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Current Issues in Lewy Body Dementia Diagnosis, Treatment and Research

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Abstract - Lewy body dementia (LBD) is not a single disorder but a spectrum of disorders, including dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), and affects between 1,000,000 and 2,000,000 older Americans. LBD is a multi-system disorder, involving disturbances of movement, cognition, behavior, sleep and autonomic function and requires a comprehensive treatment approach to maximize the quality of life for both patients and caregivers. Early and accurate diagnosis is important, as LBD patients may respond differently than Alzheimer's disease patients to certain dementia and behavioral treatments. Traditional neuroleptics should be avoided, due to potentially severe side effects. Optimum management of LBD includes both pharmacological and non-pharmacological treatments for the patient, as well as education and support for the primary caregiver. Despite LBD's common prevalence, the general public and health care providers may not be adequately informed of its importance, burden, and costs to patients, caregivers and society, which has major implications for public policy and funding for research. Research funding agencies are encouraged to place LBD research funding on an equal footing with other major neurodegenerative diseases as with Parkinson's and Alzheimer's disease. The current absence of radiological or biological markers that can reliably aid in the diagnosis of DLB has led to a search for clinical measures that can serve as markers for pathology or predictors of disease progression. Moreover, there is an absence of effective treatment for DLB, except for drugs that offer modest control of the cognitive and behavioral symptoms. There are no therapies yet that are proven to alter or delay disease progression. A concerted effort is needed to bring researchers and industry representatives together at scientific meetings on LBD to share information and explore progress into the basic sciences and translate these findings into novel diagnostic methods and treatment options.

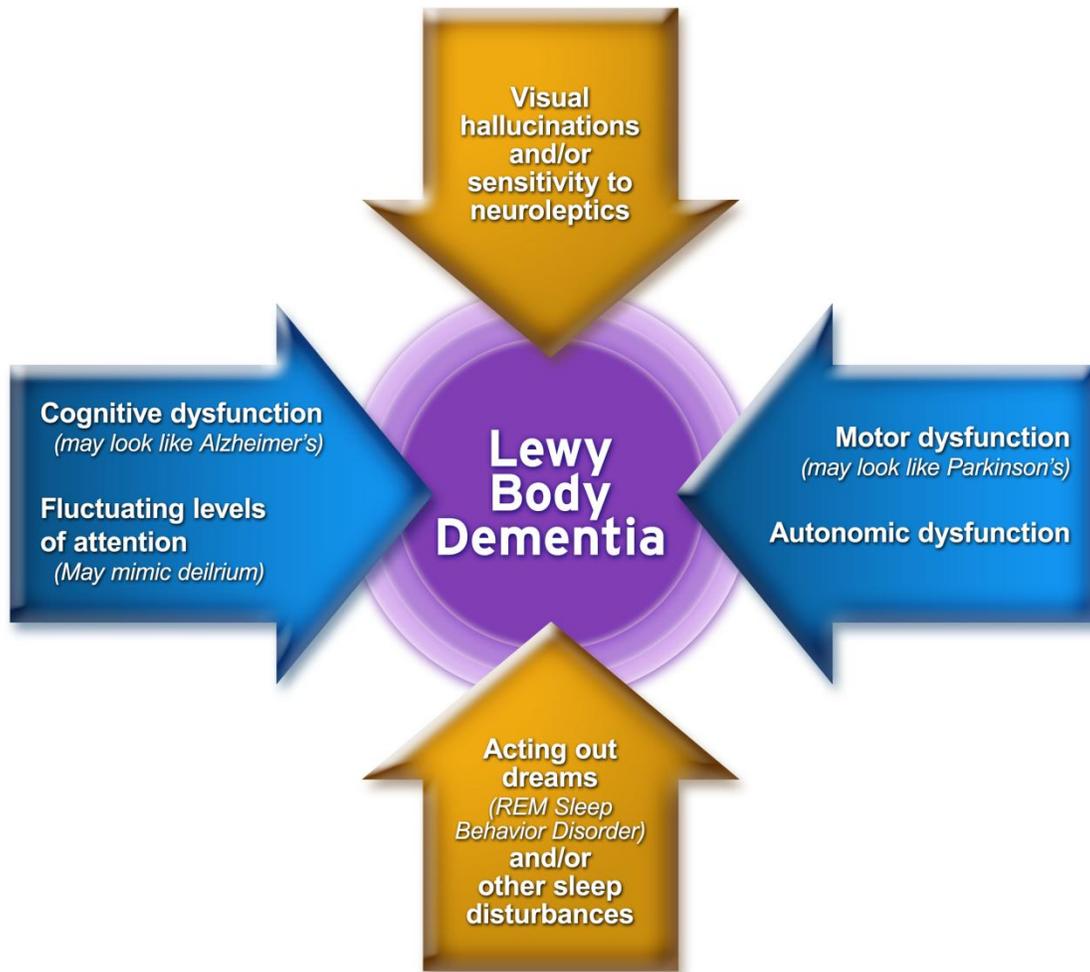
LBD is a Spectrum Disorder. LBD is not a single disorder but a spectrum of disorders involving disturbances of movement, cognition, behavior, sleep and autonomic function. LBD includes dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD). (Figure 1.)

