

# Depression in Autopsy-Confirmed Dementia with Lewy Bodies and Alzheimer's Disease

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## Abstract

Depression has frequently been cited as a manifestation of dementia with Lewy bodies (DLB). Previous studies have suggested an increase of depression in patients with DLB, compared to those with Alzheimer's disease (AD). The purpose of this study was to examine depressive symptomatology in nursing home residents, from a consecutive series of DLB (n=16) and AD (n=39) autopsy-confirmed cases. Subjects received standard neuropathological analysis and postmortem chart review for clinical assessment of depression. Depressive symptomatology did not differ between the AD and DLB groups, and there was no significant relationship between depression and cortical or subcortical Lewy body (LB) count in the locus ceruleus or substantia nigra. This study suggests that the presence or absence of depression cannot be used to distinguish between AD and DLB. Furthermore, depressive symptomatology in DLB does not appear to be related to severity of cortical or subcortical LB pathology.

**Key Words:** Dementia, depression, Lewy bodies, Alzheimer's disease, autopsy.

## Introduction

DEPRESSION IS RELATIVELY COMMON in dementia, but its prevalence may vary as a function of dementia subtype. In dementia with Lewy bodies (DLB), a disorder characterized by the presence of cortical Lewy bodies, depressive symptoms have been posited to be more characteristic, perhaps distinguishing it from Alzheimer's disease (AD) (1–5). Prevalence estimates of depression associated

with DLB have ranged from 20–65% (2–4), compared with 11–35% in AD (2, 3, 6, 7). However, studies that have directly compared depressive symptomatology between AD and DLB have been inconsistent. Some have demonstrated no difference between the two groups (5, 8–12), while others have found that depression is more common in DLB (1–4, 12, 13). As most efforts in characterizing DLB have focused on distinguishing it from AD, an important question is whether depression should be included as a distinguishing feature between the two disorders.

Equivocal findings in the literature may be a result of a number of factors. One recent study noted, for example, that depression may vary with dementia severity (14). The authors examined a large cohort of autopsy-confirmed AD and DLB patients and found that depression was more common in moderately demented DLB patients compared to moderately severe AD patients; no significant differences in depression occurred in the mild and in the severely demented groups. Furthermore, reported depression rates in DLB samples have been relatively consistent across studies, while reported depression rates in

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comparison AD groups have been quite variable, suggesting that results from some studies that have found greater rates of depression in DLB than in AD may be a result of underreporting of depression in AD rather than actual increased depression rates in DLB subjects (2, 3).

Additional factors that may explain discrepancies in findings include variability in demographic features of study subjects (e.g., age at death) and bias in referral source. In one study that found higher rates of anhedonia and anergia in DLB compared to AD, the DLB group was significantly younger than the AD group at the time of initial assessment and autopsy (5). In addition, since referral sources for study cohorts have included hospitals, outpatient clinics, long-term care settings and psychiatric units, patient referral source is a potential bias in studies of DLB. Studies that have relied on the inclusion of patients referred from psychiatric hospitals, for example, may have led to an increased number of reported psychiatric symptoms compared with a more general population of DLB patients (15).

If depressive symptoms are indeed an intrinsic component of DLB, a relationship between the degree of Lewy body pathology and depressive symptoms would be expected. Examination of the relationship between dementia and clinical symptomatology has been a common approach to elucidating the neuropathology underlying clinical presentation. For example, Haroutunian and colleagues (16) used correlational approaches to establish that Lewy body (LB) pathology and plaque pathology independently contribute to cognitive symptom severity in dementia. Studies that have examined depression in DLB have not considered the relationship between depressive symptomatology and LB pathology. Establishing whether there is a specific relationship between the severity of the neuropathology of DLB and the severity of the depressive symptomatology in clinical symptom presentation is important in determining whether depression is intrinsic to DLB. In the examination of the DLB as a cortical dementia, this study considered cortical LB pathology as a pathological correlate of depression. Furthermore, sub-cortical LB pathology is considered to be in the locus ceruleus and substantia nigra, as these nuclei have been implicated both in the neurobiology of dementia (17–19) and the neuropathology of depression (20).

