Lewy Body Dementia: The Litmus Test for Neuroleptic Sensitivity and Extrapyramidal Symptoms

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Lewy body dementia, also referred to as dementia with Lewy bodies (DLB), is a neurodegenerative disorder now considered to be the second most common cause of dementia after Alzheimer's disease. Postmortem findings suggest that DLB accounts for 20% to 34% of all dementia cases and is often underdiagnosed. Salient features of DLB include fluctuations in cognition, perceptual abnormalities (e.g., visual hallucinations), and mild parkinsonism. Other symptoms include frequent falls, nighttime agitation, and depression. DLB symptomatology can be partly explained by the extensive destruction of dopaminergic and acetylcholinergic pathways caused by neurodegeneration. For this reason, DLB patients are especially vulnerable to the antidopaminergic and anticholinergic actions of most conventional antipsychotics, which makes treatment of the psychotic symptoms of DLB extremely difficult. Patients are particularly sensitive to developing extrapyramidal symptoms (EPS) and also to the potentially fatal complication of neuroleptic sensitivity, which affects ~50% of DLB patients. Therefore, a need exists for antipsychotic drugs with less propensity to induce EPS and reduced affinity for dopamine and acetylcholine receptors. Here we review studies evaluating the efficacy and tolerability of atypical antipsychotics for the treatment of psychoses associated with DLB. Olanzapine appears to be poorly tolerated, and risperidone has been associated with high risk of neuroleptic malignant syndrome. Clozapine use remains controversial because of its potent anticholinergic action and risk of agranulocytosis. Quetiapine has been shown to reduce psychiatric manifestations of DLB without causing neuroleptic sensitivity or increasing EPS. Hence, quetiapine is an attractive candidate for the treatment of psychoses in DLB and other dementias.

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Neurodegeneration underlies many brain disorders such as Alzheimer's disease, Parkinson's disease, and dementia with Lewy bodies (DLB). DLB is now thought to be the second most common cause of dementia after Alzheimer's disease.[1] DLB is characterized by the presence of halo-enclosed, protein-rich cytoplasmic bodies in the brainstem nuclei, diencephalon, basal ganglia, and cortical and subcortical regions.[2] Postmortem findings of characteristic neuropathologic markers associated with Lewy bodies such as α-synuclein, ubiquitin, torsin A, and others in patients with dementia suggest that DLB may account for as many as 20% to 34% of all dementia cases[3] and is often underdiagnosed.

CLINICAL AND NEUROPATHOLOGIC FEATURES OF DLB

Alzheimer's disease, Parkinson's disease and DLB share some common clinical and neuropathologic features. Lewy bodies are also present in Parkinson's disease, but they tend to be located predominantly in the brainstem. Alzheimer's disease is characterized by the presence of amyloid plaques, neurofibrillary tangles, and neuronal loss, particularly in the cortex and the hippocampus.[4] Differential diagnosis of Alzheimer's disease, Parkinson's disease, and DLB may be challenging, since any of these conditions may present with dementia, movement disorders, and depression. However, accurate diagnosis is important to devising an appropriate treatment strategy. Table 1[2] presents some differentiating clinical and neuropathologic characteristics of these 3 disorders.

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Table 1. Differentiating Clinical and Neuropathologic Features of Dementia With Lewy Bodies, Parkinson's Disease, and Alzheimer's Disease[a]

Variable	Dementia With Lewy Bodies	Parkinson's Disease	Alzheimer's Disease
Neuronal loss in substantia nigra	Variable	Marked	Variable
Dementia type	Cortical	Subcortical	Cortical
Dementia course	Dementia onset usually before motor disturbance; fluctuating psychiatric features	Dementia present in a minority of patients	Usually a "pure" dementing illness
Motor disturbances	Mild parkinsonism; some rigidity; early gait disturbance; tremor uncommon	Classic movement disorder: tremor, rigidity, akinesia, postural changes	Late gait disturbance
Lewy bodies			
Brainstem	+	++	–
Neocortex	++	±	–

[a]Adapted with permission from Kalra et al.[2]
Symbols: ++ = strong, + = moderate, ± = weak, – = absent.

