REVIEW ARTICLE

Drug Safety 2002; 25 (7): 511-523
0114-5916/02/0007-0511/$25.00/0

Benefit-Risk Considerations in the Treatment of Dementia with Lewy Bodies

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Contents

Abstract

Dementia with Lewy bodies (DLB) is a relatively recently characterised syndrome with clinical and pathological features that distinguish it from classical Alzheimer's disease. These characteristics include more rapid decline, spontaneous features of parkinsonism, visual hallucinations and fluctuating cognition.

This article reviews the clinical syndrome of DLB and the agents used to treat its cognitive, motor and behavioural manifestations. Benefit-risk issues regarding the treatment of DLB are discussed based upon limited randomised, controlled clinical trials with some speculative conclusions being drawn from case reports and case series.

We conclude that patients with DLB may respond better to cholinesterase inhibitors than patients with Alzheimer's disease on both cognitive and behavioural measures. Cholinesterase inhibitor therapy may result in reduced caregiver burden and less time institutionalised. These agents are well tolerated with the majority of adverse effects being gastrointestinal in nature. Although neuropsychiatric manifestations are numerous in patients with DLB, antipsychotics should be used infrequently and with caution, although atypical antipsychotics are better tolerated than conventional antipsychotics. Physicians should exhibit

caution when prescribing these agents because of the increased risk of extrapyramidal adverse effects. Limited data suggest that the use of levodopa or other dopaminergic agents may be of benefit for the treatment of the parkinsonism that is associated with DLB. However, the increased risk of hallucinations and neuropsychiatric symptoms may negate the potential benefits of increased mobility. There is insufficient evidence to draw conclusions about the use of antidepressants; however, selective serotonin reuptake inhibitors may be of benefit.

A dementia with Lewy bodies (DLB) was initially described by Japanese investigators who termed the condition 'diffuse Lewy body disease'.[1] Subsequent investigations revealed that a condition with cortical Lewy bodies and Alzheimer's disease–like neuritic plaques was more common than diffuse Lewy body disease. This syndrome of dementia, DLB, is now believed by some to be the second most common form of dementia following Alzheimer's disease, with a frequency of between 10 to 30% of late-onset dementias.[2,3]

In the past decade recognition and knowledge of DLB has grown. There is considerable debate, especially amongst neuropathologists, concerning whether DLB is truly a separate disease entity. The clinical and pathological findings overlap with Alzheimer's and Parkinson's diseases.[4-8] There also are important differences, however, as described in the consensus criteria for the clinical and pathological diagnosis of DLB (see section 1). The average life expectancy and treatment response of DLB also help to distinguish this syndrome from Alzheimer's and Parkinson's disease (see section 1).

Controlled clinical trials of treatments for DLB are very few in number, with the majority of recommended treatments being based on clinical series, case reports and extrapolations from other conditions. A comprehensive benefit-risk analysis of the treatment of DLB is currently impossible due to the lack of controlled clinical data documenting beneficial response as well as adverse event rates. Case series and case reports may contribute to this database; however, patient numbers are generally small and comparisons among cases reported cannot be made accurately. Nevertheless, inferences from the available literature regarding potentially beneficial agents and treatments to be avoided secondary to high adverse event rates can be drawn. Limited inferences also may be drawn from controlled trial data in Alzheimer's and Parkinson's disease, the two conditions that share characteristics with DLB.

1. Diagnosis – Clinical Criteria

The diagnosis of DLB relies on the use of consensus criteria proposed by the Consortium on DLB International Workshop in 1996 and revised in 1999.[3,9] These criteria established DLB as a dementia syndrome with prominent neuropsychiatric features and have been shown to have acceptable sensitivity and specificity, with specificity being higher than sensitivity by most reports.[10-12] The duration of illness is variable with some authors reporting a more rapid decline in DLB compared with that seen in patients with Alzheimer's disease[13-15] and others finding nonsignificant differences in rates of progression.[16,17] The prominent neuropsychiatric symptoms may lead to earlier and more frequent nursing home placement than occurs in patients with Alzheimer's disease.[18]

