

Dementia with Lewy bodies – diagnosis and treatment

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Summary

Dementia with Lewy bodies (DLB) accounts for 15–20% of all autopsy confirmed dementias in old age. Characteristic histopathological changes are intracellular Lewy bodies and Lewy neurites, with abundant senile plaques but sparse neurofibrillary tangles. Core clinical features are fluctuating cognitive impairment, persistent visual hallucinations and extrapyramidal motor symptoms (parkinsonism). One of these core features has to be present for a diagnosis of possible DLB, and two for probable DLB. Supportive features are repeated falls, syncope, transient loss of consciousness, neuroleptic sensitivity, delusions and hallucinations in other modalities. DLB is clinically under-diagnosed and frequently misclassified as systemic delirium or dementia due to Alzheimer's disease or cerebrovascular disease.

Therapeutic approaches to DLB can pose dif-

ficult dilemmas in pharmacological management. Neuroleptic medication is relatively contraindicated because some patients show severe neuroleptic sensitivity, which is associated with increased morbidity and mortality. Antiparkinsonian medication has the potential to exacerbate psychotic symptoms and may be relatively ineffective at relieving extrapyramidal motor symptoms. Recently there is converging evidence that treatment with cholinesterase inhibitors can offer a safe alternative for the symptomatic treatment of cognitive and neuropsychiatric features in DLB. This review will focus on the clinical characteristics of DLB, its differential diagnosis and on possible management strategies.

Key words: dementia with Lewy bodies; diagnosis; treatment

Introduction

The late recognition of dementia with Lewy bodies (DLB) as a relatively common diagnostic entity has historical roots. Lewy bodies (LB) were first described by Forster and Lewy in 1912 [1] in the brainstem of patients with paralysis agitans (Parkinson's disease). Hassler [2] later described cortical LB in Parkinson's disease (PD), but it was not until 1961 that Okazaki [3] discussed their pos-

sible role in association with dementia. Cortical LB are difficult to detect microscopically with conventional haematoxylin and eosin staining techniques, which is why only a few cases were reported before the nineteen eighties. It was the development of immunocytochemical staining methods with antibodies against firstly ubiquitin and more recently α -synuclein, which made the visualisation

Abbreviations

AD:	Alzheimer's Disease
APOE:	Apolipoprotein E
APP:	Amyloid Precursor Protein
ChE-I:	Cholin Esterase-Inhibitors
CIT:	Carboxymethoxy-Iodophenyl-Tropane
CJD:	Creutzfeldt-Jacob-Disease
COMT:	Catechol-O-Methyl-Transferase
DLB:	Dementia with Lewy Bodies
EPS:	Extrapyramidal Motor Symptoms
HMPAO:	Hexa-Methyl-Propylene-Amine-Oxime

LB:	Lewy Bodies
LN:	Lewy Neurites
MMSE:	Mini Mental State Examination
NPI:	Neuropsychiatric Inventory
PD:	Parkinson's Disease
PDD:	Parkinson's Disease with Dementia
PET:	Positron Emission Tomography
UPDRS:	Unified Parkinson's Disease Rating Scale
SPECT:	Single Photon Emission Tomography
SSRI:	Selective Serotonin Reuptake Inhibitor
VaD:	Vascular Dementia

of cortical LB much easier [4, 5], and promoted research into the spectrum of different LB disorders (e.g. PD with and without dementia, and DLB). After Alzheimer's disease (AD), DLB is now recognised to be the second most common form of degenerative dementia accounting for up to 20% of all elderly cases reaching autopsy [6]. Different interpretations of the relative significance of cortical LB led to different nomenclatures like Lewy body variant of AD [7]; diffuse Lewy body disease [8]; senile dementia of Lewy body type [9] and others. This diversity made comparisons difficult and

was resolved at the first Consensus conference on dementia with Lewy bodies in 1995 where clinical and pathological guidelines were defined [10]. Prospective and retrospective neuropathological studies have subsequently found a high specificity (0.79–0.91) for the clinical diagnosis of probable DLB, however the sensitivity of case detection is lower and more variable (0.22–0.95) [11–13]. Under-diagnoses of DLB remain common, even when consensus criteria are used. The most common misdiagnosis of DLB is AD [11].

