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OLANZAPINE IN DEMENTIA WITH LEWY BODIES: A CLINICAL STUDY

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ABSTRACT

Objectives. Dementia with Lewy bodies (DLB) is now a well-recognized form of dementia in which psychosis and behavioural disturbance are common. Treatment with conventional neuroleptics is often very poorly tolerated. Olanzapine, a newly introduced atypical neuroleptic which binds to multiple receptor types with relatively low affinity for D_2 receptors, may be a useful treatment option in DLB.

Main outcome measures. The Behavioural Pathology in Alzheimer's Disease Rating Scale, The Neuropsychiatric Inventory, Unified Parkinson's Disease Rating Scale and The Webster Disability Scale.

Design. We present the results of eight DLB patients with associated psychotic and behavioural difficulties. All patients were given olanzapine 2.5–7.5 mg. Their psychotic phenomena and behavioural and extrapyramidal symptoms were monitored at 2-weekly intervals.

Results. Three out of the eight patients could not tolerate olanzapine even at the lowest available dose. Two patients had clear improvement in psychotic and behavioural symptoms. Three patients were able to tolerate olanzapine but gained only minimal benefit.

Conclusions. Olanzapine at the doses used conferred little advantage over conventional neuroleptics and should only be given with great caution to patients with DLB. The utility of smaller doses deserves further evaluation.

KEY WORDS—olanzapine; dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is considered to be the second most common cause of dementia, affecting 12–20% of all elderly dementia sufferers (McKeith *et al*., 1992a).

The clinical syndrome of DLB consists of progressive dementia with fluctuating cognitive impairment, prominent visual hallucinations with secondary delusions, spontaneous motor features of parkinsonism and repeated unexplained falls. Psychotic and behavioural symptoms are frequent and present a considerable challenge to those looking after patients with DLB. Adverse reactions to neuroleptic drugs are common (Ballard *et al*., 1998; McKeith *et al*., 1992a). The underlying pathophysiological mechanisms seem to be two-fold. Firstly, there is a 60–70% reduction of dopaminergic neurones in the substantia nigra (Perry *et al*., 1990b) with, in some cases, an associated failure to upregulate postsynaptic D_2 receptors in response to D_2 blocking drugs (Piggott *et al*., 1994). Secondly, neurochemical studies also document a profound cholinergic deficit in DLB (Perry *et al*., 1995; Langlais *et al*., 1993). Monoaminergic/cholinergic imbalance may be responsible for the visual hallucinations and

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fluctuating cognitive function characteristic of the disorder. These features could thus be exacerbated by the muscarinic receptor blocking action of standard neuroleptics (Perry *et al.*, 1990a).

Clozapine, an atypical neuroleptic, with its low affinity for D_2 receptors but high affinity for D_4, $5HT_2$ and muscarinic receptors subtypes, has been found to be effective in the treatment of psychotic symptoms and behavioural disturbance in patients with Parkinson's disease (Rabey *et al.*, 1995). The haematological monitoring required is, however, cumbersome and this drug has not been evaluated in DLB. Response of DLB patients to risperidone (another atypical neuroleptic which displays a dual D_2 and $5HT_2$ receptor antagonism but is devoid of anticholinergic activity) has not been uniformly convincing. Whereas Lee *et al.* (1994) and Allen *et al.* (1995) reported a favourable response with 0.5–5 mg risperidone a day, McKeith *et al.* (1995) reported severe extrapyramidal side-effects in DLB patients on risperidone 1 mg daily.

Olanzapine, which was licensed in the UK in October 1996, possesses selective receptor affinities for mesolimbic rather than nigrostriatal D_1, D_2 and D_4 receptors. As a result, it is relatively free of extrapyramidal side-effects, as has been shown in a study of younger patients (18–65 years) with schizophrenia, in which significantly fewer olanzapine-treated than risperidone-treated patients experienced parkinsonian symptoms (Tran *et al.*, 1997). Olanzapine has high affinity for serotonin $(5HT)_{2A}$, $5HT_{2C}$, $5HT_3$, α_1-adrenergic, histamine H_1 and five muscarinic receptors subtypes (Bymaster *et al.*, 1996). It is well absorbed orally with a half life of 33.8 hours, enabling once daily administration. It is metabolized by the liver and excreted renally with no active metabolites. Drug interactions appear to be minimal. Olanzapine was found in an open-label study to be an effective and well-tolerated treatment for psychosis in non-demented patients with Parkinson's disease (Wolters *et al.*, 1996).