The clinical criteria are divided into central, core and supportive features. The central feature is progressive cognitive decline sufficient to interfere with normal social or occupational functioning. Unlike Alzheimer's disease, prominent memory impairment may not be present early in the disease course. Visuospatial impairment, attentional disturbances and frontal-subcortical abnormalities are prominent.[19-21]

Core features include fluctuating cognition, recurrent visual hallucinations and spontaneous motor features of parkinsonism. Two of three core features must be present for a diagnosis of probable

DLB and one for possible DLB. Cognitive complaints and parkinsonism generally occur in concert; if signs of parkinsonism occur first, cognitive complaints occurring more than 12 months later suggests the diagnosis is Parkinson's disease with dementia.

Supportive features include repeated falls, syncope, transient loss of consciousness, depression, sensitivity to antipsychotics, systematised delusions and hallucinations in other modalities.

The prevalence of visual hallucinations in DLB has been found to range between 25 to 80% and that of delusions between 20 and 80%.[22] These rates are much higher than those reported in Alzheimer's disease (17 and 33%, respectively)[23] and the psychotic features constitute a distinguishing feature. The visual hallucinations in DLB are vivid scenes of people, children, and animals that typically are normal in size. Patients with DLB are more likely to report multiple different types of visual hallucinations that are more persistent and severe compared with those reported by patients with Alzheimer's disease.[24] The persistence and character of delusions in DLB also differ from those of Alzheimer's disease. Delusions in Alzheimer's disease are generally persecutory ideas;[25] patients with DLB have delusions with more complex bizarre content and they have more misidentification-type delusions.[26]

Fluctuating cognition includes alterations in arousal and cognitive performance. These changes can be mild to extreme including muteness, inability to stand and stupor. Although fluctuating cognition occurs in other dementias, including Alzheimer's disease and vascular dementia, the prevalence is higher in DLB.[27,28] Means of operationalising this symptom have been difficult with low rates of interrater reliability on rating scales and other clinical assessments.[11,29] Attempts have been made to quantify the fluctuations with the use of questionnaires and in a laboratory setting using electroencephalography combined with neuropsychometric measures of attention.[30,31]

Spontaneous motor manifestations of parkinsonism are the third core feature of DLB. Comparisons of these symptoms in DLB and idiopathic Parkinson's disease have been reported. There is a significant amount of overlap in the clinical manifestations of parkinsonism between DLB and Parkinson's disease. However, some differences have been reported and these features may aid in diagnosis. Louis et al.[32] reviewed the extrapyramidal signs (EPS) in patients with pathologically confirmed DLB and those with Parkinson's disease. In this series, the presence of myoclonus, absence of rest tremor or poor response to levodopa had strong predictive value for the diagnosis of DLB. These two groups of patients did not differ with respect to rigidity, bradykinesia, dystonia or gaze paresis. A retrospective review of a smaller group of patients found no significant differences in the degree of rest tremor and bradykinesia between patients with DLB and those with Parkinson's disease.[33] More recent data suggest there is an increased severity of EPS in patients with DLB when matched with those who have Parkinson's disease on duration of disease and age.[34] Differences were noted in severity of action tremor, bradykinesia, gait, facial hypomimia and rigidity. The presence of rest tremor was not a useful symptom to differentiate the two groups.

Depression, a very common feature, is a supportive feature in the report of the Second International Workshop on DLB.[9] Prevalence rates vary among studies and it is uncertain if depression is more common in DLB than in Alzheimer's disease.[18,24,26]

2. Treatment

Several large randomised, double-blind, placebo-controlled trials have been performed of treatments for Alzheimer's and Parkinson's diseases.[35-43] In contrast, with the exception of one randomised controlled trial using rivastigmine in DLB, placebo-controlled trials of the treatment of DLB have not been published. The role of cholinesterase inhibitors, dopaminergic agents, antipsychotics and antidepressants in the management of DLB are discussed in sections 2.1 to 2.4 based on the available literature with some inferences being drawn from the literature on the use of these agents in Alzheimer's and Parkinson's disease.