Neuropathology and neurochemistry of DLB

DLB shows pathological changes overlapping with AD and PD, although there are important differences [9, 10]. Beta-amyloid and senile plaque formation are common in DLB, but tau-pathology and neurofibrillary tangles are sparse ("plaque only AD") [6]. Antibodies to the protein α -synuclein, revealed α -synuclein aggregates in LB and extensive α -synuclein positive Lewy neurites (LN), which suggest neurobiological links to other synucleinopathies including PD and multiple system atrophy. The physiological function of α -synuclein has not been clarified but is thought to be important in the production of presynaptic vesicles [14]. LB and LN are not unique to DLB, they also occur in PD with a different distribution. In DLB, they can be found in the neocortex, limbic cortex, subcortical nuclei and brainstem [9]. In PD, the majority of intracellular LB are found in pigmented brainstem nuclei, the substantia nigra and are coupled with neural loss and gliosis. Although a few cortical LB can be found in nearly all PD patients [15], they are particularly common in Parkinson's disease with dementia (PDD) a situation where pathological changes are hardly distinguishable from DLB [16]. For a pathological diag-

nosis of DLB, brainstem or cortical LB are the only features considered essential, although LN, Alzheimer pathology, and spongiform changes may also be seen [10].

DLB is associated with profound *dopaminergic* and *acetylcholinergic* neurochemical changes. Striatal dopaminergic loss is severe enough to produce extrapyramidal motor symptoms (EPS), but less pronounced compared with PD and usually not present in AD [17]. Compared to PD, postsynaptic dopaminergic (D2) receptor reduction is greater in DLB and may contribute to the severe adverse effects of dopaminergic antagonists (i.e. neuroleptic sensitivity) [17, 18]. DLB is also associated with profound acetylcholinergic deficits [19–21], showing, compared to AD, less activity of neocortical choline acetyltransferase [19] indicating less presynaptic cholinergic activity, but with more functionally intact muscarinic receptors [20]. This suggests that DLB patients should be responsive to cholinergic enhancement therapy. The genesis of visual hallucinations in DLB has been related to a dopaminergic-cholinergic imbalance, and also to temporal LB density [21, 22].

Clinical features

Core clinical features include fluctuating cognition, recurrent and persistent visual hallucinations, and EPS. Supportive features may increase diagnostic sensitivity and exclusion criteria need to be considered. These features are repeated falls, syncope, transient loss of consciousness, neuroleptic sensitivity, systematised delusions, and hallucinations in other modalities. Depression and REM sleep behaviour disorder have also been suggested as additions to this list [23].

Fluctuating cognition

Fluctuating cognition is an early and prominent symptom in DLB, occurring in 80–90% of patients during the course of the disease. Limited

reliability in detecting and quantifying fluctuation is a major cause of failure to recognise DLB [23]. Two questionnaires [24, 25] have recently been designed to quantify fluctuation. The *One Day Fluctuating Assessment Scale* assesses symptoms during the previous 24 hours and can be administered by a trained interviewer. The *Clinical Assessment of Fluctuation Scale* enquires fluctuation over the preceding month and must be administered by an experienced clinician. Both have shown high correlation with variability of repeated cognitive assessment and delta rhythm slowing of the electroencephalogram [24, 25].

Extrapyramidal motor features

EPS refer to the following clinical features i) bradykinesia of the extremities or face, ii) rigidity of the limbs, iii) resting tremor, and iv) gait disturbance involving shuffling, reduced arm swing and slowness in turning. The *Unified Parkinson's Disease Rating Scale* (UPDRS) motor section [26] can reliably quantify these motor symptoms. EPS are frequent in DLB (70%) and patients with EPS may show an earlier age of disease onset, compared to those without [27]. EPS in PD and DLB appear to be equally severe, but it remains controversial if and how EPS differ qualitatively between the two disorders. Two studies [28, 29] found less resting tremor in DLB compared to PD, but their findings for differences in bradykinesia and rigidity were contradictory.

Neuropsychiatric features

Most DLB patients (80%) experience neuropsychiatric symptoms, particularly hallucinations, delusions, apathy, anxiety, depression and sleep disturbances [30]. Such disturbances can be quantified with the *Neuropsychiatric Inventory* (NPI) [31]. This is a 12-item interview with the caregiver to assess frequency, severity and carer distress of delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, aberrant motor behaviour, sleep, and appetite disturbances. Persistent visual hallucinations are particularly frequent in DLB (>70%)

[30], and characteristically occur early in the course of the disease [32]. Hallucinations often contain detailed scenes with mute people and animals [30, 33]. Affective responses to these sensations vary from indifference, to amusement or fear, and some patients may have insight into the unreality of the episode. Visual hallucinations and delusions often coexist and common delusions are phantom border delusions (i.e. the belief that strangers live in the home), or paranoid delusions of persecution and theft. Delusions and hallucinations may often trigger other behavioural problems, such as aggression and agitation and profound caregiver distress, leading to early nursing home admission [34].

Supportive features

One third of DLB patients experience repeated unexplained falls and syncope. The prevalence of falls is higher than in AD or PD patients [35], and may be associated with abnormal autonomic cardiovascular function and cardioinhibitory carotid sinus hypersensitivity. Transient loss of consciousness may represent an extreme form of fluctuating attention and cognition. Such episodes are short lived (a few minutes), usually recovering to the previous state of cognitive function [36] and are sometimes misdiagnosed as transient ischaemic attacks or seizures. REM sleep behaviour disorder and depression are common additional clinical features in DLB [23].