Studies of clinical correlates with autopsy-confirmed cases typically rely on relatively small sample sizes. Problems associated with the use of small sample sizes are particularly relevant to studies investigating clinical correlates of DLB, since differences between DLB and other dementia subtypes may be quite subtle, requiring a greater amount of statistical power to detect differences. Small sample sizes, therefore, run the risk of inflating type II errors. There has been a recent emphasis on calculating effect sizes in studies that examine brain and behavior relationships, in addition to the statistical tests traditionally reported in hypothesis-driven research (21). In our review of the literature, however, we did not identify a single study comparing AD and DLB patients on depression that reported effect sizes. Thus, it is unclear if negative findings in the literature have been due to insufficient power to detect real differences.

The aim of the current work was to compare incidence of depression in aged nursing home residents with pathologically confirmed AD and DLB. The design of the study allowed for both the comparison of severity of depressive symptomatology and for the comparison of proportion of subjects who met diagnostic criteria for either major or minor depression. A secondary goal of the study was to examine whether severity of depressive symptoms is related to severity of cortical Lewy bodies pathology, in order to further establish whether depression is an intrinsic feature of DLB.

## Methods

### Neuropathological Assessment

Brain specimens were obtained from a series of 273 consecutive autopsy cases. Subjects had been residents at the Jewish Home and Hospital (JHH) in the Bronx and Manhattan, New York, a standard nursing home care facility which houses elderly individuals with and without dementia. Brain donations were sought by JHH clinical staff and made by next-of-kin consent. Standardized neuropathological studies were conducted on the right hemisphere, after division of the brain specimens at the midsagittal level, as previously described by our group (16, 22). Briefly, hematoxylin-eosin, modified Bielschowsky, modified thioflavin S, anti-J amyloid, anti-tau, and anti-ubiquitin (Dako

Corp, Carpinteria, CA) were used to stain sections from paraffin-embedded blocks; the immunohistochemical method used was an avidin-biotin staining procedure with diaminobenzidine detection. Neuropathological assessment of severity of LB pathology was conducted in two ways. The first was with the Consortium to Establish a Registry for AD (CERAD) neuropathological battery (23), which included assessment of LBs in multiple high-power fields. Pathology ratings were made on a four-point scale (0=absent, 1=sparse, 2=moderate, and 3=severe) in midfrontal cortex, superior midtemporal gyrus, inferior parietal lobule, occipital visual cortex, substantia nigra, nucleus basalis of Meynert, locus ceruleus, and dorsal ventral nucleus of thalamus. For the purposes of this study, only ratings for the locus ceruleus and substantia nigra were included. In a subset of cases, a more quantitative estimate of cortical LB pathology was made by taking the sum of the direct LB count in three neocortical regions (i.e., superior/midfrontal gyrus, orbital frontal cortex and superior temporal gyrus), and in the anterior cingulate gyrus. The pathologist was blind to the clinical ratings of depression and the demographic characteristics of the subject, except for age.

### Clinical Assessment

As part of a formal postmortem chart review (PMCR), depressive symptomatology was assessed using a 16-item checklist based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (24) criteria for major depression. Specifically, a clinically trained rater carefully reviewed available data from JHH clinical records, which included admitting diagnoses, neurological and psychiatric consultation reports, nurses' notes, social work records, medication records, mental status testing, and all other medical records and laboratory studies, as reported in previous studies by our group (16, 22). For depressive symptoms, a score of present or absent for each criterion was assigned. The rater was blind to the neuropathological diagnoses. The results of this review were independently confirmed by a psychologist. Symptoms were endorsed as positive if they were present in the medical record. The item was excluded if insufficient information was available to make the rating. Items from the PMCR checklist were then

grouped by DSM-IV category (e.g., "significant weight change") and converted to a 9-point DSM-IV depression scale (see Table 1). Each patient's score was determined to be the sum of those items exhibited by the patient. Furthermore, subjects were divided into 3 groups based on their depression checklist score: major depression, minor depression, and no depression. "Major depression" was defined

**TABLE 1**  
*Conversion of PMCR Depression Checklist to DSM-IV Depression Checklist*

PMCR Depression Checklist	DSM-IV Depression Checklist
1. Depressed mood, dysphoria	1. Depressed mood
2. Decreased interest or pleasure in activities, anhedonia	2. Anhedonia
3. Weight loss without dieting	3. Weight change
4. Decreased appetite	
5. Weight gain or increased appetite	
6. Early insomnia	4. Insomnia or hypersomnia
7. Middle insomnia	
8. Late insomnia, early morning awakening	
9. Hypersomnia	
10. Psychomotor agitation	5. Psychomotor agitation or retardation
11. Psychomotor retardation	
12. Fatigue or loss of energy	6. Fatigue or loss of energy
13. Worthlessness, sinfulness, guilt	7. Feelings of worthlessness or excessive or inappropriate guilt
14. Delusional worthlessness, sin, guilt	
15. Ruminations, inability to concentrate, indecisiveness	8. Diminished ability to think or concentrate
16. Recurrent thought of death or suicide	9. Recurrent thoughts of death or suicidal ideation

