rivastigmine was also associated with reduced mortality in LBD, although this effect disappeared with a trial sequential analysis. Both drugs are recommended as first line treatment in DLB by the United Kingdom National Institute for Health and Care Excellence. Donepezil is licensed for the treatment of DLB in Japan, and rivastigmine for PDD in the USA and some European countries. Evidence of the efficacy of galantamine in LBD is sparse as there are only open-label trials supporting its use and these are of lower quality.
Typically the choice of ChEI is influenced by ease of administration, side effect profile, presence of comorbidities, dose titration regime, cost, care-giver preference and previous clinical experience.\textsuperscript{21} Rivastigmine may be associated with more adverse events in both PDD and DLB than donepezil\textsuperscript{14,15} although has a transdermal patch formulation which, in PDD, appears to have less gastrointestinal side effects than oral rivastigmine.\textsuperscript{22} An open-label study of seven patients with LBD supported the benefit of high-dose ChEIs\textsuperscript{23} although this was at the cost of increased side effects. An absence of improvement should not be a reason for discontinuation of ChEIs, as patients with LBD are less likely to deteriorate whilst taking them.\textsuperscript{14} There are no controlled trials of ChEI withdrawal, though an open-label trial of 19 LBD patients found that sudden withdrawal may be associated with deterioration in both cognition and neuropsychiatric symptoms.\textsuperscript{24}

Studies of memantine show that it is well tolerated in LBD, but evidence for efficacy remains mixed.\textsuperscript{14,15} Two major 24-week, double-blind, randomised control trials\textsuperscript{25,26} which included both DLB and PDD patients (271 patients in total) reported significant overall clinical global impression of change (CGI-C) improvements.\textsuperscript{14} However there was no consistency between studies in terms of which symptoms improved or whether DLB or PDD sub-groups benefited more from the drug.\textsuperscript{14} Posthoc analyses of data from 51 patients in one study\textsuperscript{25} found the improvement in CGI-C scores was related to improvements in attention.\textsuperscript{27} Other posthoc analyses from this trial and others have reported improvements in patient quality of life and a reduction in care-giver burden.\textsuperscript{28,29} A 36 month open label, follow-up study of 42 patients from one centres in one of the memantine studies\textsuperscript{25} suggested that a positive response to memantine was associated with improved survival in LBD although the small sample size may have introduced biases and precluded analysis of any covariates.\textsuperscript{30} Dosing, side effects and the use of different ChEI and memantine in LBD are described in table 1.

In summary, there is good evidence for the efficacy of rivastigmine and donepezil in LBD, but better controlled studies of galantamine are needed to draw conclusions about this agent. Memantine may have some benefits, but further studies with larger numbers of DLB and PPD subjects are needed. It is also unclear whether memantine should be used as a monotherapy or whether it should be combined with ChEI, as only one of the two trials of memantine allowed concomitant ChEI use.\textsuperscript{25}
Neuropsychiatric symptoms

Patients with LBD present with a variety of neuropsychiatric symptoms, including visual hallucinations, hallucinations in other modalities, systematised delusions, apathy, aggression, anxiety and depression. Symptoms may not always need treatment, for example, hallucinations may be regarded neutrally, or as comforting or pleasurable, and have limited or no impact on psychosocial function. Patients frequently lack insight or awareness into the extent of their neuropsychiatric symptoms, so including informant information in the clinical assessment is essential. Rating scales, e.g. for visual hallucinations, can provide a useful framework for assessing severity and frequency of symptoms and monitoring treatment response. Scales can either be specific to a symptom or composite; the latter which aggregate several symptoms, such as the Neuropsychiatric Inventory, have tended to be used as measures in clinical trials in LBD (e.g. 25,26,35,36).