Parkinson's disease (PD) is a common movement disorder that affects 1 in 100 individuals over the age of 60 and 4-5% of older adults over age 85 (approximately 1.5 million Americans). Original

descriptions of PD did not recognize cognitive problems as an important clinical feature. More recently, clinicians have come to realize that PDD occurs often and is among the most debilitating symptoms associated with disease progression. It is estimated that each year up to 14% of PD patients over age 65 will develop at least mild dementia. In one study, almost 80% of PD patients developed dementia over an 8 year period, underscoring the high prevalence of dementia in PD.

The Lewy Body Dementia Association's (LBDA) Scientific Advisory Council (SAC) was approached to establish a series of widely accessible publications, written in an easily understandable style to define and discuss LBD-related issues. This report summarizes a roundtable discussion by members of LBDA's SAC held at the American Academy of Neurology meeting in Boston, MA on May 1, 2007. Dialogue has been summarized in a question and answer (Q & A) format. Additional background information is provided herein from a comprehensive review of the medical literature and is provided as an anchor to the Q & A.

Figure 1. LBD is a spectrum disorder with heterogeneous onset.



In the past two decades, a related dementing disorder (DLB) has been described, characterized by signs and symptoms of parkinsonism, fluctuations in cognition and visual hallucinations. Diagnostic criteria derived from the third consensus conference on DLB and published in 2005 were developed with the awareness that many patients with PD develop dementia, usually within ten years of the onset of motor symptoms. Diagnostic criteria for PDD were only recently published in late 2007 and include essentially the same combination of symptoms, catalogued a bit differently. As there are no major clinical differences between DLB and PDD, a somewhat arbitrary diagnostic distinction was affirmed by the DLB consensus authors based on the temporal appearance of motor symptoms and dementia. That is, if motor symptoms precede dementia by more than 12 months, PDD is diagnosed, whereas, if dementia precedes or is concurrent with parkinsonism, then DLB is diagnosed. Because DLB and PDD share many clinical (as outlined in the DLB criteria) and pathological (Lewy

bodies) characteristics, both are classified as forms of LBD.

LBD Places a High Toll on Families. The combination of cognitive, motor and behavioral symptoms early in the course of LBD creates a highly challenging set of demands for continuing care. Recent studies demonstrate that LBD families need considerable resources and assistance from healthcare professionals and other health-related agencies, possibly even more than patients with AD.

A cross-sectional study evaluated 84 patients with DLB or AD in a secondary care setting, using the Bristol Activities of Daily Living Scale (BADLS) to assess functional impairments, the Unified Parkinson's Disease Rating Scale (UPDRS) to assess motor impairments, and the Neuropsychiatric Inventory (NPI) and Mini-Mental Status Examination (MMSE) to assess cognitive function. The study concluded that patients with DLB were more functionally impaired than patients with AD with similar

cognitive scores. Both groups had difficulties impacting a wide range of daily living skills including personal and domestic tasks and leisure activities. DLB patients were additionally impaired in self-care skills, including their ability to eat appropriately, clean their teeth, bathe independently, use the toilet, arise unaided, and walk independently. Conversely, AD patients were not shown to be significantly more impaired than DLB patients in any of the functional areas studied. DLB patients also had more motor difficulties than AD patients, and the total score on motor difficulties was highly correlated to functional impairment in areas of dressing, hygiene, teeth cleaning, bath/shower, toilet, transfers and mobility.

There are conflicting reports in the literature regarding disease progression, with some studies noting that LBD progression is more rapid than AD (6 years or less) while other reports show no difference. One study investigated whether DLB progresses more rapidly than AD to specific clinical endpoints such as nursing home placement or death, and whether the dementia itself progresses more rapidly between AD and DLB. The study revealed that individuals with DLB were 2 times more likely to die at comparable ages compared with people with AD. The average survival time for DLB was 78 years of age and for AD was 85 years of age. Men were 1.5 times more likely to die sooner than women. After diagnosis individuals with DLB had an average survival of 7 years while AD individuals lived 8.5 years. Nursing home placement was similar between DLB and AD, but length of survival after placement was impacted significantly by the presence of depression and parkinsonian signs such as rigidity and gait abnormalities, which were more common in DLB individuals. These findings suggest that there is a shorter course in DLB to long term care placement and death, which underscores the importance of accurate diagnosis for patients and families.