PMCR = postmortem chart review; DSM-IV = Diagnostic and Statistical Manual-IV

as 5 or more items, of which at least one was depressed mood or anhedonia. "Minor depression" was defined either as 3 or 4 items, of which one was depressed mood or anhedonia. Minor depression was included because of the association with functional disability, increased resource utilization and mortality (25–28). A subject was placed in the category of "no depression" when the number of items ranged from 0–2.

### Validity of Postmortem Depression Assessment

An independent sample (n=23) of JHH residents received postmortem assessment of depression symptomatology using the Hamilton Depression Scale (29). The assessment was made by a comprehensive interview with an informant who knew the patient well. Hamilton Depression Scale (HAM-D) items were converted to DSM-IV Depression Checklist scores. An independent postmortem assessment of depression, as described above, was also conducted. To measure validity, the relationship between the sum of the DSM-IV Depression Checklist, derived from HAM-D scores, and the sum of the PMCR checklist scores were examined with Pearson's product moment correlations. As the relationship between the two depression checklist scores was expected to be positive, a one-tailed test was conducted. The significant correlation ( $r=0.345$ ,  $p=0.05$ ) indicated adequate validity of the PMCR depression assessment.

In addition to the determination of the depression severity, several other variables were examined. These included gender, age at death, age at placement into JHH, and duration of stay in JHH. Clinical Dementia Rating (CDR) scores were determined for the six months prior to death, as previously described (22).

### Subject Selection

Only subjects with a CDR score of 0.5 (questionable dementia) or greater were considered for analysis. Furthermore, subjects were excluded if quantitative assessment of cortical LBs and depression data were not available. The remaining subjects (n=55) represented the final sample and were subsequently divided into two groups based on neuropathological assessment. The AD group

(n=39) met CERAD neuropathological criteria for definite AD and did not have any cortical Lewy body pathology. The DLB group (n=16) was defined as those cases in which cortical LB counts were greater than or equal to 1. This group contained both subjects with significant AD pathology (n=10) and subjects without significant AD pathology (n=6). The cohort in this study was part of a larger, ongoing clinical study of normal aging and early dementia.

### Results

The AD and DLB groups did not differ in dementia severity, gender, age at admission to nursing home, or age at death (Table 2).

**TABLE 2**  
*Demographic Comparison Between AD and DLB Subjects*

	<b>AD n=39</b>	<b>DLB n=16</b>	<b>p</b>
Age at admission (years)	83.74 ± 7.49	81.96 ± 5.96	0.40
Percent women	77	69	0.53
Dementia severity (median CDR)	3	4	0.34

AD = Alzheimer's disease; DLB = dementia with Lewy bodies; CDR = Clinical Dementia Rating

Independent samples t-tests were conducted to compare the depression scale scores between the AD (mean score ± SD = 2.08 ± 1.95) and DLB (mean score ± SD = 2.69 ± 1.96) groups. The two groups did not significantly differ:  $t(53) = -1.05$ ,  $p=0.297$ . Effect size for this analysis, using Cohen's  $d$  (30), was 0.313. According to Zakzanis's (21) interpretation of Cohen's (30) idealized population distribution, an effect size of 0.313 would indicate no effect, with approximately 78.7% overlap of depression scores between the two groups. The distribution of depressive symptomatology was compared between the two groups using Pearson's chi-square analysis for each item of the depression checklist. There were no statistically significant differences for any item; Table 3 displays the distribution of depressive symptoms. When percentages of subjects who met criteria for minor depression, major depression, or no depression were

**TABLE 3**  
*Depressive Symptom Distribution for AD and DLB Patients*

Symptom	AD (n=39) n (%) meeting criterion	DLB (n=16) n (%) meeting criterion	p
Depressed mood	17 (44%)	8 (50%)	0.67
Anhedonia	9 (23%)	5 (31%)	0.53
Weight change	17 (44%)	11 (69%)	0.09
Insomnia or hypersomnia	5 (13%)	3 (19%)	0.57
Psychomotor agitation or retardation	21 (54%)	11 (69%)	0.31
Fatigue or loss of energy	4 (10%)	2 (13%)	0.81
Feelings of worthlessness or excessive or inappropriate guilt	3 (18%)	1 (6%)	0.85
Diminished ability to think or concentrate	13 (33%)	7 (44%)	0.47
Recurrent thoughts of death or suicidal ideation	1 (3%)	0 (0%)	0.52