As for other dementias, non-pharmacological interventions are usually advocated as first line treatment for neuropsychiatric symptoms, though the evidence base for these in LBD is limited, with very few randomised controlled trials. In this context, application of approaches shown to be effective in AD may also be helpful in LBD, although there is no specific consensus as to if or how they may be adapted. Electroceutical approaches are increasingly being investigated in LBD; improvements in depression have been reported with electroconvulsive therapy in DLB in a number of case series (22 patients in total) and one case series of six DLB patients suggested rapid rate transcranial magnetic stimulation reduced depression scores significantly. In contrast, randomised sham-control trials of transcranial direct current stimulation in LBD have not shown benefits for cognitive remediation (42 patients) or hallucinations (36 patients). There is preliminary evidence suggesting that DBS (deep brain stimulation) to the nucleus basalis of Meynert in 6 PDD patients may improve neuropsychiatric outcomes and this warrants further investigation.

If symptoms are severe or distressing, or non-pharmacological measures have failed, then pharmacotherapy may be indicated. Studies of donepezil and rivastigmine have found improvements in composite scores of neuropsychiatric symptoms in LBD, although identifying specific symptom benefit is more challenging, as these are not frequently reported in studies. Scores which aggregate apathy, delusions, depression and hallucinations have indicated a benefit in DLB from donepezil but not rivastigmine. One systematic review suggested that donepezil, but not rivastigmine, may have specific benefits for delusions, hallucinations and cognitive fluctuations in DLB. Conversely in PDD, donepezil does not appear beneficial for hallucinations, hostility,
suspiciousness or unusual thought content. Interpretation is difficult, but considering findings collectively, expert opinion from our Delphi consensus group as well as national guideline bodies (e.g.10) have endorsed the use of rivastigmine and donepezil for neuropsychiatric symptoms. Open-label trial data of galantamine provides tentative evidence of improved cognitive fluctuation, sleep and psychiatric symptoms in DLB; and hallucinations, anxiety, apathy and sleep symptoms in PDD and thus could be an alternative if other ChEIs aren’t tolerated. There is no consistent evidence of a clear or significant effect of memantine on neuropsychiatric symptoms in LBD.14,15

If psychotic symptoms remain problematic despite ChEI or memantine treatment, then a trial of an antipsychotic agent may need to be considered although this needs to be balanced against a scarcity of documented efficacy of these agents when assessed systematically and the high risk (up to 50%) of severe sensitivity reactions with antipsychotics in LBD which can be life-threatening and a longer term elevated mortality risk.14,15,16 If prescribed in LBD, there needs to be a high degree of caution in their use.17 There is no evidence to favour any one anti-psychotic drug in LBD. Quetiapine appears to have the least side effects although evidence for its efficacy in PD and LBD is insufficient.14 Clozapine, effective in PD psychosis may also help in LBD, although again specific trials for use of this agent in the latter are absent. Pimavanserin, a new antipsychotic with specific inverse agonism at the 5HT2A receptor, and available in US although not Europe, has demonstrable antipsychotic properties in PD psychosis; its efficacy and safety remain to be formally evaluated in LBD.

Depression occurs in about one third of LBD patients and is often accompanied by anxiety. Pharmacological treatments for depression and anxiety in LBD have not been adequately evaluated, with the highest level of evidence from a small randomised control trial of citalopram in 14 DLB patients which failed to demonstrate efficacy and found high levels of adverse effects.52 Higher quality trial evidence exists for venlafaxine, a selective serotonin norepinephrine reuptake inhibitor (SNRI) in PD whereas data for selective serotonin reuptake inhibitors (SSRIs) and tricyclics are less conclusive.9 Given the sensitivity of LBD patients to anticholinergic side effects the expert consensus view is that antidepressants known to have these effects are best avoided.

In summary, there is a dearth of studies of non-pharmacological management of neuropsychiatric symptoms in LBD and more are needed. ChEI may help, but further studies focussing on which particular symptom domains are most likely to improve are needed. The impact of memantine on neuropsychiatric symptoms needs to be examined in large controlled studies. Studies of
pimavanserin in LBD for psychosis, and controlled trials of antidepressants for depression, are needed.

**Motor Symptoms**

Up to 85% of DLB subjects experience motor difficulties\(^3\) although rest tremor is less prevalent than in PD\(^5^3\) and motor symptoms may be less treatment-responsive in DLB.\(^5^4\) In contrast, in PDD parkinsonism 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.\(^5^5,5^6\) Thus the management of motor symptoms can differ markedly between DLB and PDD (table 2).