2.1 Treatment of Motor Impairment

Parkinsonism frequently occurs in DLB (with a prevalence of 45 to 84%) and its presence is one of the core clinical criteria (see section 1). The symptoms of parkinsonism vary slightly in those with DLB compared with those who have idiopathic Parkinson's disease (see section 1).

There is debate regarding the responsiveness of DLB to levodopa therapy, but at least partial responses have been observed.[33,44-46] Although these studies comment on the presence or absence of response to levodopa, how this was measured [change on the Unified Parkinson's Disease Rating Scale (UPDRS)[47] or Hoehn and Yahr stage score[48]] and the dose of levodopa were not recorded. In one series of patients, ten of 24 patients diagnosed with DLB were given a trial of levodopa, with seven (70%) showing a response.[32]

In those patients with EPS that interferes with functional status, low doses of levodopa/carbidopa or levodopa/benserazide can be instituted. A delicate balance between improving motility and inducing the emergence of psychotic behaviour is required with adjustments in dose up or down based on individual patients. Large double-blind, placebo-controlled trials are needed to assess the benefit-risk ratio of these drugs.

Dopamine receptor agonists such as pramipexole and ropinirole have demonstrable benefit in Parkinson's disease.[36,37,49] These agents reduce the emergence of motor manifestations such as dyskinesia associated with long-term levodopa use in patients with Parkinson's disease.[37] The reported somnolence associated with dopamine agonists[50,51] may limit their use in DLB due to the already common occurrence of fluctuating cognition in these patients. Drug-associated hallucinations may also limit their use in this patient population which has an increased prevalence of hallucinations.[35,52]

2.2 Cholinesterase Inhibitors

The US Food and Drug Administration has approved four cholinesterase inhibitors for the treatment of Alzheimer's disease: tacrine, donepezil, rivastigmine and galantamine. These agents also are being used for the treatment of the behavioural and cognitive manifestations of DLB. Patients with DLB may respond more favourably to cholinesterase inhibitors compared with those who have Alzheimer's disease.[53,54] This is because there is greater dysfunction of cholinergic systems in DLB, with presynaptic depletion in the brainstem and basal forebrain cholinergic nuclei along with relative preservation of post-synaptic receptors; the activity of choline acetyltransferase is also reduced to a greater extent than in Alzheimer's disease.[55-57]

The emergence of adverse events and adverse effects varies among the different cholinesterase inhibitors, from 10 to 40%.[39,40,42] In patients with Alzheimer's disease, these adverse effects are predominantly gastrointestinal in nature, with nausea, vomiting and diarrhoea accounting for effects that cause the majority of patients to discontinue the agents.[39,40,42] The use of cholinesterase inhibitors in DLB is well tolerated with few patients requiring discontinuation of the agent.[58-63] The most commonly reported adverse effects involve the gastrointestinal system with nausea and diarrhoea being the most frequent.[58-63] Comparisons of the adverse rates in the case series using donepezil are difficult due to different patient demographics, duration of illness and severity of neuropsychiatric symptoms. The published case reports[58-63] discuss only individual patient successes, while negative patient responses are usually not included among these reports. The rivastigmine data[64] suggests tolerability and safety is comparable with that found with the use of this drug in patients with Alzheimer's disease. Similarly, the tolerability of donepezil appears equivalent to that published in studies of Alzheimer's disease.[58,59,61,62] There have been no published reports of galantamine as a treatment for DLB.

McKeith and colleagues performed a randomised, double-blind, placebo-controlled trial using rivastigmine to treat behavioural disturbances in DLB.[64] This was a large multi-centre trial involving 120 patients with DLB. Nearly 63% in the rivastigmine-treated group showed at least a 30% improvement on the Neuropsychiatric Inventory

(NPI) compared with progressive worsening of NPI scores in the placebo-treated group.[65] Functionally, this equated to less apathy and anxiety and fewer delusions and hallucinations. Cognitive improvement, particularly in measures of attention and memory, also occurred to a greater extent with rivastigmine than with placebo. Rivastigmine in some patients produced cholinergic adverse effects (nausea 37%, vomiting 25% and anorexia 19%).