Table 2. Equilibrium Dissociation Constants (nM) for Quetiapine and Other Antipsychotics at Human Brain Receptors[a]

	Receptor Type					
Antipsychotic	D_2	5-HT_{2A}	H_1	α_1	α_2	Muscarinic
Haloperidol	2.6	61	260	17	600	> 10000
Ziprasidone	2.6	0.12	4.6	2.6	154	2440
Risperidone	3.77	0.15	5.2	2.7	8	34000
Olanzapine	20	1.48	0.087	44	280	36
Clozapine	210	2.59	3.1	6.8	15	9
Quetiapine	770	31	19	8.1	80	1400

[a]Reprinted with permission from Richelson and Souder.[9] Values are geometric means of at least 3 independent experiments. Lower values indicate higher affinity for a particular receptor and vice versa.
Abbreviations: D = dopamine, 5-HT = serotonin, H = histamine.

DLB is a rapidly progressive yet variable disorder. While clinical diagnostic criteria for DLB continue to evolve, its prominent characteristics include a dementia syndrome associated with fluctuations in cognition, the presence of perceptual abnormalities, of which visual hallucinations are the most common, and mild parkinsonism. Other symptoms include frequent falls, nighttime agitation, rapid eye movement (REM) sleep behavior disorder, and mild depression. Hallucinations and delusions are present in approximately 90% of DLB patients and are leading causes of psychiatric referrals. In a study by Klatka et al.,[5] hallucinations and depression were more frequent in DLB than in Alzheimer's disease patients, while delusions were more common in DLB and Alzheimer's disease patients than in Parkinson's disease patients. Cognitive fluctuations in DLB patients are characterized by rapid alternations in the level of consciousness, e.g., unexplained loss of consciousness (which may produce falls), along with periods of lucidity, agitation, crying, or hallucinations. Variations in concentration, attention, and short- and medium-term memory are also common. The clinical presentation of DLB could, in part, be understood in light of extensive destruction of dopaminergic and acetylcholinergic neurotransmitter systems by the underlying pathologic process.[6]

Treating the psychotic symptoms of DLB is challenging. Extrapyramidal symptoms (EPS) (muscle rigidity and cogwheeling) are common side effects of conventional antipsychotics.[7] In addition, administration of typical antipsychotics (e.g., haloperidol, thioridazine, trifluoperazine, flupenthixol, or sulpiride) to DLB patients often leads to development of severe sedation, immobility, rigidity, postural instability, falls, increased confusion, and inability to maintain adequate food and fluid intake, a syndrome often referred to as neuroleptic sensitivity.[8] Neuroleptic sensitivity affects approximately 50% of DLB patients and represents a potentially fatal complication.[8] Such extreme sensitivity may be partly explained by the antidopaminergic and anticholinergic profiles of most antipsychotics (Table 2[9]). For instance, haloperidol and risperidone have a high affinity for dopamine-2 (D_2) receptors and olanzapine and clozapine for cholinergic (muscarinic) receptors.[9] Thus, there is a need for antipsychotic drugs with a significantly lowered affinity for dopamine and acetylcholine receptors and a reduced propensity to induce neuroleptic sensitivity.

This article reviews the available data on the efficacy and tolerability of atypical antipsychotics for the treatment of psychosis in patients with the closely related disorders of DLB and Parkinson's disease.

MECHANISMS OF SENSITIVITY TO ANTIPSYCHOTICS IN DLB PATIENTS

DLB patients have an altered neurochemistry. They have a cholinergic deficit in the temporal neocortex,[2,6] and reduced levels of choline acetyltransferase may contribute to the development of visual hallucinations, an unwanted effect noted with anticholinergic drugs.[6] DLB patients have a greater cholinergic deficit and more functional cortical neurons than do Alzheimer's disease patients, and may therefore benefit from cholinergic replacement.[6]

It is not known at present if early pharmacologic interventions can prevent the development or reduce the progression of psychotic symptoms typically associated with the underlying degenerative process. If psychotic symptoms are mild, pharmacologic intervention may not be necessary. However, when hallucinations or delusions

start to interfere with the patient's daily life, then active treatment is required. Cholinergic therapy is aimed at treating cognitive impairment, atypical antipsychotics are used for hallucinations, and dopamine agonists such as levodopa or carbidopa are used to improve parkinsonism.[1]

Centrally acting acetylcholinesterase inhibitors (e.g., rivastigmine, donepezil, galantamine) are thought to ameliorate the decreased cholinergic activity in the cortex and may improve cognition, neuropsychiatric symptoms (i.e., hallucinations, mental fluctuations), and REM sleep behavior disorder.[1]