There have been no double-blind controlled trials of levodopa therapy in DLB, or of whether changing to a levodopa monotherapy regime in PDD is beneficial. However, open-label studies suggest that both acute and chronic levodopa monotherapy use can help motor function and reduce tremor in DLB and PDD.\(^5^4,5^7\) Improvements in motor function appear greater in PDD than DLB (65-70% vs. 32-50%)\(^1^4\) and in the latter approximately one in three levodopa treated patients will experience psychotic symptoms.\(^5^7\) A meta-analysis of four double-blind randomised controlled trials in 1,068 PD patients,\(^5^8\) and a Phase II trial in 158 early stage DLB patients, have reported a motor improvement with zonisamide, an anti-epileptic agent, when used as adjunctive treatment to levodopa.\(^1^9\)

In terms of non-pharmacological approaches, DBS is an effective treatment for motor symptoms in selected PD patients.\(^5^9\) However pre-existing cognitive impairment is a contraindication and DBS, in itself, may subtly impair cognitive function.\(^6^0\)

In summary, open label studies show some motor benefit for levodopa therapy in LBD, so this can be used for motor symptoms, though adverse effects including psychosis may occur in up to third. Further double-blind studies are indicated, both of levodopa and also newer agents like zonisamide.

**Falls**

Falls are common in LBD and associated with significant morbidity and mortality.\(^6^1,6^2\) Contributors to fall risk in LBD are typically multifactorial including parkinsonism, dysautonomia, and frailty.\(^6^2\)

Physiotherapy has a clear evidence base in PD and can help improve balance, power and flexibility, as well as enhance mobility, all factors which can decrease the risk of falls and improve functional
independence.\textsuperscript{62,63} Unfortunately, there is no evidence specifically in LBD, and studies are needed especially as cognitive impairment and other comorbid symptoms could adversely influence engagement with therapy.

**Autonomic dysfunction**

There are a wide range of autonomic symptoms in LBD, and these are associated with more rapid disease progression and shorter survival.\textsuperscript{64} Despite the prominence and impact of these symptoms, there is no established evidence base for their treatment in LBD so opinion on best management is largely drawn upon the more established evidence base in PD.\textsuperscript{8,65,66}

**Orthostatic hypotension**

Fludrocortisone and midodrine have been suggested as useful in PD\textsuperscript{8,9,67} although there are no LBD data and only limited data in PD (See table 3), and both agents require specific monitoring with the availability of midodrine being restricted in some countries. Droxidopa is licensed in some countries (e.g. United States) for orthostatic hypotension in PD. Whilst no data exist in LBD, given its low side effect profile\textsuperscript{68} use of droxidopa in LBD may be an option where available. Further details on these drugs are described in table 3. The importance of treating orthostatic hypotension in LBD is highlighted by the link between orthostatic hypotension and attention-executive impairments in PD raising the possibility that treatment of the former may have benefits beyond the hypotension in itself, and controlled trials are needed to assess this.\textsuperscript{69}

**Gastrointestinal dysfunction**

The full extent of the alimentary tract can be affected in LBD with symptoms ranging from sialorrhoea to dysphagia, gastroparesis and constipation.\textsuperscript{70,71} In PD the prevalence of excessive drooling has been reported in controlled studies to range from 10 to 81% with significant negative impacts on quality of life and social and emotional function.\textsuperscript{72} Drooling may be related to inefficient swallowing which leads to high rates of aspiration (>80%) in LBD.\textsuperscript{73} A randomised control trial exploring interventions to prevent aspiration including 132 PDD with dysphagia found lower rates of aspiration as evidenced on videofluoroscopy, with honey thickened fluids (59% compared to 64-69% with other interventions).\textsuperscript{74} Another study noted improved swallowing function objectively in 48 LBD patients referred for videofluoroscopy with carbonated liquids.\textsuperscript{73} Whether such interventions have clinically meaningful impacts (e.g. prevention of aspiration pneumonia) remains to be resolved. A randomised cross-over trial of glycopyrrolate (1 mg, twice or three times a day) in 23 PD patients found that 9 of patients had a clinically relevant improvement in sialorrhea\textsuperscript{75} over a four week
period; however the efficacy of this agent in LBD is not known. An evidence based review of botulium toxin injection to the salivary glands appears effective and safe in PD\textsuperscript{72}, and thus by extension in LBD, though repeated injections are needed.