The aim of our study was to evaluate the efficacy and tolerability of olanzapine given to DLB patients for the alleviation of severe behavioural and psychotic features.

METHODS

Eight patients with DLB and associated psychotic and/or behavioural problems were investigated (three women, five men). The first four cases came from the old age psychiatry department of the Herts and Essex NHS Turst; cases 5–8 came from the old age psychiatry department of the University of Newcastle upon Tyne. All eight fulfilled DLB consensus criteria (McKeith *et al.*, 1996). A detailed history was obtained from carers. Patients underwent a clinical interview, a physical examination and the following investigations: FBC, urea and electrolytes, LFTs, TFTs, vitamin B12, folate, CT or MRI brain scan. Other causes of dementia were excluded.

Patients were rated on a behavioural scale and a motor scale at 2-weekly intervals.

Patients from Herts and Essex were rated on:

1. The Behavioural Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD; Reisberg *et al.*, 1987), which assesses the neuropsychiatric symptoms associated with Alzheimer's disease in the areas of delusions, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbance, anxieties and phobias (a higher score reflects more behavioural pathology).
2. The Webster Disability Scale (Webster, 1968), which is a standardized rating scale for rating the severity of extrapyramidal symptoms (a higher score reflects more extrapyramidal symptoms).

Patients from Newcastle were rated on:

1. The Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994), which assesses psychotic and behavioural symptoms in the domains of delusions, hallucinations, agitation, depression, anxiety, elation, disinhibition, irritability, aberrant motor behaviour, apathy, appetite and sleep. A summed score of each subscale is produced by multiplying the severity and frequency scores of each subscale (a higher score reflects more behavioural pathology).
2. Unified Parkinson's Disease Rating scale (UPDRS—motor part only; Langston *et al.*, 1992), which is a standardized rating scale for Parkinsonian symptoms (a higher score reflects more extrapyramidal symptoms).

In addition, the following rating scales were used at the inception and at the end of the 12 weeks study period:

1. The Mini-Mental State Examination (MMSE; Folstein *et al.*, 1975) is the most widely used and studied screening measure of cognitive

impairment. It has the advantage of brevity, ease of administration and high interrater reliability (a lower score reflects poorer performance).

2. The Cornell Scale for Depression in Dementia (CDS; Alexopoulos *et al*., 1988) is a 19-item instrument specifically designed for the rating of depression in dementia. Ratings are based on two interviews (patient and carer) and an overall clinical judgement. This scale was completed for the Herts and Essex patients only (a higher score indicates more depressive symptomatology).
3. The Clinical Dementia Rating (CDR; Berl, 1988) is intended for rating of primary degenerative dementia. Its advantage is that it incorporates the clinicians' assessments of patients' varying educational, cultural, socio-economic and other biases in its scoring. This scale was completed for the Herts and Essex patients only (the score goes up with severity of dementia).

CASE DESCRIPTION

Case 1

A 76-year-old man with a 19-month history of confusion, low mood, anxiety and irritability experienced prominent visual and auditory hallucinations, delusions of persecution and mild extrapyramidal features. Thioridazine given by a general practitioner worsened his psychosis. On initial assessment his MMSE score was 19/30. A month later his MMSE score dropped to 15/30, his CDR was 1 and his CDS was 9. He was started on olanzapine 5 mg daily. After 2 days of treatment he developed marked extrapyramidal side-effects (stiffness, tremor, parkinsonian gait and stooped posture), disorientation in place and person, and worsening of his visual hallucinations, delusions of persecution and aggressive behaviour. Olanzapine had to be stopped. He was treated with diazepam 5 mg three times daily and temazepam 10 mg nocte. The acute disorientation and parkinsonism improved over the next 3 days. He was subsequently treated with risperidone 0.5–1 mg twice daily which temporarily improved his psychotic symptoms and behavioural disturbance. His MMSE score dropped further to 11/30. He continued to deteriorate rapidly and eventually needed care on a long-stay ward. He was a major management problem and his MMSE score became 0/30. He died a year after being admitted to a long-term ward.