Clinical diagnosis of DLB

The diagnosis of DLB relies on the use of the clinical consensus criteria [10, 23] (table 1), which requires the existence of progressive cognitive decline that interferes with normal social or occupational function. Two of the core features have to be present for a diagnosis of probable DLB and one

for possible DLB. In early DLB, cognitive and functional impairment may be very variable due to fluctuation. An individual patient may be moderately impaired in one assessment and relatively unimpaired in the next. This can be confusing for caregivers and doctors. Therefore, it can be useful

Table 1
Consensus criteria for clinical diagnosis of probable and possible DLB [10].

The central feature required for a diagnosis of DLB is a progressive cognitive decline of sufficient magnitude to interfere with normal social and occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of frontal-subcortical skills and visuospatial ability may be especially prominent.

Two of the following core features are essential for a diagnosis of probable DLB and one is essential for possible DLB:

- a) fluctuation of cognition with pronounced variations in attention and alertness
- b) recurrent visual hallucinations that are typically well formed and detailed
- c) spontaneous motor features of parkinsonism

Features supportive of the diagnosis are:

- a) repeated falls
- b) syncope
- c) transient loss of consciousness
- d) neuroleptic sensitivity
- e) systematised delusions
- f) hallucinations in other modalities
- g) REM sleep behaviour disorder [23]
- h) depression [23]

A diagnosis of DLB is less likely in the presence of:

- a) stroke disease, evident as focal neurological signs or on brain imaging
- b) evidence on physical examination and investigation of any physical illness or other brain disorder sufficient to account for the clinical picture

and important to observe a patient at different time intervals and to get as much information as possible from the caregiver. Clinical diagnosis is based on a detailed history of past and current symptoms, the results of neuropsychological testing, and findings of neuroimaging. Before a final diagnosis is made haematological, biochemical, pharmacological causes of cognitive impairment have to be excluded and differential diagnosis carefully considered (table 2).

Neuropsychological assessment

Compared to healthy controls, cognitive function of DLB patients is impaired in all areas of cognition and shows higher variability [37]. DLB patients may have less severe memory impairment [38], more visuo-perceptual, visuospatial, and constructional disabilities compared to AD [37–40]. Visuo-constructive functions can be easily assessed

by pentagon copying and clock drawing (figure 1). Nevertheless, there is no unique neuropsychological pattern of cognitive impairment in DLB, that clearly differentiates DLB from AD in an individual patient and fluctuating attention, neuropsychiatric symptoms or EPS can all interfere with neuropsychological testing.

Neuroimaging

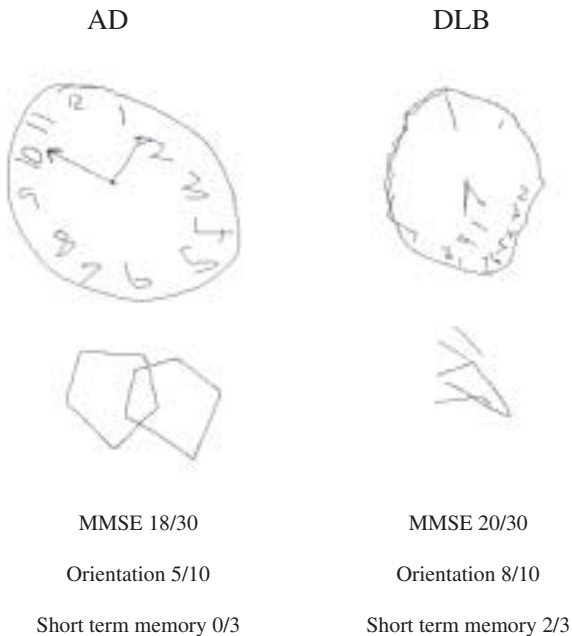
Hippocampal and medial temporal lobe atrophy are, compared to AD, less pronounced in DLB [41, 42]. Global brain atrophy and ventricular enlargement, periventricular and white matter hyperintensities do not differentiate DLB from either AD or Vascular dementia (VaD) [43]. Functional neuroimaging studies with SPECT and PET in DLB and AD have found similar parieto-temporal hypoactivity, whereas occipital hypoactivity is more pronounced in DLB [44]. Nigrostriatal dopaminergic function can be visualised using specific tracers for presynaptic dopamine transporters (e.g. carboxymethoxy-iodophenyl-tropane (CIT)-SPECT or PET). Using this method recent studies [45, 46] have found severely impaired dopaminergic function in DLB, an abnormality shared with PD but not present in AD. These findings suggest that CIT-SPECT might be helpful in the future, particularly for distinguishing between DLB and AD.