Gastric emptying appears even slower in DLB than in PD\textsuperscript{76} and correlates with severity of motor impairment.\textsuperscript{77} Impairments in gastric motility can lead to fullness, reflux and excess eructation and importantly impact on drug absorption. Management includes avoidance of high fat foods, drinking during meals as well as walking after meals plus an awareness that dopaminergic medications can exacerbate gastroparesis.\textsuperscript{70,78} Domperidone, a peripheral dopamine blocker may have efficacy in the treatment of gastroparesis in PD\textsuperscript{78,79} but there are significant concerns with regard to cardiotoxicity and the risk of QT prolongation so it is not available in all countries, e.g. not in the United States.

Constipation is one of the most common symptoms in LBD.\textsuperscript{80} Prolonged colon transit time and pelvic floor dyssynergia have been implicated as causes\textsuperscript{70,71}. Constipation can also be exacerbated by opiates and anticholinergics,\textsuperscript{80,81} poor fluid intake, reduced fibre intake and sedentary behaviour. Polyethylene glycol (macrogrol) and psyllium increase bowel frequency in PD\textsuperscript{82,83} and along with dietary modification, increased fluid intake and suppositories are advocated as treatments for constipation in LBD (expert opinion). Stronger laxatives, suppositories or enemas may be needed in severely affected patients.\textsuperscript{66} Lubiprostone, a bicyclic fatty acid which activates type-2 chloride channels (ClC-2) in the gut and enhances intestinal secretions has been shown to have short term benefits in PD.\textsuperscript{80,84}

In summary, controlled trial evidence supports the use of thickened liquids to reduce aspiration in LBD, but studies of interventions to help other symptoms such as constipation are needed. Until then, the evidence-base for PD can be used to inform management of gastrointestinal symptoms in LBD.

\textbf{Urinary symptoms}

Urinary symptoms in LBD are very common and include urgency, frequency and incontinence.\textsuperscript{85} Despite this, there are no LBD specific trials with data coming instead from PD. In this context, a double blind randomised controlled trial of solifenacin over 12 weeks in 23 PD patients with urinary frequency, incontinence and nocturia reported significant reduction in micturition frequency.\textsuperscript{86} However anti-muscarinics (including solifenacin) have high levels of adverse effects including cognitive\textsuperscript{87} which may be a contraindication for their use in LBD. An alternative drug without
cognitive side effects is mirabegron, a beta 3-adrenoceptor agonist; a retrospective cohort study which considered 50 patients between 2012 and 2017 suggested this agent was well tolerated in PD and offered benefit.88

Excess sweating
Hyperhidrosis is reported by two thirds of PD patients,89 is associated with disease severity and may be associated with motor fluctuations90,91 although how common it is in LBD is not known. It has significant social and emotional impacts and may occur with other autonomic disturbances.89 There are no treatment trials but there was a consensus from our Delphi panel group that patients may benefit from the use of loose fitting clothing, cotton bedding for night sweats and antiperspirants as well as avoidance of triggers e.g. alcohol, spicy foods, hot rooms. For those with dyskinesias and hyperhidrosis, reducing dopaminergic medication should be considered.89,91

Nocturnal sleep disturbances
Sleep disturbances in LBD can be severe and include insomnia, sleep fragmentation, REM sleep behaviour disorder (RBD), motor-related sleep disturbances, restless legs syndrome (RLS), periodic limb movements, obstructive sleep apnoea (OSA) and excessive daytime sleepiness.3 Most of the evidence base for the management of these comes from studies conducted in PD and idiopathic RBD rather than in LBD. Management begins with education on good sleep hygiene, and avoidance of any drugs that may affect sleep or alertness.8