The toxic effects of typical or atypical antipsychotic therapy are usually more severe and acute and may even be irreversible in patients with DLB.[8] Furthermore, survival time in DLB patients may be shortened when treated with antipsychotics.[6] Therefore, extra care when selecting and administering any antipsychotic must be taken. The dopaminergic blocking activity of typical antipsychotics, together with the intrinsic parkinsonian features of DLB, make these patients extremely sensitive to these agents.[4]

Possible explanations for this increased sensitivity could be the relative loss of dopaminergic neurons in the brains of DLB patients, particularly in the substantia nigra,[6] and the failure of postsynaptic striatal neurons to up-regulate D_2 receptors in response to a dopaminergic deficit or D_2-blocking drugs.[10]

Therefore, more selective agents, e.g., dopamine blockers that target the mesocorticolimbic system while sparing the dopamine-deficient nigro-striatal pathway, may decrease the psychotic symptoms of DLB without worsening EPS. For instance, clozapine has a high affinity, while displaying a low propensity for EPS, for D_4 receptors, which concentrate in the limbic system and may improve cognitive and emotional symptoms.[11] In contrast to typical antipsychotics, which bind to D_2 receptors with a high affinity, the mode of action of atypical antipsychotics is thought to involve low to moderate affinity for D_2 receptors, associated with a high affinity for serotonin-2 (5-HT_2) receptors.[12] Positron emission tomography studies have shown that quetiapine and clozapine can be displaced within minutes from D_2 receptors by physiologic concentrations of dopamine, whereas displacement occurs much more slowly with drugs such as haloperidol, chlorpromazine, or olanzapine.[12] It could be speculated that this "loose binding"[13] to D_2 receptors would therefore allow normal dopaminergic neurotransmission to take place and avoid the neuroleptic sensitivity and movement disorders that are likely in DLB patients treated with D_2 receptor blockers. The relatively low affinity of quetiapine for D_2 receptors, together with its low affinity for acetylcholine receptors, may explain its placebo-like tendency to cause EPS.[14]

In DLB, dopamine levels are reduced in the caudate region, but usually preserved on the temporal cortex.[6] Together with preserved 5-HT levels, this results in a monoaminergic/cholinergic imbalance that may be responsible for the development of visual hallucinations.[6] Since dopamine blockers cause unacceptable morbidity in DLB patients, selective 5-HT receptor antagonism may play a role in treating the psychotic and affective symptoms of DLB and other psychoses. Serotonin receptors are thought to be involved in the control of mood, cognition, and motor behavior directly and through the modulation of other receptors.[15] In theory, a reduction of 5-HT levels in the temporal cortex by a 5-HT antagonist would help diminish the monoaminergic/cholinergic imbalance, which in turn would reduce hallucinations. Of note, hallucinogenic drugs such as lysergic acid diethylamide (LSD) are partial 5-HT_2 receptor agonists, while atypical antipsychotic drugs are 5-HT_2 receptor antagonists (Table 2[9]), thus indicating that drugs which preferentially block these receptors may help reduce hallucinations. Consistent with this finding, DLB patients experiencing hallucinations have relatively preserved 5-HT_2 receptors in the temporal cortex compared with nonhallucinating DLB patients or patients with Alzheimer's disease.[6]

EFFICACY OF ATYPICAL ANTIPSYCHOTICS FOR THE TREATMENT OF PARKINSON'S DISEASE DEMENTIA

Psychotic symptoms have a negative impact on the quality of life of Parkinson's disease patients and their caregivers. Also, they pose a major risk factor for permanent nursing home placement.[16]

The main pathologic feature of Parkinson's disease is the degeneration of dopamine-producing cells in the substantia nigra and the ventral tegmental area of the midbrain.[16] There may also be varying degrees of degeneration of the central cholinergic, noradrenergic, and serotonergic systems.[17] The dopamine deficiency in the striatal regions results in abnormal motor behavior, while in the mesocorticolimbic system, it may cause psychomotor retardation, anxiety or depression, and cognitive dysfunction. The loss of frontal cholinergic activity may also contribute to delusions, hallucinations, and attentional deficits. The cholinergic deficit in Parkinson's disease patients with dementia appears to be more prominent than that in Alzheimer's disease or DLB patients.[17]