Another study compared resource use and cost in patients with DLB and AD, and assessed determinants in cost of care in DLB. In this study, DLB patients used more than double the amount of resources compared to AD patients. Specifically, DLB patients used greater resources in accommodations (long term residential care), and required more outpatient care, informal care (measured by caregivers' lost production and lost leisure time), community services and pharmacological therapy. AD patients utilized more inpatient care than DLB

patients. DLB patients' cost of care correlated significantly with dependency in basic self-care, and even more strongly with instrumental activities of daily living. Apathy, along with other neuropsychiatric features, was measured and found to be higher in DLB patients than AD patients. Cost of care for DLB patients with apathy was almost three times as high as in AD patients with apathy.

DIAGNOSING LBD

DLB Diagnostic Criteria. The diagnostic criteria for probable DLB require the presence of dementia with at least two of three core features: fluctuating attention and concentration, recurrent well-formed visual hallucinations, and spontaneous parkinsonian motor signs. Suggestive clinical features include rapid eye movement (REM) sleep behavior disorder and severe neuroleptic sensitivity. In the absence of two core features, the diagnosis of probable DLB can also be made if at least one suggestive feature is present with one core feature. Supportive clinical features include repeated falls, syncope, a transient loss of consciousness, severe autonomic dysfunction, depression, systematized delusions, or hallucinations in other sensory and perceptual modalities. While these features may support the clinical diagnosis, they lack diagnostic specificity and can be seen in other neurodegenerative disorders. These criteria have a sensitivity of 83% (17% clinical false negative rate) and a specificity of 95% (clinical false positive rate of only 5%) for the presence of neocortical Lewy bodies (LBs) at autopsy, the current diagnostic gold standard. However, these criteria are more predictive of autopsied cases with the relatively rare "pure" form of LBD rather than the much more common cases with a mixture of LBD and the pathology of AD. The criteria cannot reliably differentiate between the two clinical entities. The DLB criteria tangentially address PDD as very similar to DLB with the exception of temporal appearance of extrapyramidal signs. (i.e., in PDD the motor symptoms precede the onset of dementia by at least one year.)

The current absence of radiological or biological markers that can reliably aid in the diagnosis of DLB has led to a search for clinical measures that can serve as markers for pathology or predictors of disease progression. Moreover, there is also an absence of effective treatment for DLB, except for drugs that offer

modest control of the cognitive and behavioral symptoms. There are yet no therapies that have proven to alter or delay disease progression. Early clinical detection of dementia or the identification of pre-clinical markers of different dementia pathologies may provide insight into early disease mechanisms and pave the way for the development of disease modifying therapy, which of necessity must be initiated at the earliest possible juncture, ideally before symptoms have developed.

The importance of early, aggressive treatment is supported by recent data suggesting that LBD patients might have better responses to cholinesterase inhibitors than AD patients. In addition, an early diagnosis of LBD implies that treating physicians will know to avoid medications that can aggravate the clinical picture, such as the traditional neuroleptics. It is estimated that almost 60% of LBD patients may exhibit exaggerated extrapyramidal signs, sedation, immobility, or neuroleptic malignant syndrome (NMS) with fever, generalized rigidity and muscle breakdown following exposure to neuroleptics. NMS is a life-threatening condition and the higher prevalence in LBD suggests that traditional neuroleptics such as haloperidol, fluphenazine or thioridazine should be avoided.

Early diagnosis will also allow families and caregivers the time to plan for the expected decline. Preventive steps to improve safety in the home environment should be taken, given the tendency to recurrent falls and rapid attentional fluctuations. Families will also have time to develop a better understanding of their role in patient care, including assistance with daily activities and provision of social and cognitive stimulation.

PDD Diagnostic Criteria. A consensus statement by a task force from the Movement Disorder Society for the diagnosis of PDD has just been published, providing criteria for probable and possible PDD.

A diagnosis of probable PDD requires the core features (Table 1) and a typical presentation of clinical features which is defined as having deficits in at least two out of four cognitive domains (below). There may or may not be behavioral symptoms, although their presence would support a diagnosis of *probable* PDD. There must not be any features present from groups III and IV, as the abnormalities and conditions described in these categories can cause too much uncertainty in a potential diagnosis.

A diagnosis of *possible* PDD also requires the core features, but can have a more non-characteristic pattern of symptoms in at least one of the cognitive domains. There may or may not be any behavioral symptoms. One or more features of group III may be present, and none in Group IV.

What issues do physicians face in diagnosing LBD? Awareness of LBD among doctors, especially primary care physicians and other general healthcare providers appears to be very limited and is likely caused by multiple factors. For example:

1. A generalist needs an enormous amount of information to practice effectively in the 21st century. Their practice is typically filled with the more common, less time consuming and easily identifiable problems such as hypertension, high cholesterol, diabetes, etc. Because primary care physicians are so busy with the demands of daily practice, they may not have adequate opportunity to learn about less common disorders. This may lead them to view all dementias as due to Alzheimer's disease (AD.)
2. The complexity of understanding the full spectrum of the LBD symptoms and signs may not be practical for most general physicians. (Table 2.) Despite its complexity, the four most common causes of dementia - AD, LBD, stroke and frontotemporal dementia (FTD)— could easily become core knowledge.
3. Because LBD has such a wide array of non-cognitive symptoms, patients and caregivers do not know to report certain symptoms to their physician when seeking a diagnosis for cognitive decline.
4. There are no widely-accessible biomarkers for LBD.