Genetics

Genetic testing cannot presently be recommended as part of the routine diagnostic process. Most DLB cases occur sporadically and there are only a few reports of autosomal dominant LB disease families [47]. The APOE $\epsilon 4$ allele is over-represented in DLB as in AD, but not in PD without dementia [48, 49]. Most studies find no associations between polymorphism in genes involved in familial AD (e.g. presenilin 1 or 2) and DLB. The APP717 mutation however, can be associated with familial AD and extensive cortical LB [50].

Figure 1

Visuo-constructive abilities in clock drawing and pentagon copying of a DLB and AD patient for comparison.



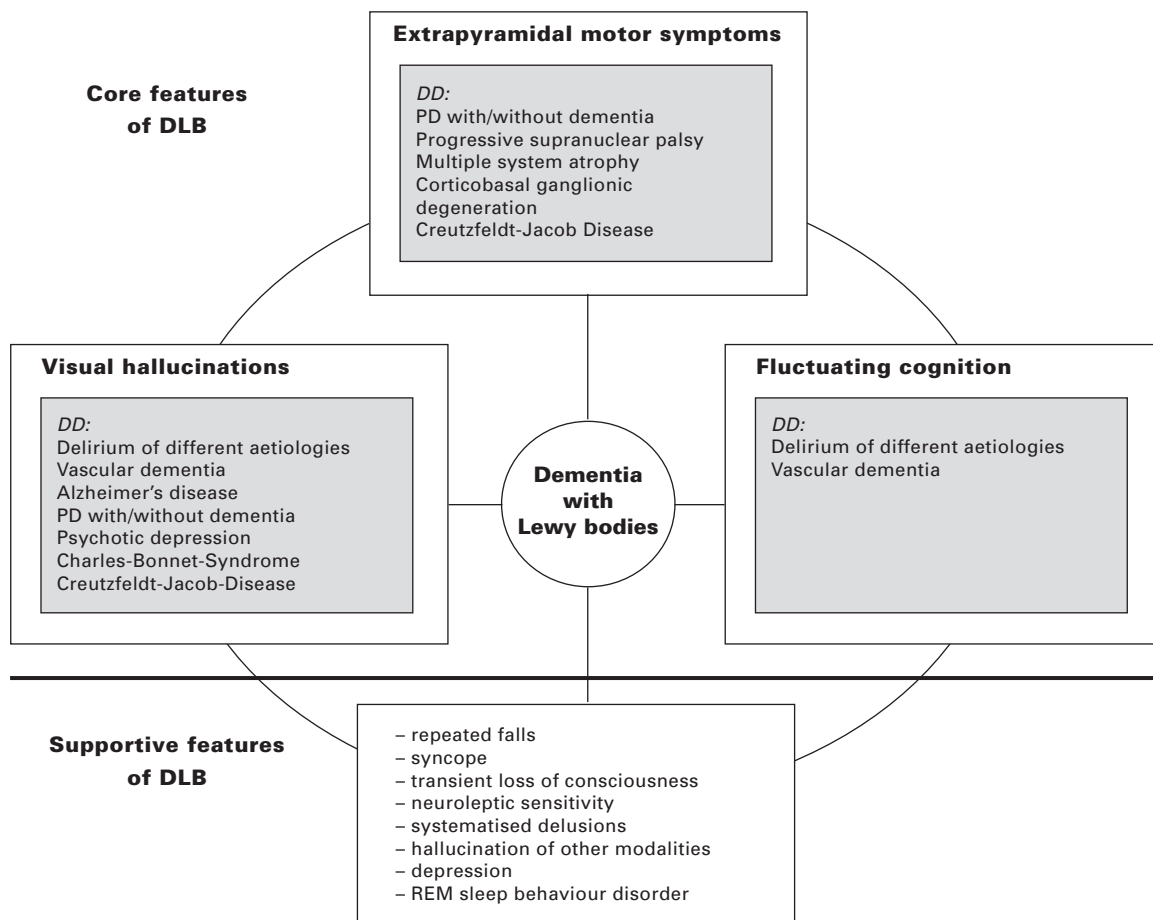
Course of disease

The composition of clinical features and the order of their appearance during the course of the disease can be variable and different from patient to patient, depending on the localisation of the major pathology. Patients with early and prominent EPS, for example, show prominent nigrostriatal changes, those with early hallucinations and cognitive impairment have pronounced cortical or limbic involvement, and patients with postural instability and falls have major spinal cord and (para-) sympathetic ganglia pathology [10]. Patients with LB disease may accordingly present to different medical specialists. Neurologists see those patients

with pronounced motor features, psychiatrists those with prominent neuropsychiatric features and geriatricians may see DLB patients with autonomic dysfunction, whilst general practitioners may see the whole spectrum. Mean disease duration in DLB is five to six years (range 2–20) and the rate of progression, as evidenced by change in global cognitive measures, is typically 4–5 MMSE points per year [51]. Whether progression of DLB is more rapid than in AD is not clear: some authors reported more rapid decline [51, 52], whilst others did not find significant differences [53, 54].