AD = Alzheimer's disease; DLB = dementia with Lewy bodies

compared, there were no significant differences between the groups (chi-square=1.662,  $p=0.436$ ). Sixty-one percent of AD patients were not depressed, 18% met criteria for minor depression, and 21% met criteria for major depression; 44% of the DLB subjects were not depressed, 31% met criteria for minor depression, and 25% met criteria for major depression. Minor and major depression were then considered together (i.e., "depressed") and percentages of subjects who met this criterion for depression were compared. The difference between AD subjects and DLB subjects did not reach statistical significance (chi-square=1.46,  $p=0.227$ ), with an extremely small effect (Cohen's  $d$ ) of 0.054.

Within the DLB group the relationship between cortical and anterior cingulate LB pathology (i.e., sum count) and depressive symptomatology was examined with Pearson's Product Moment correlation. Cortical LB count and the depression checklist score did not significantly correlate ( $r=0.162$ ,  $p=0.237$ ). Similarly, the relationship between CERAD LB severity ratings in locus ceruleus and substantia nigra, and depression checklist scores was examined using Spearman's rank order correlation. The relationship between

severity ratings and depression checklist scores did not reach statistical significance for any of these regions ( $r=0.012$ ,  $p=0.963$  and  $r = -0.006$ ,  $p=0.982$ , respectively).

## Discussion

This study examined whether depressive symptoms distinguished between very old, autopsy-confirmed AD and DLB nursing home residents. Depressive symptoms did not significantly differ between these two groups, either by item, or when expressed in symptom clusters defined as major or minor depression. Additionally, in DLB patients, there was no significant relationship between depressive symptoms and distribution of Lewy body pathology or between depression and number of cortical Lewy bodies.

Depressive symptoms are common in DLB and AD, with the literature reporting prevalence rates from 11–35% in AD and 20–65% in DLB. Our results of 21% prevalence of major depression in AD and 25% in DLB are consistent with these findings. When the threshold for depressive symptoms was reduced to include "minor" depression, the prevalence rates of any depression (i.e., minor or major) in our sample was 39% in AD and 55% in DLB. The absolute percentages were higher in the DLB group but did not differ significantly from the AD group, raising the possibility of insufficient power to detect real differences. Our method of characterizing depression in AD and DLB patients yielded similar depression rates, as reported in the literature (2–4). This finding supports the validity of the depression rating method used in this study.

The findings in this relatively older cohort (mean age of over 80 years) of demented nursing home patients may be more generalizable to the overall population of dementia subjects than studies with younger or less severely demented patients. The sample was very well characterized neuropathologically, with accepted criteria for the neuropathological diagnoses of AD and DLB (1). Our clinical measures of depression were retrospective, based on postmortem chart review by trained clinicians. The limitation of retrospective chart review has been present in all of the clinical neuropathological studies comparing rates of depression in AD and DLB patients. A prospective study would have the advantage of more precise clinical characterization and examination of whether the time course in the

development of depressive symptoms is different between these two dementia subtypes. Our patients were not new to the nursing home when they died (time spent in nursing home was  $3.27 \pm 3.16$  years), so the stresses of adjustment to the new environment would not be expected to be a major contributor to the development of depressive symptoms in either of the dementia groups.

The patients in our cohort were similar in dementia severity, a quality not shared by all other clinical-neuropathological studies in this area. Differences in dementia severity between groups may have confounded results in other studies. For example, the more severely demented patients may have increased psychosocial stressors, more severe neuropathological changes and increased degrees of medical comorbidity. These factors may influence the presentation of depressive symptoms, independent of dementia subtype.

This study relied on chart review and, indirectly, the documentation practices of the nursing home staff. The depression rates are in the expected range that has been reported in the nursing home setting. Depression rates in the nursing home have historically been under-recognized (31, 32). We would not expect there to be a selective underreporting of depression in the DLB patients that would explain our differences from those studies that reported higher rates of depression in the DLB cases. In fact, if DLB patients have a higher prevalence of behavioral manifestations, some of the disturbances may erroneously be diagnosed as depression. This hypothesis of an overreporting of depressive symptoms in the DLB patients may be one explanation for the studies that did find an increase in depressive symptoms in DLB compared to AD groups.