Many generalists also do not typically recognize non-tremor parkinsonism. For example, if a primary care physician sees a patient who is slow and stiff, but has no tremor, the physician might see him just as an older patient who is slow and stiff. In reality, he might have parkinsonism. It is important to heighten awareness that parkinsonism comes in different shapes and sizes and the combination of parkinsonism and dementia should raise the flag of LBD.

Table I. Features of dementia associated with Parkinson's disease

Group I - The core feature requires a prior diagnosis of Parkinson's disease, and dementia causing a decline in function severe enough to impair the patient in daily activities and in at least one cognitive domain.

Group II - The clinical features include both the cognitive and behavioral domains described below:

Cognitive domains:

- Attention – The patient shows a level of impairment in attention, which may fluctuate over time
- Executive function – Impairment in complex thought processes such as in initiating an action, planning, or organization
- Visuo-spatial ability – Marked deficits in the processing of visuo-spatial material
- Memory – There is noticeable impairment in both the recall of existing memories and in the learning of new material
- Language – Basic language features are largely intact, although there may be difficulties in finding words and understanding complex sentences.

Behavioral domains:

- Apathy – Decreased spontaneity, motivation, effortful behavior
- Changes in personality and mood – Can include depression and anxiety
- Hallucinations - Usually complex and visual
- Delusions - Usually paranoid delusions, such as infidelity or perceived unknown guests in the home
- Excessive daytime sleepiness

Group III - The third category includes two features that will not rule out a diagnosis of PDD, but may make the diagnosis more uncertain:

- Existence of an abnormality such as vascular disease which causes cognitive impairment although not determined to cause dementia
- If the duration of time between the onset of motor and cognitive symptoms is not known

Group IV - The last domain contains two features which suggest that other existing conditions impair the patient's cognitive functioning to such an extent that reliable diagnosis of PDD becomes impossible.

- Cognitive or behavioral symptoms which occur only in the context of existing conditions, such as systemic diseases, drug intoxication, or major depression
 - Symptoms compatible with vascular dementia, confirmed by an established relationship between brain imaging results and impairment in neurological testing
-

Raising awareness and diagnostic rates of LBD will require a multi-pronged approach:

1. Preparing a simplified list of LBD symptoms specifically for use by primary care physicians, to enable them to more readily identify possible cases of LBD and refer them to a specialist for further evaluation
2. Because caregivers are highly motivated and persistent in seeking a diagnosis, educating them about the disease will encourage them to report all LBD symptoms to their doctors, and also likely drive physicians to learn more about LBD.
3. Adding more information on dementia to the curricula of most internal medicine residency training programs, or medical school courses is encouraged.
4. Non-physician healthcare personnel should be educated as well. Nurses, nurse practitioners, physician assistants, social workers or the other allied health professionals were educated to symptoms and signs, they could be the vanguard for recognizing these disorders.

Table 2. Dementia plus any combination of symptoms on this chart is adequate reason to suspect Lewy body dementia and pursue a differential diagnosis.

Symptom/Area of Deficit	Dementia with Lewy Bodies (DLB)	Parkinson's Disease Dementia (PDD)
Diagnostic Criteria:	<p><i>Probable =</i></p> <ul style="list-style-type: none"> • Dementia plus 2 Core • Dementia plus 1 Core, 1 Suggestive <p><i>Possible =</i></p> <ul style="list-style-type: none"> • Dementia plus 1 Core • Dementia plus 1 Suggestive 	<p><i>Probable =</i></p> <ul style="list-style-type: none"> • Parkinson's, Dementia plus 2 Core <p><i>Possible =</i></p> <ul style="list-style-type: none"> • Parkinson's, Dementia plus 1 Core
Dementia	Required	Required
<ol style="list-style-type: none"> 1. Memory impairment 2. Language impairment 3. Visuo-spatial function impairment 4. Executive function impairment 	<p>X</p> <p>X</p> <p>Usually prominent</p> <p>Usually prominent</p>	<p>Core</p> <p>Core</p> <p>Core</p> <p>Core</p>
Parkinsonism	Core (can occur around the same time OR after dementia)	PD diagnosis required (usually years before dementia)
Fluctuating Cognition	Core	X
<ol style="list-style-type: none"> 1. Reduced attention 2. Excessive daytime sleepiness 	<p>Usually prominent</p> <p>X</p>	<p>Core</p> <p>Supportive</p>
Visual hallucinations	Core	Supportive
Severe neuroleptic sensitivity	Suggestive	X
REM sleep behavior disorder	Suggestive	X
Changes in personality and mood		Supportive
<ol style="list-style-type: none"> 1. Depression 2. Anxiety 	<p>Supportive</p> <p>X</p>	<p>X</p> <p>X</p>
Delusions	Supportive	Supportive
Apathy	X	Supportive
Hallucinations in other modalities	Supportive	X
Severe autonomic dysfunction	Supportive	X
Repeated falls and syncope	Supportive	X
Transient, unexplained loss of consciousness	Supportive	