Figure 2

Core diagnostic features and their differential diagnoses (DD).



Differential diagnosis

Major syndromes to be considered for differential diagnosis are 1) other neuropsychiatric syndromes with hallucinations and delusions, 2) other degenerative brain disorders with EPS and 3) syndromes with profound fluctuations in cognition (figure 2).

Other neuropsychiatric syndromes with visual hallucinations and delusions

Neuropsychiatric symptoms are common in most degenerative brain disorders. Compared to DLB, PD and AD patients suffer less frequently from visual hallucinations and delusions, and the frequency of these symptoms typically increases with disease progression [30, 32]. Initial manifestations of Creutzfeldt-Jacob-Disease (CJD) may be neuropsychiatric symptoms, e.g. depression, anxiety, delusions before dementia and neurological features, e.g. myoclonus, cerebellar ataxia, extrapyramidal and pyramidal signs, manifest. Disease progression in CJD is usually more rapid than in DLB and may lead to death in less than 6 months [55]. Delirium of different aetiologies (e.g. general medical condition, substance-induced) is characterised by fluctuating confusion, and often by visual hallucinations. Delirious patients show profound diurnal changes, with marked worsening of symptoms at night, which is not so typical of DLB.

Hallucinations and delusions in old age can also be caused by other psychiatric disorders, e.g. psychotic depression, late onset delusional disorder or by complex partial seizures (temporal lobe epilepsy). Rarely, mentally healthy elderly patients experience visual hallucinations, most commonly in association with visual impairment (Charles Bonnet Syndrome) [56].

Other degenerative brain disorders with extrapyramidal features

In VaD and AD EPS are uncommon (10–12%), relatively mild and usually not apparent until the late stages of the disease [57, 58]. All patients with idiopathic PD have EPS and are at risk of developing dementia; with about a six times increased risk compared to the general population. At least 25–30% of PD patients are reported as demented in cross-sectional studies [27], and the prevalence is probably much greater with a mean onset of dementia 10 years after initial motor symptoms [59]. Risk factors for dementia in PD are older age at onset of motor symptoms [60], greater motor disability [61], and symptoms of depression or hallucinations [62, 63]. Despite many neuropathological and clinical symptoms with DLB [27], consensus guidelines [10, 23] recommend that PD patients who develop dementia more than

Table 2

Comparison of Parkinson's disease (PD), Dementia with Lewy bodies (DLB) and Alzheimer's disease (AD).

	PD	DLB	AD
Neuropsychiatric symptoms			
Visual hallucinations	++	+++	+
Delusions	+	+++	++
Depression	++	++	++
Apathy	+	++	++
	in association with anticholinergic dopaminergic drugs	persistent hallucinations early in course of disease	hallucinations in late stages of disease
Extrapyramidal motor symptoms			
Tremor	+++	++	–
Rigor	+++	+++	+
Bradykinesia	+++	+++	+
	first manifestation of disease, initially often asymmetric	similar severity as in PD, pronounced rigidity and bradykinesia	rare, usually mild in late stages
Fluctuation of cognition	–	+++	+
		prominent, severe, early in the course	
Neuropsychology	impaired executive functions	early disturbances in attention, visuo-perceptive functions	early impairment of declarative memory and attention
Neuroimaging			
Global brain atrophy	–	++	++
Medial temporal lobe atrophy	–	+	+++
Occipital hypoperfusion	+	+++	–
Impaired dopaminergic activity	+++	+++	–
Neuropathology and chemistry			
Senile plaque density	–	++	+++
Tangle density	–	+	+++
Subcortical LB	+++	++	–
Cortical LB	+	+++	–
Cholinergic deficit	+	+++	++
Dopaminergic deficit	+++	++	–
Genetics			
Overrepresentation Apo ε4	–	++	++

+++ typical manifestation of the disease, ++ usually present, + present, – unusual manifestation

12 months after the initial motor symptoms should be diagnosed as PDD rather than DLB. Ongoing and future research has to clarify, whether PDD and DLB are different representations of the same neuropathological process with different early clinical manifestations [64], or whether they are independent disease processes ending in a similar common pathway. EPS can also occur in other relatively uncommon degenerative disorders, e.g. CJD, progressive supranuclear palsy, multiple system atrophy, and corticobasal ganglionic degenerations [14].

Syndromes with profound fluctuation of cognition

In DLB, the prevalence and severity of fluctuation is greater compared to VaD (35–50%) or AD (20%) [65]. Acute and unexpected fluctuation of cognition and attention are typically associated with delirium of different aetiologies. It is therefore important that systemic and pharmacological precipitants be excluded in the differential diagnosis of DLB.