An open-label trial examining the usefulness of rivastigmine as long-term therapy for DLB showed significant improvement from baseline after 12 and 24 weeks of therapy. At 96 weeks of treatment, scores had declined but the change in Mini Mental State Examination (MMSE),[66] NPI and UPDRS scores were not significantly different compared with baseline suggesting there had been no deterioration in function or cognition.[67]

Donepezil also has been reported to have a beneficial effect in DLB, although blinded studies are lacking. An open-label study of donepezil in patients with DLB or Alzheimer's disease showed greater improvement on MMSE scores and a greater reduction in the Behavioural Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD),[68] a scale designed to examine psychopathology in dementia, in patients with DLB than in patients with Alzheimer's disease.[54]

Several case series and reports of donepezil in patients with DLB have shown an improvement in cognition using the MMSE, with up to a 4 point increase.[58,59] Neuropsychiatric improvement, including reduction in hallucinations, agitation and the delirium-like features, has been reported following treatment with donepezil.[60-63] These changes in cognition and neuropsychiatric manifestations can lead to increased independence in performing activities of daily living (ADLs) and a delay in institutionalisation. These benefits have not been specifically analysed in the ChE-1 studies in DLB.

In the few series that reported adverse events and discontinuation rates, donepezil appeared to be generally well tolerated in patients with DLB, with the majority of adverse evens being gastrointestinal in nature.[58,61] However, worsening of parkinsonism has been reported following use of donepezil and its effect on EPS needs to be monitored.[58]

2.3 Antipsychotics

Sensitivity to antipsychotics is a supportive feature of the diagnosis of DLB. However, neuropsychiatric symptoms such as delusions and hallucinations are core features of the disorder and often require pharmacological management. The combination of a high rate of these neuropsychiatric symptoms and the exaggerated response to antipsychotics makes treatment very challenging.

The atypical antipsychotics clozapine, olanzapine and risperidone have been used to treat the neuropsychiatric aspects of DLB. Data on the use of quetiapine and ziprasidone in patients with DLB are not available. Clozapine was the first atypical agent tried in an attempt to control neuropsychiatric features of DLB and initial reports varied from dramatic efficacy[69] to worsening of behaviour and increasing confusion.[70] Some patients reported before the development of the consensus criteria for the diagnosis of DLB, had an unusual presentation for suspected DLB, lacked pathological confirmation, and may not have had DLB.[69]

Success with risperidone has varied among the available case reports. A series of three patients with improvement in psychotic symptoms and without EPS following the use of risperidone was reported by Allen et al.[71] However, McKeith et al.[72] reported three patients with DLB who developed severe EPS after risperidone use. Risperidone has been reported to induce the neuroleptic malignant syndrome in patients with DLB.[73] While these studies do not completely discourage the use of risperidone, they do indicate the need for vigilance for any evidence of EPS in those being treated.

Olanzapine can be used in the behavioural management of DLB, but again with caution. An initial report showed a variable response ranging from clear improvement, to no benefit, to intolerable adverse effects.[74] A *post-hoc* analysis of patients with DLB who were included in a larger study of

olanzapine for Alzheimer's disease found a significant reduction in hallucinations and delusions at dosages of 5 and 10 mg/day.[75] Higher dosages did not confer any additional benefit and were not superior to placebo. There was no increase in parkinsonism among the patients receiving therapeutic dosages. Lower dosages of olanzapine (2.5 mg/day) may be used. In all cases, vigilance for the emergence or worsening of EPS is important.

2.4 Antidepressants

The reported frequency of depression in DLB varies between 30 and 50%.[9,18] Rates may be slightly less frequent when Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)[76] criteria for major depression are utilised and slightly higher if depressive symptoms not meeting criteria for major depression are assessed.[24,26] The literature is also conflicting regarding whether depression is more or less common in DLB when compared with that in Alzheimer's Parkinson's diseases (see section 1).