For insomnia, meta-analysis of melatonin from 9 randomised control trials across a range of neurodegenerative conditions such as PD (including a study of 40 patients) found improvements in subjective sleep quality although not objective measures and appears to be well tolerated.92,93 Z-drugs (non-benzodiazepine) such as eszopiclone, zopiclone, or zolpidem, have no evidence base in LBD but expert consensus opinion suggested that they may be considered for short term treatment of insomnia if there is no evidence of sleep apnoea, with the caveat that they may have negative impacts on cognition, daytime sleepiness and increase the risk of fractures and falls.94 If sleep disturbances occur secondary to nocturnal parkinsonism, the use of long-acting levodopa preparations has been advocated.95 Randomised controlled studies have demonstrated that dopaminergic medications such as ropinirole, pramipexole, and rotigotine have efficacy in treating idiopathic RLS.95 but there is no clear evidence for the management of RLS in LBD. A meta-analysis of 35 studies in 7333 participants with RLS found that gabapentin may be equally effective.96 However all of the above agents would need to be used with caution in LBD given their attendant cognitive
side effects (expert opinion). OSA may occur in up to a third of patients with LBD and is often unrecognised. Patients may experience excessive daytime somnolence, worsening cognitive function, unrefreshing sleep, and early morning headaches. Pauses in breathing whilst asleep and regular snoring raise the suspicion of this particular sleep symptom and there are a number of associated risk factors (overweight, male, smoker, on sedatives, alcohol use, reflux and anatomical considerations e.g. collar size >43 cm or 17 inches) which should be assessed for.

RBD is a parasomnia manifested by recurrent dream enactment behaviour that includes movements mimicking dream content and associated with an absence of normal REM sleep atonia. Between half to three quarters of patients with LBD experience RBD and it is a core symptom for the diagnosis of DLB. It can antedate the onset of PD and LBD by many years or may emerge during the dementia phase. However it is important to recognise that obstructive sleep apnoea, narcolepsy, as well as nocturnal arousal events coupled with confusion may mimic RBD. Determining the origin of sleep disturbance in LBD may therefore require polysomnography. Delphi consensus opinion highlighted a number of non-pharmacological strategies which have been tried in RBD in LBD including, for example, lowering bed or placing mattress on the floor, removal of potentially dangerous objects in the bedroom such as sharp or glass objects, or if necessary, that bed partners to sleep separately from the patient. Some medications may worsen RBD (e.g. antidepressants) and in terms of active treatment, retrospective case series in idiopathic and secondary RBD support the use of clonazepam, though caution is needed in people with LBD who are more prone to gait disturbance, sleep apnoea, marked cognitive impairment and are at significant risk of falls (see for discussion). Pramipexole has been evaluated in observational studies as potentially effective for treating RBD in PD but is associated with an increased risk of psychosis. Melatonin (3 mg to 12 mg before bedtime), has a better side effect profile, and has an evidence base in the treatment of idiopathic RBD. Another option is memantine; this agent decreased physical activity during sleep over 24 weeks in a controlled study of 20 LBD patients, while patients in the placebo group (n=22) worsened.

Excessive Daytime Sleepiness
This is common in LBD and 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 which might exacerbate the sleepiness. An open label trial of 20 DLB patients with hypersomnia with armodafinil reported improvements in sleepiness, neuropsychiatric symptoms and carer quality of life. A trial of methylphenidate for gait
dysfunction in PD\textsuperscript{110,111} found improvements in excessive sleepiness as a secondary outcome, but there are no studies assessing sleepiness as a primary efficacy outcome measure in PD or LBD. Other treatments such as atomoxetine, sodium oxybate, istradefylline and caffeine have been investigated for sleepiness (in PD) but evidence to support their efficacy remains insufficient at present.\textsuperscript{112} In LBD memantine did not improve day time sleepiness in a small controlled trial of 42 patients.\textsuperscript{108}

In summary, extrapolating from the evidence base in PD and related disorders, management of sleep problems in LBD includes attention to sleep hygiene and the avoidance of exacerbating factors. RBD treatment may include clonazepam, melatonin, or potentially memantine. Management of OSA is best undertaken by specialist sleep services. Further studies of management strategies for specific sleep disturbances in DLB, including RBD and excessive daytime sleepiness are needed.