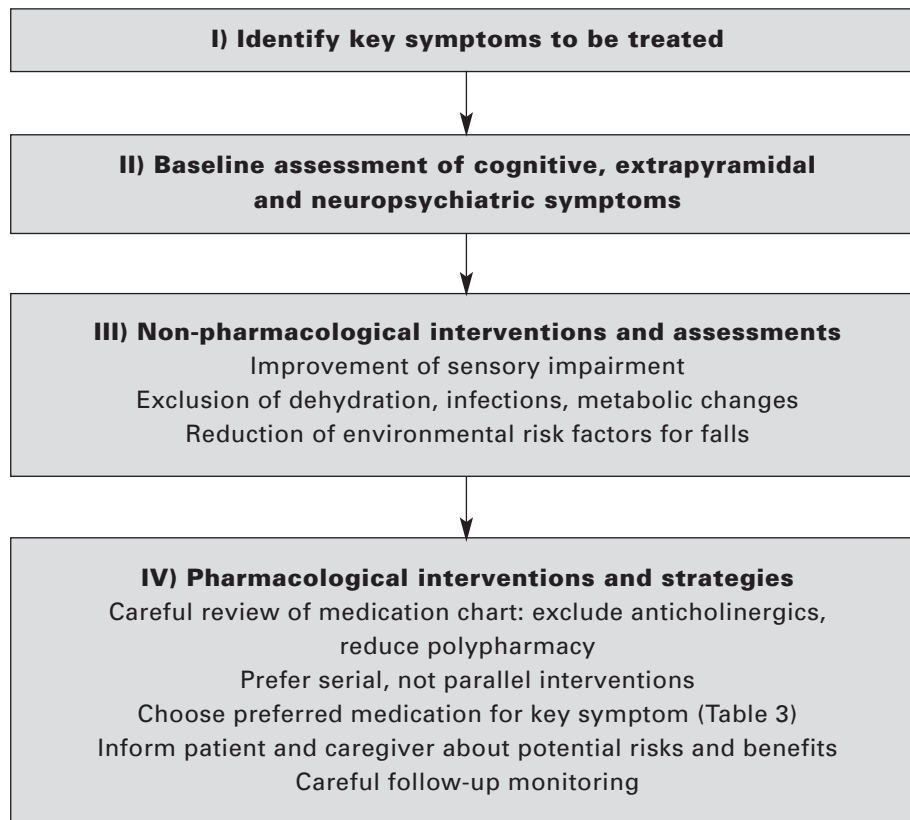
Clinical management

Currently no disease-modifying therapy is available. Accurate diagnosis and the identification of the most prominent symptoms are important pre-conditions for symptomatic treatment. If pos-

sible, clinicians should assess cognitive (e.g. MMSE) [66], neuropsychiatric (e.g. NPI) [31] and motor features (e.g. UPDRS) [26] before treatment, as the improvement of one symptom may be

Figure 3

Treatment strategies of patients with dementia with Lewy bodies.



achieved at the expense of another. Serial interventions, i.e. one after another with a sensible time interval in-between and not parallel interventions, i.e. more than one intervention at the same time, are to be recommended, because the latter approach will make it difficult to link improvements or side effects to treatment, particularly in a disorder characterised by fluctuating symptomatology. Treatment recommendations for the present review are primarily based on controlled and open label studies, and if published evidence is lacking, on the clinical experience of the authors (figure 3).

Non-pharmacological interventions

The improvement of potentially treatable sensory impairments, e.g. poor hearing or vision, may reduce hallucinations and falls. The reduction of environmental risk factors, e.g. loose carpets, doorsteps and poor lighting, physiotherapy, exercise programs and hip protectors have the potential to minimise falls or their complications. In demented patients with newly and acutely apparent neuropsychiatric symptoms, co-morbid infection, dehydration and metabolic disturbance should be excluded.

Pharmacological interventions

Pharmacological treatment in DLB patients requires a careful balancing of potential risks and benefits [67]. Potential drug related benefits include improved functioning, enhanced cognition and reduced neuropsychiatric symptoms. The risks are side effects, interactions and secondary complications such as falls. Despite the widespread use of polypharmacy, the safety and tolerability of

such combinations are poorly investigated. Before the prescription of any new medication, alternative non-pharmacological treatment should be considered and the current medication carefully reviewed. All drugs with anticholinergic side effects, e.g. tricyclic antidepressants, low potency neuroleptics, antiparkinsonian anticholinergic drugs, antispasmodics for bladder or gastrointestinal tract should be avoided as they have the potential to exacerbate psychotic symptoms and may be associated with orthostatic hypotension particularly in DLB patients (table 3). Key symptoms which may need treatment are motor and neuropsychiatric features as well as cognitive impairment.