Randomised, placebo-controlled trials comparing the various classes of antidepressants in DLB have not been published; case reports and case series also are lacking. The severity of the cholinergic deficit in DLB should make the family of tricyclic antidepressants (TCAs) a less than optimal choice because of their anticholingeric adverse effects. The selective serotonin reuptake inhibitors (SSRIs) and the multi-receptor antidepressants venlafaxine, mirtazapine and nefazodone may be a better choice when efficacy and adverse effect profiles are examined. These newer agents have mild to moderate anticholinergic properties which can be problematic in this patient population; however, they appear to be well tolerated in patients with Alzheimer's disease.[77-79]

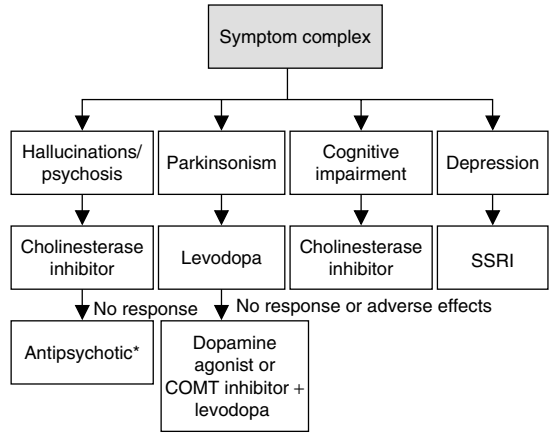
A summary of the agents used to treat the various symptoms of DLB is found in figure 1.

3. Benefit-Risk Considerations

Detailed studies focusing on the benefit-risk ratio of the treatments for the various manifestations of DLB have not been systematically performed. The clinical trials published assessing treatment responses and adverse effect rates are too few to provide a quantitative benefit-risk analysis. However, available results, along with those published in clinical series and case reports, allow limited inferences to be drawn. Table I summarises the benefit-risk issues for the treatment for DLB.

A benefit-risk analysis involves projecting a putative balance between the advantages of using a drug to treat a disorder and the potential for adverse events. In DLB, drug-related benefits include improved functioning, enhanced cognition, reduced neuropsychiatric symptoms and improved quality of life (QOL). Secondary benefits such as reduced caregiver stress or burden and delay to nursing home placement also might be considered. Functional improvements could involve ADLs, ambulation, speech, social activities or sexual activity depending on the effects of the agent and the assessments used to gather the data.

Adverse events to be considered in a benefit-risk analysis include adverse effects of agents used, interactions with other agents employed to treat the patient's condition, and interactions with



* Olanzapine, clozapine, risperidone, quetiapine

Fig. 1. Treatment algorithm for dementia with Lewy bodies. **COMT** = catechol-*O*-methyltransferase; **SSRI** = selective serotonin reuptake inhibitor.

Table I. Potential benefits and risks associated with various treatments for dementia with Lewy bodies (DLB)

Symptom	Treatment	Benefit	Risk
Visual hallucinations/ psychosis	Cholinesterase inhibitors	Demonstrated efficacy, minimal adverse effects, few drug interactions, may also enhance cognition	Bradycardia in susceptible population, rarely may worsen parkinsonism
		Will not increase hallucinations, also useful for cognition and neuropsychiatric symptoms	Limited data to support efficacy
	Atypical antipsychotics	Effective treatment for hallucinations and psychosis	Frequently may worsen signs of parkinsonism, can cause NMS
Parkinsonism	Levodopa	Potentially effective treatment for parkinsonism	May worsen hallucinations
	Dopamine agonists	Less dyskinesia, very effective in treatment of parkinsonism	Limited data available, may be sedating
	COMT inhibitors	Can reduce dose of dopamine required, may reduce risk of hallucinations and dyskinesia	No data reported to support their use in DLB
Depression	SSRIs	Well tolerated, mild anticholinergic activity	Limited data to support efficacy in DLB

COMT = catechol-*O*-methyltransferase; **NMS** = neuroleptic malignant syndrome; **SSRIs** = selective serotonin reuptake inhibitors.