Conclusions and future directions
This review has summarised the evidence base for pharmacological and non-pharmacological management of LBD which can inform patient management. It is important that treatment of any single symptom should not be done in isolation, as benefit in one domain may sometimes be gained at the cost of deterioration in another. A multi-specialist/ interdisciplinary approach is likely to produce greatest therapeutic gains, although delivery of that may present practical and logistical challenges for health care services.

There are many areas which need further research (table 4)\textsuperscript{113} and a major unmet challenge is the relative paucity of evidence from high quality, large scale clinical trials in LBD. Given the heterogeneous nature of LBD 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 and to identify novel targets for therapeutic intervention. Inclusion of LBD in formal diagnostic classifications such as DSM-5 and ICD-11 is a significant step forward as this is expected to drive interest in developing therapeutics for these conditions which are needed in equal measure across all of the symptom domains discussed above. It appears that there already is an increase in trial activity in LBD (table 5). International strategic efforts such as European DLB consortium (E-DLB) and the US based LBD Research Centres of Excellence networks (https://www.lbda.org/rcoecenters) are also providing important research infrastructure to support such work and resources need to be directed into
developing and strengthening these. The scale of costs and unmet need in LBD is high, and although LBD management may be complex, the potential benefits are also substantial.

**Search strategy and selection criteria**
The full search and paper selection criteria for interventions in LBD are described in the Appendix. In brief, clinical trials and intervention studies in LBD were identified as described in\(^1^4\) and \(^1^8\) through bibliographic databases, trials registers, and gray literature. Search terms for identification of these studies included (Lewy OR Park* /parkinson) and dementia and we extended these searches from our original systematic reviews to 13\(^{th}\) of February 2019. In these two systematic reviews, at least two reviewers independently assessed search results for inclusion by title and abstract with papers reviewed in full if participants had a diagnosis of DLB, PDD, or LBD (or were the caregivers of patients with these diagnoses) and were relevant. Reference lists of relevant studies and previous systematic reviews were also examined. In addition, for the purposes of the present review we also sought input from members of the Delphi expert consensus panel (listed in Appendix) for any missing literature as well as relevant trials in AD and PD and papers pertinent to LBD symptom aetiology and epidemiology. We prioritised articles published in the past five years (from 1\(^{st}\) January 2013) as well as systematic reviews and meta-analyses where these were available. Older articles for citation were chosen for their historical value, importance, ease of access, and timeliness.

**Author’s contributions**
John-Paul Taylor and Ian McKeith directed the Delphi process which is described in the Appendix, with Dan Weintraub and Brad Boeve contributing as experts.

John-Paul Taylor produced the first draft of the manuscript, including the tables, with assistance from Ian McKeith and John O’Brien.

All authors contributed equally to revising and re-revising the manuscript and all authors approved the final submission.

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References


Appendix

Section I: Description of search methods

The review was underpinned by two major systematic reviews conducted by the Diamond-Lewy study group focussing on pharmacological\(^1\) and non-pharmacological\(^2\) management strategies in Lewy body dementia (LBD). Details of the search strategy, study selection and data synthesis as described in Stinton et al.\(^1\) and Connor et al.\(^2\) are described below.

**Pharmacological management strategies\(^1\)**

**Search Strategy**

Studies were identified through bibliographic databases, trials registers, and gray literature (see the registered protocol for full details). Reference lists of relevant studies and previous systematic reviews were also examined, and input was sought from experts on Lewy body dementia. We used the keywords “Lewy or parkinson” and “dementia,” conducting searches until March 2015, without restrictions on time or language.

**Study Selection**

Titles and abstracts were screened independently by four of the authors, with non-English language papers screened by native speakers. Discrepancies were resolved through discussion between screeners. Potentially relevant studies were obtained in full and examined in detail by the first author against the following criteria: 1) participants had a diagnosis of DLB, PDD, or Lewy body dementia (or were the caregivers of patients with these diagnoses); 2) studies examined pharmacological strategies; and 3) outcome measures and scores were specified. No restrictions were placed on study design, but opinion papers were excluded.

**Data Extraction**

Data were extracted by two reviewers and recorded in an Excel spreadsheet. We collected information related to participant demographic characteristics, selection criteria, study design, management strategies, outcome measures and scores, adverse events, and withdrawals.