Antiparkinsonian medication in DLB

The aim of antiparkinsonian medication is to improve motility without inducing or exacerbating psychotic symptoms or confusion. There is debate regarding the responsiveness of levodopa therapy in DLB patients, although partial response has been observed in retrospective studies [28, 29]. Levodopa monotherapy with careful titration to the lowest effective dose should be the first choice treatment. Potential side effects include visual hallucinations, delusions, orthostatic hypotension and gastrointestinal upset. Studies assessing potential benefits and risks of other antiparkinsonian medication in DLB are still lacking. Anticholinergic drugs are, as mentioned, contraindicated and the reported somnolence experienced with dopamine agonists, e.g. pramipexole, ropinirole [68, 69] may limit their use in DLB. Evidence for treatment effects of combined levodopa and COMT-inhibitor therapy (entacapone) in DLB is

Table 3

Pharmacological treatment of dementia with Lewy bodies.

	Antiparkinsonians	Cholinesterase inhibitors	Neuroleptics	Antidepressants
Treatment of	extrapyramidal motor symptoms	cognitive impairment, neuro-psychiatric symptoms	visual hallucinations, delusions	depression, anxiety, aggression
Key messages	lowest effective dose levodopa monotherapy	to be considered as first choice treatment	to be avoided no depot-medication by experienced experts	treatment of affective disturbances
Avoid drugs with (e.g.)	anticholinergic, antimuscarinic effects: biperiden, benztropine		<i>high D2 affinity:</i> haloperidol, zuclopenthixol <i>cholinergic side effects</i> promazine, levomepromazine,	<i>cholinergic side effects:</i> (<i>tricyclics</i>): amitriptyline, clomipramine
Preferred drugs (e.g.)	levodopa	rivastigmine, donepezil, galantamine	quetiapine, clozapine, olanzapine	SSRI: citalopram, sertraline, paroxetine <i>multi-receptor antidepressants:</i> nefazodone, mirtazapine, venlafaxine
Potential benefits	reduction of EPS	less neuropsychiatric symptoms, improved cognition	reduction of delusion and hallucinations	less anxiety and depression, aggression
Potential side effects	visual hallucinations, delusions, orthostatic hypotension and gastrointestinal upset	gastrointestinal symptoms, cardiac symptoms (bradycardia), rarely worsening of EPS	increased rigidity, immobility, confusion, sedation and postural falls	gastrointestinal, hypo / hypertension

lacking. In clinical situations, where patients receiving antiparkinsonian medication develop hallucinations, reduction to the lowest effective dose of levodopa monotherapy is preferable to any combined treatment. The following order of stopping antiparkinsonian medication is suggested [64]: anticholinergics, L-deprenyl, amantadine, direct dopamine agonists, COMT-inhibitors, and finally levodopa. Such reduction procedures need careful surveillance, as exacerbation of parkinsonian features is associated with discomfort and the risk of falls.

Neuroleptics in DLB

Neuroleptic treatment of hallucinations and delusions in DLB patients is a potentially hazardous enterprise that requires the informed agreement of patient and caregiver. Reported side effects include increased rigidity, immobility, confusion, sedation and postural falls, and can be associated with a 2–3 fold increased mortality risk [70, 71]. About 50% of treated patients develop severe side effects, and it is not possible to predict neuroleptic sensitivity reactions in an individual patient before treatment starts. The low density of D2 receptors in the striatum of patients with DLB is likely to contribute to the severe adverse effects [18]. Although atypical neuroleptics, e.g. clozapine, olanzapine, risperidone, quetiapine interact with a greater variety of receptors, and are probably associated with a lower incidence of EPS [72], severe side effects have been reported with them in DLB [73–75], and studies comparing typical, e.g. haloperidol, zuclopenthixol, and atypical neuroleptics are lacking. Any neuroleptic depot medication is absolutely contraindicated. In clinical

situations, where neuroleptics are unavoidable, atypical neuroleptics should be given in the lowest possible daily dose, e.g. clozapine 12.5 mg, olanzapine 2.5 mg, risperidone 0.25 mg, quetiapine 12.5 mg. Treatment should usually be carried out by an experienced specialist with careful monitoring, and possibly short-term hospitalisation in the start phase, when side effects usually appear (after the first few doses, or in the first two or three weeks). A recent study [76] assessed the effect of a six-week quetiapine treatment (25 mg/day) in 5 DLB patients with neuropsychiatric features and reported significant reductions of hallucinations, delusion, anxiety and irritability, without any side effects. Although these pilot data are promising, caution is still advised.