drugs administered to treat other conditions manifested by the patient (e.g. non-neurological illness in an elderly patient). Secondary adverse effects include falls, hospitalisations and caregiver stress/burden. In the case of DLB, risk considerations include known adverse effects of each agent considered (levodopa, cholinesterase inhibitors, antipsychotic agents, antidepressants); interactions between these agents; interactions between the drugs used to address the symptoms of DLB (motor dysfunction, cognition, psychosis, mood) and those used to treat comorbid conditions commonly present in the elderly (cardiovascular, genitourinary, ocular); enhanced vulnerability to adverse effects associated with the neurobiology of DLB (e.g. increased susceptibility to EPS and psychosis); and secondary consequences such as institutionalisation, hospitalisation, increased use of community resources (e.g. day care, respite care, transportation, meals-on-wheels) and adverse effects on caregivers (e.g. time devoted to patient assistance, emotional stress, isolation, physical impairments).

Some of these benefits and risks have been considered in isolation in DLB but no comprehensive study or model exists. In sections 3.1 to 3.4, we review the elements to consider in a benefit-risk analysis of this disorder.

3.1 Treatment of Motor Impairment

The detrimental physical effects of parkinsonism include diminished ability to move freely and to perform ADLs. These result in restricted independence, increased reliance on assistive devices and caregivers, as well as lowered self-esteem. Scales such as the 39-item Parkinson's Disease Questionnaire (PDQ-39)[80] have examined patient QOL, finding a direct correlation between QOL and physical mobility and inability to perform ADLs.

The use of dopaminergic compounds in the treatment of Parkinson's disease is beneficial and widely accepted. Levodopa, dopamine agonists and the newly approved catechol-*O*-methyltransferase (COMT) inhibitor entacapone provide symptomatic relief for the motor manifestations of Parkinson's disease.[35,81-83] Successful management of the motor symptoms of Parkinson's disease with dopaminergic medications has been shown to enhance QOL, minimise dependence on assistive devices to perform ADLs, raise patient self-esteem and decrease the economic burden of the disease.[84-86] Reported adverse effects of dopaminergic agents in Parkinson's disease include hypotension, gastrointestinal upset, and hallucinations and delusions.[50-52] An additional reported effect is enhanced attention and concen-

tration which may be an added benefit rather than an 'adverse' effect.

The benefits seen in improved QOL, mobility and independence in Parkinson's disease also may be seen in DLB, given the large amount of overlap between the motor dysfunction in these two conditions and the partial response to treatment reported. The use of these compounds, however, in the treatment of DLB has not been systematically studied. The few reports of these agents in the treatment of DLB suggest that they provide benefit ranging from minimal to moderate.[33,44-46] Adverse event profiles are similar across the two diagnostic groups with regard to incidence of hypotension and gastrointestinal adverse effects.[33,44-46]

Neuropsychiatric symptoms including hallucinations and delusions are common following treatment with levodopa and dopamine agonists.[87] These manifestations are generally seen in patients with more advanced Parkinson's disease and in patients with cognitive impairment. Early-onset drug-induced hallucinations are suggestive of the diagnosis of DLB.[88] The psychiatric effects of levodopa commonly limit the dose that can be used in patients with DLB, a population with an already high frequency of hallucinations and delusions. In select cases, use of these agents may be warranted to minimise the risk of falls and to diminish functional impairment that could lead to earlier institutionalisation; however, close monitoring for the emergence of neuropsychiatric symptoms is required.

The dopamine agonists may provide additional benefit when compared with levodopa; however, the questionable increase in hallucinations and the reported sedating effects with these agents may increase their risk (see section 2.1). Controlled studies using these agents in DLB have not been published.

The newest agent for the treatment of Parkinson's disease, the COMT inhibitor entacapone, is effective when used as an adjunct to levodopa.[35,89] This agent may have potential benefit in the treatment of DLB. In Parkinson's disease this agent is well tolerated with only dyskinesia (29%), diarrhoea (9%) and mouth dryness (6%) occurring significantly more often than with placebo.[35] The favourable adverse effect profile and the potential for reduced neuropsychiatric symptoms make this agent a reasonable adjunct to levodopa in the management of patients with DLB.