In Parkinson's disease, dementia is usually of the subcortical type, and, until recently, Parkinson's disease was considered a classic movement disorder often treated with dopaminergic drugs. However, psychotic symptoms may be present in up to 25% of Parkinson's disease patients and can be intrinsic to the disease (i.e., caused by dopaminergic/cholinergic deficiencies) or extrinsic, induced by anticholinergic or dopaminergic medications.[17] As in DLB, psychotic symptoms in Parkinson's disease patients are difficult to treat because motor dysfunction may be exacerbated by antipsychotic treatment, and anticholinergic and dopaminergic medication may in turn ex-

acerbate psychotic symptoms. In particular, dopaminergic agents may induce dopamine hypersensitivity in the frontal and limbic dopamine projection regions.[17]

Several studies have looked into using antipsychotics for the treatment of the dementia symptoms of Parkinson's disease.

In an early double-blind, placebo-controlled trial, Wolters and colleagues[18] examined the effect of clozapine in dopaminomimetic psychosis and parkinsonism in a group of 6 patients. Although clozapine prevented psychosis in 2 patients, 3 patients had to be withdrawn due to excessive sedation or incapacitating delirium.[18] Two larger, double-blind studies of clozapine found that it alleviated psychosis without a decline in motor function.[19,20] Two subsequent studies, one double-blind and one open-label, comparing clozapine versus olanzapine reported better efficacy of clozapine for psychotic symptoms but worsened EPS with olanzapine,[21,22] and one trial was stopped because of intolerable EPS with olanzapine.[22] In a 12-week, double-blind study of clozapine versus risperidone in 10 patients, similar relief of psychotic symptoms was achieved with both drugs, but EPS worsened with risperidone.[23] A 12-week, open, pilot study in 17 patients reported efficacy and tolerability with risperidone.[24]

Preliminary studies with quetiapine reported psychotic symptom relief and few EPS,[25,26] and the results were supported by data from a 24-week, open-label study in which 29 patients with Parkinson's disease–related psychosis showed significant improvements in cognitive function after quetiapine treatment.[27] A subsequent retrospective study in 43 patients found that quetiapine improved psychosis in 81% of Parkinson's disease patients presenting with or without dementia, although patients with dementia appeared to have a higher propensity for developing EPS.[28]

Of interest, several reports have recently recommended clozapine and quetiapine as first-line agents for the treatment of Parkinson's disease patients with psychosis.[29,30] Due to the fact that clozapine can cause agranulocytosis and patients require regular hematological monitoring during clozapine therapy, other investigators prefer quetiapine over clozapine for the treatment of drug-induced psychosis in Parkinson's disease patients.[31]

EFFICACY AND TOLERABILITY OF ATYPICAL ANTIPSYCHOTICS IN DLB

Recently, a literature review of double-blind, placebo-controlled studies of antipsychotics for the treatment of psychosis and agitation in elderly patients with dementia reported that mean improvement rates were 61% with typical or atypical antipsychotics and 35% with placebo.[32] Although additional controlled, large-scale studies are needed, several of the small-scale studies reviewed suggested that atypical antipsychotics such as clozapine, risperidone, olanzapine, and quetiapine may be able to treat psychoses associated with dementia.[32] However, available data suggest that these drugs may not be equally beneficial to patients with DLB. Also, it is important to note that the antipsychotic doses required to ameliorate psychotic symptoms in DLB patients are usually substantially lower than are those required for other indications, and it is necessary to carefully titrate any antipsychotic medication, starting at a low dose. Dose increments should be small and made every 3 to 5 days.[30]

Table 3 presents a summary of studies evaluating the efficacy and tolerability of atypical antipsychotics in patients with DLB, including case histories, open-label studies, and double-blind studies.[8,10,33–51]

The use of clozapine in DLB patients remains controversial because of its potent anticholinergic action and the risk of agranulocytosis, which requires frequent blood monitoring.[27,30] Although 2 studies have reported efficacy and few EPS with clozapine,[33,34] in some patients it may irreversibly exacerbate psychotic symptoms[35] or induce coma.[36]

There have been a small number of studies showing the efficacy of risperidone either alone or in combination with levodopa for the treatment of DLB.[37–40] However, the use of risperidone in DLB patients has been associated with a high risk of neuroleptic malignant syndrome[10,41] and delirium.[42]