**Data Synthesis**

Studies were grouped and analyzed according to pharmacological strategy. For each strategy, studies of the highest level of evidence were included in the review. Classification of level of evidence was determined using guidelines from the Oxford Centre for Evidence-Based Medicine (https://www.cebm.net/2016/05/cebm-levels-of-evidence).

**Methodological Quality**

Methodological quality was assessed by three of the authors using the Quality Assessment Tool for Quantitative Studies (QATQS, www.ephpp.ca/tools.html)\(^3\), which was developed to assess quality across study designs, aiding consistency and clarity of reporting. The QATQS examines selection bias, study design, confounders, blinding, data collection methods, withdrawals, and dropouts. Domains are rated as being of weak, moderate, or strong quality, which feed into an overall rating of study quality. The reliability and validity of the QATQS have been demonstrated.\(^4\)

**Statistical Analysis**

Meta-analysis was conducted using the Cochrane Collaboration’s RevMan, version 5.3 (www.tech.cochrane.org/revman), employing the inverse variance method. Heterogeneity was assessed using the chi-square and I\(^2\) statistics and considered significant with p values <0.10 for chi-square and >40% for I\(^2\). We employed random-effects models when there was significant study heterogeneity and fixed-effect models when heterogeneity was not significant. Missing data were sought from study authors; for data that were not
obtainable, values were estimated using methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (www.cochrane-handbook.org). We estimated risk ratio with 95% confidence intervals for dichotomous outcomes and weighted mean difference or standardized mean difference with 95% confidence intervals for continuous outcomes. Descriptive summaries were provided when studies could not be combined.

Non-pharmacological management strategies review

Search strategy

The search identified studies through bibliographic databases, trial registers, and the grey literature. Bibliographic databases and trial registers included the following: Medline (1946–present); PreMedline, PubMed; EMBASE (1974–present), Scopus, Web of Science (1900–current); PsychInfo (1806–present); CINAHL (1981–present); Cochrane libraries: Cochrane database of systematic reviews (2005–October 2016), Cochrane central register of controlled trials (August 2016), Cochrane Methodology register (3rd–Quarter 2012); other EBM databases: ACP journal club (1991–September 2016), Database of Abstracts of Reviews of Effects (1st-quarter 2015), Health technology assessment (3rd-quarter 2016), and NHS economic evaluation (1st-quarter 2015); Ageline (1978–present); ALOIS; AMED (Allied and Complementary Medicine; 1985–present); PEDro (Physiotherapy Evidence Database; 1992–present); Social work Abstracts (1968–present); and the National Association of Social Workers (NASW) clinical register (14th edition). The grey literature was searched using such resources as SIGLE (System for Information on Grey Literature in Europe), NTIS (National Technical Information Service) database, and PsychEXTRA (1908–present).

The search strategy used only population and intervention terms to maximise the likelihood of identifying relevant studies (comparator and outcome terms were not used). The population was people with Lewy body dementia or their carers. This was identified using the search terms: [(Lewy OR Park*) AND Dementia]. Interventions were any non-pharmacological treatment and identified using a wide range of terms: (activit*, acupuncture, alternative, animal, aromatherapy, art therapy, assisted, balance, behav*, bicycle, calisthenics, carer intervention, caregiver intervention, CBT, Chi gong, cognit*, cognitive behavioral therapy, cognitive behavioural therapy, counsel*, creative arts, dance, dancing, diet, direct current stimulation, drama, ECT, educat*, electroconvulsive therapy, enhance*, environmental intervention, environmental modification, exercise, flexibility, humor therapy, humour therapy, hydrotherapy, intervention*, leisure, light therapy, management, martial arts, massage, meditation, Montessori, multisensory, music, non-pharm*, nonpharm*, nutrition, occupational therapy, pet therapy, physical activity, physical therapy, physiotherapy, pilates, psychoeducation, psychol*, psychosocial, psychotherapy, Qi gong, reality orientation, recreation*, reminiscence, resistance training, run*, sensory, simulated presence, stimulation, Snoezelen, support*, support group*, swim*, tai chi, therap*, therapeutic activity, TMS, training, training carers, training caregivers, transcranial magnetic stimulation, treatment*, validation, weight training, yoga). Searches were conducted on 30 October 2016.