X = Common symptom not required for diagnosis

Beyond basic awareness, some physicians don't feel that the cost-benefit ratio for treating dementia patients is favorable. This is due, in part, to the modest response to cholinesterase inhibitors and memantine in Alzheimer's patients. LBD is a multi-system disorder, affecting motor, cognitive, behavioral, sleep, and autonomic systems. Broadening physicians' and caregiver's understanding of how to identify and manage the symptoms that respond to interventions may lead to improvement in the patient's and family's quality of life.

What symptoms are not usually reported at time of diagnosis? Nearly all LBD patients exhibit some form of sleep disorder, including restless legs syndrome, REM sleep behavior disorder, nocturnal leg cramps, and sleep apnea. Unfortunately, few patients and caregivers know to report these symptoms to their physician when seeking an explanation for cognitive decline. All patients and their sleep partners should be asked about sleep issues, and referred to a sleep specialist for a polysomnogram when appropriate.

Several studies showed that patients with Lewy body dementia/Lewy body disease had a tendency to have more abnormalities in the electrocardiogram (ECG), especially an abnormal Q-T interval. This has been reported in patients who never complained of chest pain or other cardiovascular problems. The presence of low uptake in a myocardial scintigraphy has been included in the recently revised criteria for DLB as a supportive feature. In the context of the person who's having autonomic dysfunction, an ECG is warranted before prescribing atypical antipsychotics.

THERAPEUTICS

Cognitive Symptoms

Symptomatic approach using acetylcholinesterase inhibitors (AChEIs). The therapeutic benefits of different pharmacologic approaches on the cholinergic system have been evaluated in both AD and LBD. While acetylcholine precursors and postsynaptic receptor agonists had poor results in clinical trials in AD, inhibition of acetylcholinesterase has demonstrated to provide symptomatic benefits. Acetylcholinesterase inhibitors (AChEIs) approved by the FDA for the treatment of AD include tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon),

and galantamine (Razadyne). To date, there is no compelling evidence that any one AChEI is better than the others. Three independent clinical studies of AChEI treatment using donepezil, galantamine or rivastigmine in patients with LBD suggest that all AChEIs improve cognitive and neuropsychiatric measures. Usually there is no significant increase in Parkinsonism with AChEI use.

a. Rivastigmine: Rivastigmine is a noncompetitive and reversible inhibitor of both acetylcholinesterase and butylcholinesterase available as a tablet, oral solution and transdermal patch. In the treatment of AD, it has been associated with improvement in cognition, behavioral symptoms, and functional abilities including activities of daily living (ADLs). In a double-blind, placebo-controlled, multi-center trial of DLB patients, treatment with rivastigmine 12 mg/day for 20 weeks was completed. On discontinuation of the drug, the differences between rivastigmine and placebo tended to disappear. The rivastigmine group had better performance on tests of attention, working memory and episodic memory compared to placebo. Patients given placebo showed a significant deterioration in attentional functions from baseline scores at 12 and 20 weeks, whereas patients on rivastigmine performed significantly above their baseline levels. Three weeks after discontinuation of rivastigmine, most parameters of cognitive performance returned to pretrial levels. Rivastigmine received FDA indications for the treatment of dementia associated with Parkinson's disease in 2007.

b. Donepezil: Donepezil is a reversible noncompetitive AChEI. It has a favorable pharmacokinetic profile available as once per day oral dosing either as tablet or oral-disintegrating forms with high specificity to acetylcholinesterase in brain tissue. Most of the side effects reported with donepezil are mild, dose-related and involve the gastrointestinal system and the central nervous system. An open label trial of donepezil compared treatment in 12 AD patients and 4 DLB patients. There was an improvement by 4.8 in MMSE scores in LBD, compared to 0.6 in AD. A randomized clinical trial of 5 mg/day of donepezil in patients with mild to moderate LBD reported marked improvements in behavioral and psychological symptoms of dementia but was not associated with cognitive improvement. The NPI-11 (behavioral) scores were significantly improved at weeks 8 and 12

compared with baseline. This dose was tolerated with no motor deterioration in the treatment group.

c. Galantamine: Galantamine is a reversible and competitive inhibitor of acetylcholinesterase and can amplify the actions of other receptors such as glutamate, serotonin, dopamine and GABA. The efficacy and safety of galantamine in LBD has been demonstrated in a 24 week open label study in 50 patients. There were beneficial effects in the NPI and the Clinician's Global assessment of change with mild side effects. In particular, there was improvement in visual hallucinations, nighttime behavior, and fluctuating cognitive deficits. There was also a benefit in sleep abnormalities and REM sleep behavior disorder.