In a study of olanzapine for the treatment of DLB,[43] 8 patients with psychotic and behavioral difficulties were given olanzapine, 2.5 to 7.5 mg/day, for 12 weeks and monitored for psychotic symptom improvement and EPS. It was found that 3 of 8 patients could not tolerate olanzapine even at the lowest doses available, 3 others could tolerate it but gained minimal benefit, and only 2 patients showed improvement. Although one subsequent case history described worsening of both psychotic symptoms and EPS after olanzapine treatment,[44] a post hoc analysis of a subset of 29 patients who met criteria for Alzheimer's dementia but were thought to meet criteria for DLB as well reported significant reductions in hallucinations and delusions without exacerbating EPS.[45]

Unlike other typical or atypical agents, quetiapine has a placebo-level incidence of EPS across the wide dose range.[14,46] Several small-scale, open-label or retrospective studies in DLB patients have found that quetiapine alleviates psychosis, agitation, and anxiety without exacerbating EPS or causing neuroleptic sensitivity (Table 3).[27,47–50]

In a recent open-label study of 8 patients with DLB,[51] it was shown that after 12 weeks of quetiapine treatment (≤ 150 mg/day), psychotic symptoms were significantly reduced, as measured by the Neuropsychiatric Inventory (NPI) scores and Brief Psychiatric Rating Scale (BPRS) scores. Importantly, the largest reductions were observed in the NPI hallucinations and nighttime behavior subscales.[52] Quetiapine appeared to be well tolerated in this

Table 3. Studies of Antipsychotics in Dementia With Lewy Bodies

Antipsychotic	Study	N	Duration	Study Design	Dose, mg/d	Efficacy	Tolerability
Clozapine	Chacko et al[33]	1	6 months	Case report	75	Hallucinations stopped, mood improved	No worsening of orthostatic hypotension or EPS
	Geroldi et al[34]	1	3 months	Case histories	37.5	Hallucinations decreased	No parkinsonian side effects
	Burke et al[35]	2	1 dose or a few days	Case reports	6.5–12.5	Exacerbation of hallucinations, delusions, and paranoia, which persisted after clozapine discontinuation	No worsening of EPS
	Sadek and Rockwood[36]	1	1 dose	Case report	175 (accidental)	NA	Coma lasting 14 days
Risperidone	Allen et al[37]	3	28 days	Case histories	0.5–1.0	Improvement of psychotic and behavioral symptoms	Slight worsening of EPS in 1 patient
	McKeith et al[10]	3	1–4 days	Case histories	0.5–1.0	NA	Extrapyramidal rigidity, shuffling gait
	Ballard et al[8]	2	Few days	Case histories	0.25–5.00	1 patient had marked cognitive impairment	1 patient experienced oversedation, parkinsonism, confusion, and died within 3 weeks
	Shiwach and Woods[38]	1	2 weeks	Case report	4	Psychotic symptom resolution	No worsening of EPS
	Geizer and Ancill[39]	1	2 months	Case report	0.25 (plus donepezil, 5 mg)	Improvements in BPRS and MMSE scores	NA
	Kato et al[40]	1	20 months	Case report	1 (plus L-dopa, 300–750 mg)	Psychotic symptom improvements	No worsening of motor or cognitive function
	Sechi et al[41]	1	10 days	Case report	2.5	NA	Developed neuroleptic malignant syndrome
	Morikawa and Kishimoto[42]	1	2 days	Case report	1	NA	Stopped due to severe delirium
Olanzapine	Walker et al[43]	8	12 weeks	Open label	2.5–7.5	2 patients had clear improvement	3 patients could not tolerate olanzapine
	Baldwin and Avery[44]	1	Not stated	Case report	Not stated	Worsening of psychotic symptoms	Worsening of motor function
	Cummings et al[45]	29 (placebo, N = 10; olanzapine, N = 19)	6 weeks	Post hoc analysis of subset of Alzheimer's disease patients	Fixed dose, 5–15	Significant reduction in delusions and hallucinations in patients receiving 5–10 mg/d	No worsening of motor function
Quetiapine	Parsa et al[47]	10	NA	Retrospective chart review	25–300 (plus donepezil, 5–10 mg)	Improvement in psychotic and behavioral symptoms	No worsening of motor function
	Elliott[48]	9	12 weeks	Open label	12.5–275.0	Significant reductions in level of psychosis	No worsening of EPS or cognition
	Takahashi et al[49]	9	8 weeks	Case histories	25–75	5 patients showed a reduction in psychotic symptoms (NPI scores)	No change in Simpson-Angus Scale scores; 2 patients reported somnolence and 1 patient had orthostatic hypotension
	Fernandez et al[50]	11	NA	Retrospective chart review	69	10 patients had partial resolution of psychosis	Mild motor worsening in 3 patients
	Baskys[51,52]	13	12 weeks	Open label	25–150	Significant reductions in psychotic symptoms	No worsening of motor function