3.2 Cholinesterase Inhibitors

Cholinesterase inhibitor therapy is routinely used in the treatment of Alzheimer's disease to improve cognitive function and behaviour. The combination of enhanced cognition and improved behavioural response may lead to improved functional independence and a delay in nursing home placement. Better performance of ADLs, increased social interaction and engagement in activities, and diminished need to take psychotropic medications have been found to improve patient and caregiver QOL.[90,91]

The beneficial effects of cholinesterase inhibitors in DLB may prolong independent functioning in a disease with a high rate of institutionalisation. Substantial behavioural benefit from these agents has been reported in DLB. Both donepezil and rivastigmine have shown a marked improvement in the neuropsychiatric features of DLB, with the majority of patients treated showing reductions in delusions, hallucinations and agitated behaviours (see section 2.2). This benefit makes these agents an acceptable choice for the treatment of these symptoms without the associated risk of EPS and neuroleptic malignant syndrome that occurs with the use of antipsychotics.

Cholinesterase inhibitors may be of benefit in the treatment of patients with Parkinson's disease who have dementia and neuropsychiatric symptoms. A study evaluating the use of tacrine in Parkinson's disease found that this agent reduced the frequency of hallucinations and, additionally, the severity of parkinsonism was reduced, as measured by the UPDRS.[47,92] Rivastigmine also has been found to improve cognitive performance and the neuropsychiatric symptoms of advanced Parkinson's disease.[93] The use of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms, cognitive abnormalities and parkinsonism

may enable clinicians to use them as monotherapy for the treatment of DLB rather than risk interactions with multiple medications.

3.3 Atypical Antipsychotics

Typical antipsychotics produce marked parkinsonism in patients with DLB and may shorten life.[3] These agents have excessive risk and should be avoided.

The atypical antipsychotics affect a variety of receptors resulting in greater benefit with lower incidence of EPS compared with typical antipsychotics.[94] The atypical antipsychotics, as well as the typical agent haloperidol, significantly reduced behavioural disturbances in patients with Alzheimer's disease compared with placebo.[23,95-98] The reduction in neuropsychiatric symptoms provides substantial benefit by delaying nursing home placement[99,100] and may reduce caregiver stress/burden.

Initial reports suggested that clozapine was well tolerated in patients with DLB; however, subsequent case studies describe exaggerated sensitivity with increased parkinsonism in patients receiving this agent (see section 2.3).[69,70] Risperidone has been associated with increased EPS and neuroleptic malignant syndrome in several case series (see section 2.3). This agent may be acceptable in lower dosages beginning with 0.25 to 0.5 mg/day with slow titration upward to an effective dosage. Careful clinical examination to note the presence of bradykinesia, changes in mentation, rigidity and tremor should be documented prior to each increase in dosage and routinely thereafter.

Olanzapine is another atypical agent studied in the treatment of DLB. This drug, like other atypicals, is associated with variable response rates, with limited controlled data in the treatment of DLB (see section 2.3). A *post-hoc* analysis of its use in DLB suggested a beneficial effect along with good tolerability when used in lower dosages (5 to 10 mg/day).[75] Controlled trials using quetiapine and ziprasidone have not been published.

The atypical antipsychotics as a class do not need to be avoided in the treatment of DLB, but they should be used with caution and with careful monitoring for the presence or worsening of EPS. They may be effective in the select cases when a demonstrable behavioural response is not achieved with cholinesterase inhibitors. When the use of an atypical antipsychotic becomes necessary, the agent should be chosen based on lowest incidence of EPS. Although there is very limited data on quetiapine, this agent has the lowest risk of EPS[101-104] and seems a reasonable alternative choice in patients who develop EPS in response to olanzapine or risperidone. Administration should begin with low dosages of 12.5 to 25mg nightly with increments of 12.5mg based on treatment response and adverse effects. A dosage of 300 mg/day may be required.

Coadminstration of antipsychotics and cholinesterase inhibitors may reduce the frequency of nausea and vomiting associated with the latter.