Case 2

An 83-year-old woman was diagnosed as suffering from DLB, following the development of marked cognitive impairment subsequent to a diagnosis of Parkinson's disease. At her first assessment she displayed verbal and physical aggression, florid visual and auditory hallucinations with delusions of persecution and features of depression. She was treated with sulpiride 100 mg daily for a month which worsened her agitation and made her unsteady without alleviating her psychotic symptoms.

The sulpiride was stopped and she continued with Sinemet. At this time her CDR was 3, her CDS was 22 and she was unable to cooperate with MMSE. Olanzapine 1.25 mg daily was increased after 1 month to 2.5 mg daily. Her depression remained disabling and needed treatment with lofepramine 140 mg daily. Her aggressive behaviour gradually disappeared and she became less agitated, though continued to experience psychotic symptoms at a milder level. She remained on olanzepine 2.5 mg daily. Her CDR continued to be 3 and she was still untestable on MMSE but her CDS score improved to 9.

Case 3

A 79-year-old man suffered visual and auditory hallucinations, delusions of persecution, fluctuating cognitive impairment and symptoms of depression. His CDR was 1, his MMSE was 15/30 and his CDS was 10. In addition to probable DLB, he had ischaemic heart disease and essential hypertension with probable white matter ischaemic changes but no cortical infarcts on his MRI brain scan. He was treated with olanzapine 2.5 mg daily and paroxetine 20 mg daily. Over a period of 8 weeks his hallucinations and delusions improved, though they did not disappear altogether. His CDR continued to be 1, his MMSE score went down to 15/30 and his CDS decreased to 7. His wife reported that she had accidentally given him olanzapine 10 mg daily for a few days and that during this time his confusional state became markedly but transiently worse. He remains on olanzepine 2.5 mg/day and paroxetine 20 mg/day.

Case 4

An 83-year-old woman gave a 2-year history of memory and language difficulties with marked day-to-day fluctuation. On bad days she was unable to recognize her daughter. Her mobility was poor; she had had a number of falls. On examination she had vivid visual and auditory hallucinations of children in the house and people outside her window. Her MMSE was 18/30. Over the next 3 months her MMSE score dropped to 12/30. Her CDR was 2 and her CDS was 11. She was treated with olanzapine 2.5 mg daily. This had to be stopped after 6 days of treatment as she became more disturbed, with worsening of visual hallucinations and an increase in frequency of falls. However, there was little change in her rating scale scores (MMSE 12/30, CDR 2 and CDS 11). There was clear worsening of her mobility. She continued to hallucinate and became very restless at night. While attending an outpatients clinic she was inadvertently prescribed 20 mg of thioridazine at night. She became extremely distressed about the children in her house and would repeatedly ask neighbours or ring her daughter at work to take them away. On urgent admission to an acute psychiatric ward her MMSE score was 9/30 and she continued to hallucinate. She made no improvement on the ward and was discharged to a nursing home.

Case 5

A 74-year-old man about whom little history was available, living with his alcohol-dependent brother in considerable squalor, presented to the general medical team 'off his legs' and was noted to be hallucinating (seeing policemen on the ward), disorientated and parkinsonian. A small dose of risperidone resulted in a fall. After initial assessment (MMSE 16/30) a diagnosis of DLB was made and he was transferred to a psychiatric inpatient ward and started on olanzapine 2.5 mg nocte. This was increased after 2 weeks to 5 mg, resulting in an increasing confusion (MMSE 11/30) and postural instability. The olanzapine was reduced to 2.5 mg nocte and his mental state and postural stability improved (MMSE 16/30). He was discharged to EMI nursing care, where he continues on olanzapine and has only very fleeting hallucinations.