Abbreviations: BPRS = Brief Psychiatric Rating Scale, EPS = extrapyramidal symptoms, MMSE = Mini-Mental State Examination, NA = not applicable, NPI = Neuropsychiatric Inventory.

group of DLB patients and caused no worsening of EPS. In this study, however, 2 patients remained without improvement, and, although no explanation could be found, this may be due to the mental fluctuations typically associated with DLB.[51]

There are no data on ziprasidone and aripiprazole for the treatment of DLB patients at present. A recent 10-week, placebo-controlled study evaluated the efficacy and tolerability of aripiprazole, 2 to 15 mg/day, in 208 patients with Alzheimer's disease.[53] Although BPRS scores on the hallucinations and delusions subscales were significantly reduced compared with placebo, NPI psychosis subscale scores were similar between aripiprazole and placebo. More studies on these and other atypicals for the treatment of psychosis in DLB patients are desirable.

CONCLUSION

DLB and Parkinson's disease are neurodegenerative disorders that share several clinical and neuropathologic features, including the presence of Lewy bodies in various brain regions, movement abnormalities, and dementia. Psychotic symptoms in DLB patients are particularly difficult to treat due to these patients' extreme sensitivity to anticholinergic and antidopaminergic medications. Available data on atypical antipsychotics suggest that these agents may be useful for treating delusions, hallucinations, and agitation in DLB and Parkinson's disease patients, and, as such, both clozapine and quetiapine are considered first choices in treating Parkinson's disease–related psychosis.[29] However, important differences in the tolerability of the various atypicals remain, and these differences will determine the usefulness of these agents for the treatment of DLB patients. For instance, olanzapine and risperidone are not well tolerated due to worsening of EPS and neuroleptic sensitivity, and the use of clozapine remains controversial because of the extra risks associated with this antipsychotic. Quetiapine is an attractive candidate for the treatment of psychoses associated with DLB due to its ability to relieve hallucinations and delusions and its low propensity for EPS. Currently, there are no data on ziprasidone and aripiprazole in this patient population.

More direct comparisons between the atypical agents, and in a larger number of patients, would be of interest to ascertain the best treatment strategies for psychoses associated with DLB as well as other dementias.

Drug names: aripiprazole (Abilify), carbidopa (Lodosyn), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril and others), donepezil (Aricept), galantamine (Reminyl), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), rivastigmine (Exelon), trifluoperazine (Stelazine and others), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, aripiprazole, chlorpromazine, clozapine, donepezil, galantamine, haloperidol, olanzapine, quetiapine, risperidone, rivastigmine, trifluoperazine, ziprasidone, flupenthixol, sulpiride, and thioridazine are not approved by the U.S. Food and Drug Administration for the treatment of Lewy body dementia.