3.4 Antidepressants

Trials assessing treatment response to the various classes of antidepressants in patients DLB have not been performed. However, concepts regarding the use of these agents in the treatment of depression associated with Alzheimer's disease may be applied to DLB. TCAs should generally be avoided because of their anticholinergic properties. SSRIs are considered first-line therapy. Reported adverse effects associated with the SSRIs in the general population of depressed patients include exacerbation of or new-onset movement disorders,[105] hallucinations and apathy.[105] These adverse effects are concerning because the conditions are frequent in DLB and constitute some of the core clinical features necessary for the diagnosis. Other commonly reported adverse effects of SSRIs in the general population include nausea, vomiting, diarrhoea and sexual dysfunction.[106-110] The gastrointestinal adverse effects may worsen similar adverse effects reported with cholinesterase inhibitors; sexual dysfunction may have adverse effects on patient QOL and self-esteem. Controlled trials examining the treatment of depression and the safety and tolerability of these agents in DLB are warranted.

As previously noted, QOL is an important issue to consider when therapeutic agents are administered. Assessing QOL can help determine the effectiveness of the drug and is also important in addressing patient and caregiver self-esteem and opinion about their disease. By utilising QOL measures, physicians can better target a specific symptom or symptom complex that the patient feels is contributing to the morbidity of their condition. The majority of recent studies assessing QOL and antidepressant medications have found consistent improvement on standardised measures. These studies appear more robust for the SSRIs compared with TCAs, perhaps in part due to the improved adverse effect profile of the latter.[111,112]

Unfortunately, QOL scales have not been validated in DLB. The clinician may be able to determine QOL in patients with DLB by assessing the patient's reported response to medication changes or adjustments. QOL dimensions include the patient's ability to maintain independent function, perform their ADLs, spend less time institutionalised, and pursue hobbies and interests. Antidepressant medications may have a beneficial affect on mood with a resultant improvement in outlook and re-engagement in social activities. Agents such as the SSRI citalopram should be considered first-line therapy; this drug has limited anticholinergic properties and is well tolerated in Alzheimer's disease.[77,78]

4. Conclusions

DLB is a newly described clinical syndrome characterised by progressive cognitive decline. A diagnosis of probable DLB is made when two of three core features (parkinsonism, visual hallucinations and fluctuating cognition) are present in addition to the cognitive decline. Supportive features for the diagnosis include repeated falls, syncope, transient loss of consciousness, sensitivity to antipsychotics, systematised delusions, and hallucination in other modalities.

Treatment options for DLB can be divided into those for the motor manifestations, cognitive manifestations, and neuropsychiatric manifestations including both psychotic features and depression. There are limited data indicating that levodopa is beneficial for the treatment of the motor features. When signs of parkinsonism are disabling, therapy with dopaminergic agents is warranted. Cholinesterase inhibitors can be used for the treatment of cognitive decline and may reduce the neuropsychiatric symptoms. Atypical antipsychotics can be used with caution for the treatment of hallucinations and delusions in those patients without a behavioural response to cholinesterase inhibitors. There is essentially no role for typical antipsychotics in the treatment of DLB. For the treatment of depression, SSRIs are the best class of agents based on available efficacy and tolerability data.

No studies have addressed the complex issues involved in a comprehensive benefit-risk analysis of treatments for DLB. Extrapolated data from studies of Alzheimer's and Parkinson's diseases suggest that the use of cholinesterase inhibitors and atypical antipsychotics are warranted. SSRIs may be of benefit in patients with depression and dopaminergic agents can be used with caution in a subgroup of patients.

Acknowledgements

This program was supported by a National Institute on Aging Alzheimer's Disease Research Center grant (AG 16570), an Alzheimer's Disease Research Center of California grant, and the Sidell-Kagan Foundation. Dr Cummings has provided consultation to Eisai, Pfizer, Lilly, Janssen, Novartis, Bristol-Meyers Squibb, Astra-Zeneca and Parke-Davis relevant to compounds discussed in this article.

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