NMDA antagonists (memantine): The excitatory neurotransmitter glutamate plays important roles in memory and learning. Glutaminergic dysfunction is well documented in AD and possibly contributes to the cognitive dysfunction. Overstimulation of NMDA receptors by glutamate results in calcium mediated excitotoxicity and cell death. Memantine (Namenda) is a noncompetitive voltage dependent antagonist with moderate affinity for the NMDA receptor. The efficacy and safety of memantine in moderate to severe AD have been reported in clinical trials and use of memantine in combination with donepezil has been reported to be more effective than the use of donepezil alone. It was approved by the FDA for the treatment of moderate to severe AD in 2003 but has not been adequately studied in LBD.

Do all Alzheimer's medications have a role to play in treatment of the cognitive decline in LBD? AChEI's have been considered by LBD experts to be the gold standard in treating cognitive and psychiatric symptoms of LBD. A recent comparative analysis of independent clinical studies of AChEI's in LBD demonstrated all AChEI's significantly improved cognitive and neuropsychiatric measures and that there was no significant increase in United Parkinson's Disease Rating Scale (UPDRS-III) scores. However, the study revealed no compelling evidence that supports any one AChEI as better than any other in treating DLB.

There is little published data on the use of memantine in LBD patients. Given that both AChEIs and memantine are often considered by various prescribers, until more research demonstrates clear

benefits, a cholinesterase inhibitor would be preferable to memantine.

Parkinsonism

There are no clinical trials on the best treatment of motor features in LBD. However, levodopa is generally the first-line treatment of PD and some improvement is seen in motor function with levodopa therapy in most cases of LBD. There is a risk, however of provoking behavioral or psychotic symptoms.

Dopamine agonists are associated with more side effects especially drug induced psychosis even at low doses. In head to head trials comparing levodopa to dopamine agonists in early PD, dopamine agonists have been found to be less effective and less well tolerated with a higher incidence of drug induced psychosis than levodopa. However, there is some suggestion that early treatment of PD with dopamine agonists, versus levodopa, may lower the risk of drug-induced dyskinesias. There are no direct head to head trials comparing dopamine agonists with levodopa in LBD. However, in the LBD patient the best risk-benefit ratio (motor improvement versus psychosis and dyskinesias) for treatment of motor features likely is achieved with levodopa. Therefore, a trial of levodopa is recommended in LBD with slow titration of the dose to produce symptomatic benefit.

Other PD medications such as amantadine, COMT inhibitors, MAO inhibitors and anticholinergics have the risk of exacerbating cognitive impairment and should be avoided if possible. Furthermore, the cognitive impairment in LBD makes those patients poor candidates for deep brain stimulation. AChEIs can potentially worsen parkinsonism. In a study of rivastigmine in PDD, approximately 10% of patients experienced worsening of tremor but it was not usually associated with significant medical concern.

How early should treatment of parkinsonism in LBD begin? Some LBD patients may not demonstrate overt or disabling parkinsonism for years. Given the potential negative side effects, physicians should be conservative when treating parkinsonism in LBD, and start with a slow titration of levodopa only if pharmacological intervention is necessary.

Behavioral changes

The first line intervention in treating problematic behaviors in LBD patients should be non-pharmacologic measures including evaluating for physical ailments that may be provoking behavioral disturbances (e.g. fecal impaction, pain, decubitus ulcers, urinary tract infection). Avoidance of, or reduction of doses of other medications that can potentially cause agitation should also be attempted. Affective disorders (anxiety and depression) are common in LBD and anecdotally, LBD patients respond to antidepressants and anxiolytics, although they have not been rigorously studied. A general rule is that when medications are needed to modify behaviors, they should be used for the shortest duration possible. Benzodiazepines should not be first-line agents given their risk of sedation and paradoxical agitation.

a. Antipsychotics. Visual hallucinations occur in up to 80% of patients with LBD and are considered one of the core features. Cholinergic deficits appear to be related to psychosis in LBD correlating with low CHAT activity and increased muscarinic receptor binding. Visual hallucinations have been suggested as predictors of a good response to the AChEI rivastigmine.

The management of psychosis in LBD has been mostly based on results of trials in AD and follows the general guidelines of pharmacotherapy in geriatric populations. In addition, some recommendations for the use of antipsychotics in LBD are based on studies in PD patients without dementia. Treatment can be very challenging given the sensitivity of these patients to even low doses of antipsychotics.