REFERENCES

1. Zesiewicz TA, Baker MJ, Dunne PB, et al. Diffuse Lewy body disease. Curr Treat Options Neurol 2001;3:507–518
2. Kalra S, Bergeron C, Lang AE. Lewy body disease and dementia: a review. Arch Intern Med 1996;156:487–493
3. Luis CA, Mittenberg W, Gass CS, et al. Diffuse Lewy body disease: clinical, pathological and neuropsychological review. Neuropsychol Rev 1999;9:137–150
4. Raskind MA, Peskind ER. Alzheimer's disease and related disorders. Med Clin North Am 2001;85:803–817
5. Klatka LA, Louis ED, Schiffer RB. Psychiatric features in diffuse Lewy body disease: a clinicopathologic study using Alzheimer's disease and Parkinson's disease comparison groups. Neurology 1996;47:1148–1152
6. Beck BJ. Neuropsychiatric manifestations of diffuse Lewy body disease. J Geriatr Psychiatry Neurol 1995;8:189–196
7. Luis CA, Barker WW, Gajaraj K, et al. Sensitivity and specificity of three clinical criteria for dementia with Lewy bodies in an autopsy-verified sample. Int J Geriatr Psychiatry 1999;14:526–533
8. Ballard C, Grace J, McKeith I, et al. Neuroleptic sensitivity in dementia with Lewy bodies and Alzheimer's disease [letter]. Lancet 1998;351: 1032–1033
9. Richelson E, Souder T. Binding of antipsychotic drugs to human brain receptors: focus on newer generation compounds. Life Sci 2000;68:29–39
10. McKeith IG, Ballard CG, Harrison RWS. Neuroleptic sensitivity to risperidone in Lewy body dementia [letter]. Lancet 1995;346:699
11. Jardemark K, Wadenberg ML, Grillner P, et al. Dopamine D3 and D4 receptor antagonists in the treatment of schizophrenia. Curr Opin Investig Drugs 2002;3:101–105
12. Goldstein JM. The new generation of antipsychotic drugs: how atypical are they? Int J Neuropsychopharmacol 2000;3:339–349
13. Kapur S, Seeman P. Does fast dissociation from the dopamine D_2 receptor explain the action of atypical antipsychotics? a new hypothesis. Am J Psychiatry 2001;158:360–369
14. Kasper S, Müller-Spahn F. Review of quetiapine and its clinical applications in schizophrenia. Expert Opin Pharmacother 2000;1:783–801
15. Baskys A, Remington G, eds. Brain Mechanisms and Psychotropic Drugs. 1st ed. Boca Raton, Fla: CRC Press; 1996
16. Aarsland D, Larsen JP, Tandberg E, et al. Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. J Am Geriatr Soc 2000;48:938–942
17. Wolters EC, Berendse HW. Management of psychosis in Parkinson's disease. Curr Opin Neurol 2001;14:499–504
18. Wolters EC, Hurwitz TA, Mak E, et al. Clozapine in the treatment of parkinsonian patients with dopaminomimetic psychosis. Neurology 1990;40:832–834
19. The French Clozapine Parkinson Study Group. Clozapine in drug-induced psychosis in Parkinson's disease [letter]. Lancet 1999;353:2041–2042
20. The Parkinson Study Group. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. N Engl J Med 1999;340:757–763
21. Giménez-Roldán S, Mateo D, Navarro E, et al. Efficacy and safety of clozapine and olanzapine: an open-label study comparing two groups of Parkinson's disease patients with dopaminergic-induced psychosis. Parkinsonism Relat Disord 2001;7:121–127
22. Goetz CG, Blasucci LM, Leurgans S, et al. Olanzapine and clozapine: comparative effects on motor function in hallucinating PD patients. Neurology 2000;55:789–794
23. Ellis T, Cudkowicz ME, Sexton PM, et al. Clozapine and risperidone treatment of psychosis in Parkinson's disease. J Neuropsychiatry Clin Neurosci 2000;12:364–369
24. Mohr E, Mendis T, Hildebrand K, et al. Risperidone in the treatment of dopamine-induced psychosis in Parkinson's disease: an open pilot trial. Mov Disord 2000;15:1230–1237
25. Menza MMA, Palermo B, Mark M. Quetiapine as an alternative to clozapine in the treatment of dopamimetic psychosis in patients with Parkinson's disease. Ann Clin Psychiatry 1999;11:141–144
26. Parsa MA, Bastani B. Quetiapine (Seroquel) in the treatment of psychosis in patients with Parkinson's disease. J Neuropsychiatry Clin Neurosci