In addition to bibliographic database searches, the reference lists of papers included in the review and previous systematic reviews on both Lewy body dementia and non-pharmacological interventions were checked for relevant papers. Advice was also sought from experts in the field.

Study selection

Two reviewers independently assessed search results for inclusion by title and abstract. All articles deemed relevant by either reviewer were obtained in full. Both reviewers then independently evaluated full-text articles for inclusion. Any disagreements were resolved through discussion or, if necessary, with a third reviewer.

Data extraction

Two reviewers independently extracted relevant data from publications using a standardised form. This included participant details (e.g. demographics, number, recruitment, clinical context, dementia severity), intervention type, study design, measures, and results. Qualitative data were also collated.

The primary outcomes were measures of cognition, function, neuropsychiatric symptoms, and motor symptoms. The secondary outcomes were measures of any other clinically relevant outcomes, such as quality of life, carer burden, financial costs, other symptoms (sleep or autonomic disturbances), and objective endpoints (e.g.
falls, hospitalisation, institutionalisation, mortality). Secondary outcomes also included the perceived acceptability of treatments, reported side effects, and dropout rates (a measure of treatment acceptability).

Quality assessment

Two reviewers independently assessed study quality and risk of bias using standardised tools. These included the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies (http://www.ephpp.ca/tools.html) and the NICE Methodology Checklist: Qualitative Studies (https://www.nice.org.uk/process/pmg10/). Any disagreements were resolved through discussion.

References
Section II: Summary of expert consensus panel approach and method

Structured expert consensus approaches such as the Delphi method can provide a complimentary framework to evidence based medicine for defining treatment approaches particularly in areas where there is an absence of high quality evidence.\(^1\)\(^2\) Typically the process is iterative, with expert feedback provided in successive rounds helping to refine previous statements of practise and best management. It also offers, particularly if administered electronically, advantages in incorporating multiple opinions and managing conflicting perspectives, whilst overcoming challenges of groupthink, as it is done individually and anonymously.\(^2\)\(^3\)

This Delphi expert consensus approach supported key statements in our review and also underpins the development of our management guideline and toolkits which are available online at https://research.ncl.ac.uk/diamondlewy/

We took a process led approach:

1) Establishment of the existing evidence base in LBD: as noted in Section I, formal systematic reviews and meta-analysis were conducted to capture all available, recent published information about the pharmacological and non-pharmacological management of LBD.\(^4\)\(^5\)

2) Public-patient workshops: Two public-patient workshops were held with participation of 38 people with LBD and their family/care-givers, with the first event focussing upon identifying best practice in LBD clinical management, based on their own experiences. The emergent themes were developed further in the second event and refined into a set of guiding principles.

3) Using the systematic reviews and public-patient feedback an initial draft of the guidelines was developed by two authors (J-P.T and IGM). Specific statements, framed under symptom domains were created and submitted to an online anonymised online platform for review by our Delphi expert panel. The panel comprised experts in the field (n=26; psychology, geriatrics, psychiatry, neurology, primary care, physiotherapy, nursing, academic experts as well as internationally recognised key opinion leaders), identified through consultation with relevant stakeholder groups and supported by an extensive search of the literature for their publications, and/or the role as keynote speakers on management of LBD at major conferences. The Delphi process was conducted over three rounds. A high level of agreement was sought across the three rounds (85% for rounds 1 and 2 and 75% for round 3). Controversial statements were modified on the basis of feedback and rerun in subsequent rounds or removed. Of 252 original statements, 161 were kept, with 78 of these (48.4%) gaining full consensus panel agreement for inclusion, 52(32.3%) with 90% to 99% consensus agreement and 31 statements (19.3%) agreed by 75% to 89% of the panel. After this process, the guideline statements were re-collated and formulated into one document.

4) Where there was an absence of evidence in our review, we draw upon the statements and the opinion of our Delphi expert group to inform best clinical practise.

References

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