Typical neuroleptics (such as haloperidol) and atypical neuroleptics with D2 receptor antagonism (such as olanzapine and risperidone) should be avoided due to the risk of severe neuroleptic sensitivity reactions, neuroleptic malignant syndrome, parkinsonism, somnolence and orthostatic hypotension. Experience with atypical antipsychotics in LBD has been mixed. Risperidone and olanzapine have been shown to control psychosis and agitation in AD in randomized trials. Although low doses of risperidone (0.5 mg) and olanzapine (2.5 mg) are usually well tolerated and do not usually result in motor deterioration, in advanced LBD patients motor deterioration can still be seen.

Quetiapine and clozapine may be preferred when psychosis warrants treatment. Clozapine has been

demonstrated to be effective for PD psychosis in a randomized clinical trial. However, due to the potentially fatal adverse event of agranulocytosis and need for blood monitoring, it is not first-line. Aripiprazole has not been studied in LBD. Quetiapine has become a popular treatment of psychosis in LBD given the low incidence of motor deterioration and its ability to control visual hallucinations with low doses. Tolerability has been documented in both PD and DLB. However, measures of efficacy have had mixed results and most data is from either unblinded, open-label studies or small placebo-controlled studies

b. AChEI for behavioral symptoms. A meta-analysis of six large trials in AD showed a small but significant benefit for AChEI in treating neuropsychiatric symptoms. There also appears to be a differential effect of AChEI on different psychiatric symptoms, with psychosis, agitation, wandering, and anxiety being the most consistently responsive while negative symptoms of depression, apathy and eating behaviors are less responsive. Similarly, a few reports are available for behavioral improvement with the use of the AChEI rivastigmine in LBD. In a large multicenter trial, rivastigmine resulted in improvement by 30% from baseline in psychiatric symptoms. In a recent case control study of rivastigmine, treatment was associated with reduction in total behavioral scores, hallucinations and sleep disturbance compared to AD. There were lower rates of apathy, anxiety, delusions and hallucinations in the treatment group compared to controls. It is not clear whether this preferential effect on behavior is due to drug effect or more severe behavioral pathology already present in LBD.

How does the 'black box warning' on atypical antipsychotic medications relate to LBD?

According to the FDA, "in analyses of seventeen placebo-controlled studies of four drugs in this class (atypical antipsychotics), the rate of death for those elderly patients with dementia was about 1.6 to 1.7 times that of placebo. Although the causes of death were varied, most seemed to be either heart-related (such as heart failure or sudden death) or from infections (pneumonia)."

The FDA's 'black box warning' indicates these drugs are not approved for the treatment of behavioral symptoms in elderly patients with dementia. Physicians should discuss the risks and benefits of these types of

medications, so that LBD patients and caregivers can consider issues of quality of life against the risks associated with these medications.

REM sleep behavior disorder and insomnia.

Clonazepam has been the mainstay of medical therapy for REM behavior sleep disorder (RBD), usually effective at 0.25-0.5 mg/night, but doses above 1 mg are necessary in some patients. Melatonin may also offer some benefit either as monotherapy or in conjunction with clonazepam, particularly considering the lower risk of side-effects with melatonin compared to clonazepam. Melatonin may reduce the percentage of REM sleep without muscle atonia and decrease the number of stage shifts in REM sleep, suggesting it has a more direct mode of action on RBD pathophysiology. Other drugs reported to improve RBD include pramipexole, donepezil, levodopa, carbamazepine, triazolam, clozapine and quetiapine. For insomnia, treatment can be attempted with low doses of benzodiazepines or with agents such as zolpidem, trazodone, or chloral hydrate. These medications have not been extensively studied in LBD and daytime sedation is a potential side effect.

Autonomic dysfunction. Initial management of orthostatic hypotension consists of simple measures such as leg elevation, elastic stockings, increasing salt and fluid intake, and if possible avoiding medications that can exacerbate orthostasis. If simple measures fail, medications such as midodrine and fludrocortisone can be used. Midodrine is a vasoconstrictor and side effects include urine retention and supine hypertension. Fludrocortisone has mineralocorticoid activity and causes fluid retention.

Medications with anticholinergic activity such as oxybutynin, tolterodine tartrate, bethanechol chloride, propantheline can be used to treat urinary urgency, frequency and urge incontinence. They should be used cautiously however, given their risk of exacerbating cognitive problems. As LBD is more common in males, the risk of producing urine retention in the setting of prostatic hypertrophy should be considered.

Constipation can usually be treated by exercise and dietary modifications. Laxatives, stool softeners and mechanical disimpaction may be needed. The prokinetic effect of cholinergic stimulation by AChEIs might improve the symptoms in some patients.