1998;10:216–219
27. Juncos JL, Roberts VJ, Evatt ML, et al. Tolerability, efficacy and cognitive effects of quetiapine in patients with Parkinson's disease treated for psychotic symptoms [poster]. Presented at the 13th European College of Neuropsychopharmacology Congress; Sept 9–13, 2000; Munich, Germany
28. Reddy S, Factor SA, Molho ES, et al. The effect of quetiapine on psychosis and motor function in parkinsonian patients with and without dementia. Mov Disord 2002;17:676–681
29. Olanow CW, Watts RL, Koller WC. An Algorithm (Decision Tree) for the Management of Parkinson's Disease (2001): Treatment Guidelines. Neurology 2001;56(11, suppl 5):S1–S88
30. Motsinger CD, Perron GA, Lacy TJ. Use of atypical antipsychotic drugs in patients with dementia. Am Fam Physician 2003;67:2335–2440
31. Friedman JH. Atypical antipsychotics in the EPS-vulnerable patient. Psychoneuroendocrinology 2003;28(suppl 1):39–51
32. Kindermann SS, Dolder CR, Bailey A, et al. Pharmacological treatment of psychosis and agitation in elderly patients with dementia: four decades of experience. Drugs Aging 2002;19:257–276
33. Chacko RC, Hurley RA, Jankovic J. Clozapine use in diffuse Lewy body disease. J Neuropsychiatry Clin Neurosci 1993;5:206–208
34. Geroldi C, Frisoni GB, Bianchetti A, et al. Drug treatment in Lewy body dementia. Dement Geriatr Cogn Disord 1997;8:188–197
35. Burke WJ, Pfeiffer RF, McComb RD. Neuroleptic sensitivity to clozapine in dementia with Lewy bodies. J Neuropsychiatry Clin Neurosci 1998;10:227–229
36. Sadek J, Rockwood K. Coma with accidental single dose of an atypical neuroleptic in a patient with Lewy body dementia [letter]. Am J Geriatr Psychiatry 2003;11:112–113
37. Allen RL, Walker Z, D'Ath PJ, et al. Risperidone for psychotic and behavioural symptoms in Lewy body dementia [letter]. Lancet 1995; 346:185
38. Shiwach RS, Woods S. Risperidol [sic] and withdrawal bruxism in Lewy body dementia [letter]. Int J Geriatr Psychiatry 1998;13:65–66
39. Geizer M, Ancill RJ. Combination of risperidone and donepezil in Lewy body dementia [letter]. Can J Psychiatry 1998;43:421–422
40. Kato K, Wada T, Kawakatsu S, et al. Improvement of both psychotic symptoms and parkinsonism in a case of dementia with Lewy bodies by the combination therapy of risperidone and L-DOPA. Prog Neuropsychopharmacol Biol Psychiatry 2002;26:201–203
41. Sechi G, Agnetti V, Masuri R, et al. Risperidone, neuroleptic malignant syndrome and probable dementia with Lewy bodies. Prog Neuropsychopharmacol Biol Psychiatry 2000;24:1043–1051
42. Morikawa M, Kishimoto T. Probable dementia with Lewy bodies and risperidone-induced delirium [letter]. Can J Psychiatry 2002;47:976
43. Walker Z, Grace J, Overshot R, et al. Olanzapine in dementia with Lewy bodies: a clinical study. Int J Geriatr Psychiatry 1999;14:459–466
44. Baldwin SH, Avery E. Lewy body dementia. J Miss State Med Assoc 2002;43:107–108
45. Cummings JL, Street J, Masterman D, et al. Efficacy of olanzapine in the treatment of psychosis in dementia with Lewy bodies. Dement Geriatr Cogn Disord 2002;13:67–73
46. Arvanitis LA, Miller BG, and the Seroquel Trial 13 study group. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. Biol Psychiatry 1997;42:233–246
47. Parsa MA, Poggi EV, Barte L, et al. Treatment of dementia patients with psychotic and behavioral symptoms with quetiapine and donepezil [poster]. Presented at the 154th annual meeting of the American Psychiatric Association; May 5–10, 2001; New Orleans, La
48. Elliott TJ. A pilot study to evaluate the effectiveness of quetiapine in the management of psychosis in dementia with Lewy bodies [abstract]. In: Programme Book of the International Psychogeriatric Association (IPA) European and Mediterranean Regional Meeting; April 17–20, 2002; Rome, Italy: 28
49. Takahashi H, Yoshida K, Sugita T, et al. Quetiapine treatment of psychotic symptoms and aggressive behavior in patients with dementia with Lewy bodies: a case series. Prog Neuropsychopharmacol Biol Psychiatry 2003; 27:549–553
50. Fernandez HH, Trieschmann ME, Burke MA, et al. Quetiapine for psychosis in Parkinson's disease versus dementia with Lewy bodies. J Clin Psychiatry 2002;63:513–515
51. Davis P, Baskys A. Quetiapine effectively reduces psychotic symptoms in patients with Lewy Body dementia: an advantage of the unique pharmacological profile? Brain Aging 2002;2:49–53
52. Baskys A. Quetiapine treatment of hallucinations and agitation of Lewy body disease (LBD): linking the unique receptor profile and neuroprotective pathways. Presented at the 156th annual meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco, Calif
53. De Deyn PP, Jeste D, Mintzer J. Aripiprazole in dementia of the Alzheimer's type. Presented at the 16th annual meeting of the American Association for Geriatric Psychiatry; March 1–4, 2003; Honolulu, Hawaii