Cholinesterase inhibitors in DLB

There is converging and consistent evidence [77–85] that cholinesterase inhibitors (ChE-I) are effective and relatively safe for the treatment of neuropsychiatric and cognitive symptoms in DLB (table 4). Three pilot studies [82–84] compared the efficacy of ChE-I in DLB and AD and gave evidence for similar or superior treatment effects in DLB. The largest placebo controlled study [85] assessed the effect of rivastigmine (12 mg/day) in 120 DLB patients over 20 weeks, followed by a 3-week withdrawal period. Patients taking rivastigmine were less apathetic, less anxious and had fewer delusions and hallucinations compared to placebo controls. Treatment effects disappeared on drug withdrawal. Long-term effects of ChE-I were assessed in an open label study [81] over 96 weeks. This study found improvements in cognitive and neuropsychiatric symptoms after 24 weeks return-

Table 4

Effects of cholinesterase inhibitors in dementia with Lewy bodies.

Reference	nb patients	follow up (weeks)	substance	most common dose (mg/day)	effects on			side effects
					cognition Δ MMSE	neuropsychiatric features	EPS	
Shea 1998 [77]	9	12	Donepezil	10	+ 4.4	less visual hallucinations	worsening of EPS (33%)	worsening of EPS (33%)
MacLean 2001 [78]	8	NR	Rivastigmine	9	NR	Improved sleep (i.e. nocturnal agitation, yelling out)	NC	gastrointestinal features (25%)
Lanctot 2000 [79]	7	8	Donepezil	5	+ 4.3	less visual hallucinations, agitation and apathy	NC	somnolence, syncope, bradycardia, worsening COPD (45%)
McKeith 2000 [80]	11	12	Rivastigmine	9	+ 0.7	less visual hallucinations, delusions, agitation, apathy	tend to improve	Transient nausea and gastrointestinal features
Grace 2001 [81]	29	96	Rivastigmine	9	- 3.7	reduction of psychotic features	tend to improve	nausea and vomiting (14%), flue-like symptoms (3%), cardiac arrhythmia (3%)
Lebert 1998 [82]	19	14	Tacrine	120	NR	NC	NC	Side effects not specified
Querfurth 2000 [83]	6	24	Tacrine	80	NC	NC	NC	prostatism (17%)
Samuel 2000 [84]	4	30	Donepezil	5	+ 4.8	less neuropsychiatric features	NC	no side effects no drop outs
McKeith 2000 [85]	120	23	Rivastigmine	12	+1.6	less visual hallucinations, delusions and apathy	NC	nausea (37%), vomiting (25%), anorexia (19%), somnolence (9%)

NR: not reported, NC: no change

ing to pre-treatment levels after 36 weeks. Similar effects have been found in PDD patients treated with ChE-I [86–90]. ChE-Is were well tolerated, and drop out rates (10–31%) and side effects were similar to those found in AD, mainly gastrointestinal symptoms with nausea, vomiting and diarrhoea. A small study [77] reported worsening of parkinsonism in two of nine patients treated with donepezil. This finding has not been replicated in other studies [78–90], which reported either no change or improvement of EPS during treatment. To treat DLB patients with ChE-I may require confirmation from healthcare funders because ChE-I are in most countries still only approved for the treatment of mild to moderate AD.

Antidepressants in DLB

There are no placebo-controlled studies which assess the effects of antidepressants in DLB. Tricyclic antidepressants, e.g. amitriptyline, clomipramine, nortriptyline should be avoided because of their anticholinergic side effects [91]. Selective serotonin reuptake inhibitors (SSRI), e.g. citalopram, sertraline, paroxetine and the multi-receptor antidepressants, e.g. nefazodone, mirtazapine and venlafaxine, may be better choices in the treatment of depressed DLB patients [92].

Other medications

Sleep disturbances particularly REM sleep behaviour disorder can be cautiously treated with low

dose clonazepam (0.25–1.0 mg) at bedtime [93]. All sedating medications in elderly demented patients have the potential risk for falls and confusion. Low potency antipsychotic drugs, e.g. thioridazine should be avoided (although often used as sedatives and anxiolytics) because of the dose dependent anticholinergic side effects. Anticonvulsants, e.g. carbamazepine, sodium valproate may be used by the experienced specialist to treat behavioural disturbances in dementia [94].

To conclude, DLB remains challenging to diagnose and treat. It is the combination of EPS and neuropsychiatric features together with neuroleptic sensitivity, which makes pharmacological treatment difficult. Before adding new medications to improve one symptom at the expense of worsening another, careful review of all medication should be carried out. Medications with anticholinergic effects, and typical neuroleptics should be avoided. Whenever possible, levodopa monotherapy in the lowest effective dose, is preferable for treating EPS. There is increasing evidence that ChE-I can improve neuropsychiatric symptoms and cognitive functions in DLB. Given the potential hazards of neuroleptics in DLB we suggest that ChE-I are the treatment of choice and low doses of atypical neuroleptics should be cautiously used by the experienced specialist only when absolutely necessary.

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