Impotence in LBD is likely multifactorial. While autonomic dysfunction plays a major role, often there is contribution from other factors such as depression and motor impairment with nocturnal akinesia. Treatment is complex and often requires specialized care and a urologic consultation should be considered. Options include sildenafil, tadalafil, vardenafil, yohimbine, or a small bedtime dose of levodopa. If mood disturbances are associated with the sexual dysfunction, therapy with antidepressants can be considered.

Is there a role for nutraceuticals (herbal supplements) in the treatment of LBD symptoms?

To date, there is very little information in the scientific literature on the use of nutraceuticals in LBD and none are recommended by LBD experts as part of standard treatment.

Caution should always be taken when considering herbal supplements. Nutraceuticals do not go through the same rigorous testing for FDA approval as prescription medications and some can interact with other medications, lessening the effects of important medications or even creating a toxic reaction. Patients and caregivers should inform their physicians of every medication (including prescriptions, over-the-counter medications and herbal supplements) they are taking.

What non-pharmacological therapies should be considered in treating LBD?

Optimum management of LBD includes both pharmacological and non-pharmacological treatments for the patient, as well as education and support for the primary caregiver.

Physical therapy options include gait training, and cardiovascular, strengthening, and flexibility exercises. Physicians may also recommend exercise programs such as aerobic exercise, strengthening program, or water exercise.

LBD patients may be responsive to speech therapy for low voice volume and poor enunciation. Speech therapy may also improve inspiratory muscular strength and swallowing difficulties.

Occupational therapy may help maintain skills and promote function and independence.

Education of and support for the primary caregiver is essential to maintain optimum quality of life for both the patient and caregiver. Caregivers need to be educated about the symptoms of LBD, standard treatment options, and how to find the supportive services they will likely need during the course of LBD.

OVERVIEW OF THE NATIONAL INSTITUTE OF HEALTH (NIH) FUNDING FOR LBD RESEARCH

There are two institutes at the NIH which are largely responsible for funding research in LBD. The National Institute on Aging (NIA) has, as part of its mandate, funding for dementia research as well as other disorders of older adults. The National Institute of Neurological Disorders and Stroke (NINDS) is largely responsible for research funding for neurological disorders including Parkinson’s disease.

Between 2000 and mid-2007, the National Institutes of Health (NIH) funded 2895 projects directly related to AD including 29 Alzheimer Disease Centers through a number of earmarked funding programs (Source: <http://crisp.cit.nih.gov>). In contrast, during **this same time period, NIH funded only 29 grants directly related to clinical, basic science and educational projects related to LBD.** This disparity impedes progress in LBD research and leaves patients with LBD with a host of unmet needs.

A quick review of the dollars spent in the last fiscal year (2006) gives some overview of the funding shortfall for LBD research. (Table 3)

Table 3. NIA Funding in 2006

NIA funding for AD for 2006:	\$502,838,000
NINDS funding for AD for 2006:	\$45,087,000.
Total funding for AD for 2006	\$547,925,000
	With 4,000,000 estimated patients, that’s nearly \$137 per person for the year.
NIA funding for PD for 2006:	\$20,872,000
NINDS funding for PD for 2006:	\$113,489,000
Total funding for PD for 2006:	\$134,361,000
	With 1,500,000 estimated patients, that’s nearly \$90 per person for the year
Total funding for Lewy body dementias for 2006:	With 800,000 estimated DLB patients, that’s about \$21 per person for the year With 1,500,000 estimated PDD and DLB patients, that’s about \$11 per person for the year.
Total funding for all Lewy body disease (LBD and PD)	\$151,230,647 With 2,300,000 estimated patients, that’s about \$65 per person for the year

What are some of the biggest obstacles that LBD researchers are facing? The LBD patient population (DLB and PDD combined) is estimated to be approximately the same size as that of all cases of PD. Thus, it is necessary for those organizations currently funding research (i.e. the federal government, and industries like pharmaceuticals and imaging) to place LBD research funding priorities on an equal footing with PD. However, with NIA and NINDS both funding research on degenerative neurological conditions related by symptoms or biology to LBD, there is no

clear leader in LBD funding opportunities in the United States.

A concerted effort is needed to bring researchers and industry representatives together at scientific meetings on LBD to share information and explore progress into bench science, diagnostic methods and treatment options. Among its research goals for the next three years, the Lewy Body Dementia Association is planning to sponsor a Lewy Body Dementia Biomarker Symposium in 2009. This will be the first scientific meeting designed to discuss the current state of imaging, cerebrospinal fluid and other

biological markers for LBD. This is essential for determining what may be responsive to disease modifying interventions.

With the new consensus that LBD is a spectrum disorder, clinical trials are needed that include both PDD and DLB patients. There are very few clinical trials currently seeking any DLB patient participation.

Additional research is needed to make LBD research attractive to the pharmaceutical industry. Epidemiological studies are needed to establish a firm understanding of LBD prevalence. Additionally, the development of a mouse model for DLB would provide a clear biologic target to which drug discovery can be led.

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