Case 6

An 84-year-old widow, with no previous psychiatric history, presented with visual hallucinations, persecutory delusions and fluctuating cognition. She was not coping at home and was admitted for assessment and investigations. Her MMSE was 17/30 and she was started on olanzapine 2.5 mg nocte. This was increased by 2.5 mg at 2-weekly intervals to 7.5 mg nocte. On discharge home her MMSE was 18/30. She is now self-caring and attends day care 2 days per week. Her family declined follow-up post discharge but said they were 'delighted' by her improvement.

Case 7

An 83-year-old man presented to the old age psychiatry services with a 1-year history of forgetfulness and several months of visual hallucinations, persecutory delusions and intermittent confusion. On admission he had minimal parkinsonian symptoms but was preoccupied by his persecutory delusions, at one point throwing a fellow patient to the floor to avoid a sniper's bullet and at another time trying to use the ward fire extinguisher to put out a 'fire in the boiler-house' (the nurses' station). He had been given haloperidol 1 mg bd which had resulted in an increase in his confusion and marked hypersalivation. A trial of risperidone had worsened his parkinsonism. Carbamazepine and chlormethiazole had had no effect on his behavioural disturbance. His MMSE was 19/30 when he was started on 2.5 mg of olanzapine. The dose was gradually increased to 7.5 mg. Olanzapine resulted in a large diminution of his behavioural disturbance and his psychotic phenomena. However, his MMSE score dropped to 14/30 and he became slightly more parkinsonian. He was discharged to nursing care and remains a management problem.

Case 8

An 89-year-old man with marked aphasia presented to the old age psychiatry services with visual hallucinations (seeing Victorian women) and intermittent periods of confusion and multiple falls. He had had a diagnosis of Parkinson's disease for 6 years before presentation and had been treated by the general practitioner with Madopar 125 mg nocte. His admission to the inpatient unit was precipitated by worsening memory (MMSE 0/30) and exacerbation of persecutory delusions. On the ward he repeatedly lashed out at the nursing staff. He was started on olanzapine 2.5 mg nocte, which was discontinued after 2 days when his confusion increased and he had repeated falls. He was started on trazodone, which had only minimal

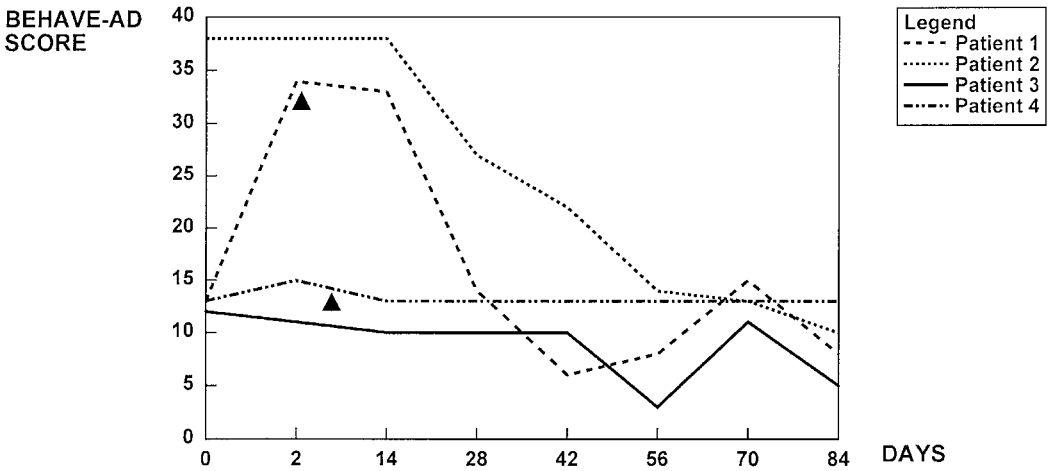

Fig. 1. 'BEHAVE-AD' ratings for patients 1–4 during the study period; arrowheads show when olanzapine was discontinued