Differences between our findings compared with those that found higher rates of depression in the DLB patients might also be attributed to differences in referral source. For example, some studies recruited patients from inpatient geriatric psychiatric units, which may have relatively high rates of depression compared to other referral sources. Our subjects were referred from the nursing home facility.

Depression in the elderly may have an atypical presentation (e.g., more anxiety and somatic complaints and less depressed mood), which results in failure to meet DSM-IV criteria for a diagnosis. Thus, if the number of reported depressive symptoms is decreased, then minor depressive symptoms may actually

reflect a major depression because of the threshold effects for number of symptoms required. In this study, minor depression was found in 31% of the DLB group compared to 18% of the AD group. The difference was not statistically significant. If this difference is a false negative due to inadequate sample size, then future studies with greater power will be required to bear this out.

Our study included patients with average dementia levels in the moderate-to-severe range and does not answer the question of whether the rates of presenting depressive symptoms differ between AD and DLB groups. There is evidence that first onset depression in later life may be a harbinger for dementia (33), but this has not been prospectively examined for patients who eventually reach autopsy and have confirmed DLB.

Depression may be an epiphenomenon of dementia in general, not specific to dementia subtype (DLB or AD). Depressive symptoms, relatively common in both dementia subtypes, may be a reaction to having a dementia and the attendant psychosocial stressors and functional deficits. This hypothesis is in opposition to the view that depression is a direct manifestation of the pathology underlying the specific dementia subtype. Alternatively, the neuropathology underlying dementia may be distinct from the neuropathology underlying depression in dementia. For example, in AD patients as compared to normal controls, there is an increased degeneration of pigmented brainstem nuclei, decreased levels of cortical norepinephrine and decreased amounts of serotonin metabolites in cortical and subcortical brain regions. These changes have been shown to correlate with depressive symptoms in patients with dementia (34, 35). The neuropathological correlates of depression in DLB are not as well described, but the presence of Lewy bodies in the cortex and brainstem nuclei are postulated to alter affective functioning (18). Furthermore, the neurochemical substrates in depression appear to differ from the neurochemical changes in dementia (36).

The neuropathological changes in both AD and DLB may disrupt the functional circuitry involved in mood regulation, explaining the relatively common occurrence of depression in both conditions. Although there was no observed relationship between LB location or severity and depressive symptoms, the presence of LB pathology may increase the risk of

developing depressive symptoms, which would explain the common occurrence of depression in DLB and AD (14). Depressive symptoms may also increase the risk of institutionalization of DLB patients as compared with AD patients (37), possibly explaining a selection bias that results from using pathologically confirmed cases from the nursing home setting. That is, perhaps DLB patients are overrepresented in the nursing home and thus overrepresented in the samples that come to autopsy.

Cholinergic deficits are present in both AD and DLB, with some evidence that the cholinergic deficits in DLB are more pronounced (14, 18, 32, 38). Cholinergic overactivity may contribute to the presentation of depression (39) and perhaps the depressive symptoms in DLB are less pronounced than they would otherwise appear if cholinergic tone were preserved. This hypothesis could be tested when larger numbers of both AD and DLB patients are treated with cholinesterase inhibitors, effectively raising the cholinergic tone. In addition to changes in cholinergic function, deficits in noradrenergic, serotonergic and dopaminergic tone have been reported in depression associated with dementia. The present study was not designed to compare neurochemical differences between dementia subtypes. Further prospective work may attempt to correlate neurochemical changes with depressive symptoms in the various dementia subtypes.

This study found no significant relationship between distribution of LB pathology and depressive symptomatology in DLB patients. This suggests that depression may not be intrinsic to DLB.

The study's limitations include the dementia severity of the residents, the use of a retrospective chart review and relatively small sample sizes. The strengths of the study include the use of effect size analyses to reduce the probability of a type II error. Nursing home subjects with dementia may have improved generalizability compared to referral sources in other studies. Finally, the DLB and AD subjects did not significantly differ in demographic features and were neuropathologically well characterized.

### Summary

Depressive symptoms do not distinguish between older moderately-to-severely demented

AD and DLB nursing home residents, and depressive symptoms do not appear to be intrinsic to DLB. However, the relatively high rates of depression in both dementia subtypes should prompt clinicians and caregivers to recognize and address this important contributor to excess disability.

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