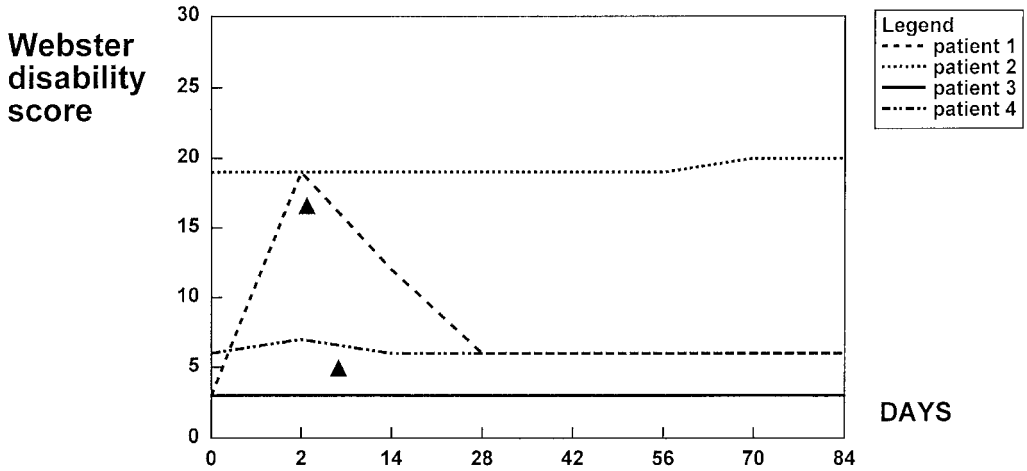

Fig. 2. Webster disability scores for patients 1–4 during the study period; arrowheads show when olanzapine was discontinued

effect on his behaviour and he had to be discharged to EMI nursing care.

RESULTS

The patients' ages ranged from 74 to 89 years (mean 81.4). The patients' ratings on a behavioural and a motor scale at 2-weekly intervals during their trials of olanzapine are shown in Figs 1 and 2 and Figs 3 and 4. Three (cases 1, 4 and 8) out of the eight patients could not tolerate olanzapine due to increases in confusion and hallucinations and worsening of parkinsonian symptoms. Two patients (cases 5 and 6) had good responses. One of these two cases was previously observed to have hypersensitivity to neuroleptics. Three patients (cases 2, 3 and 7) could tolerate olanzapine but gained only limited benefit from it. Two patients were able to return home, the rest were transferred into different types of placements, ranging from long-stay ward to residential home (see Table 1).

DISCUSSION

Our study sample is small and heterogeneous. Two cases started with a diagnosis of PD. Two cases had concomitant depression. Cases 2 and 8 had severe cognitive impairment, while the remainder had

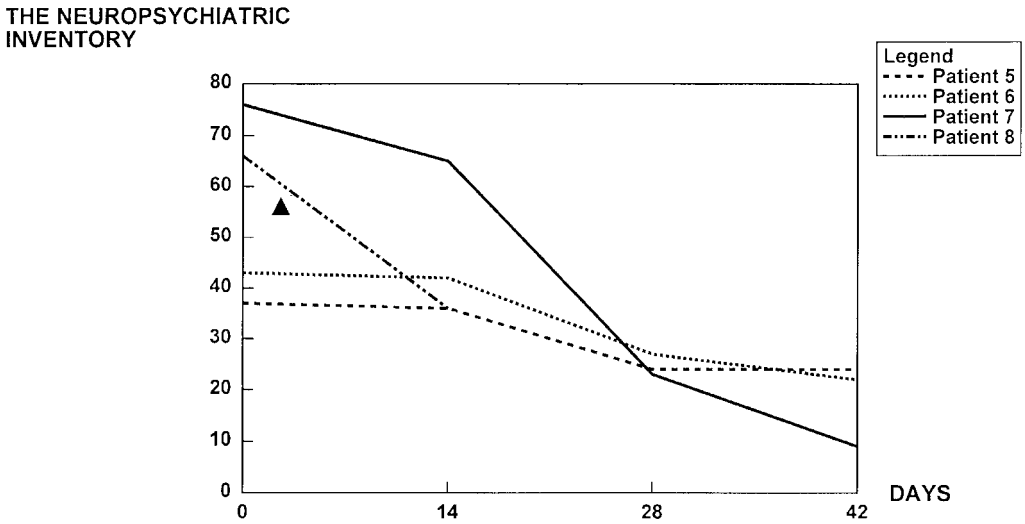

Fig. 3. NPI ratings for patients 5–8 during the study period; arrowhead shows when olanzapine was discontinued

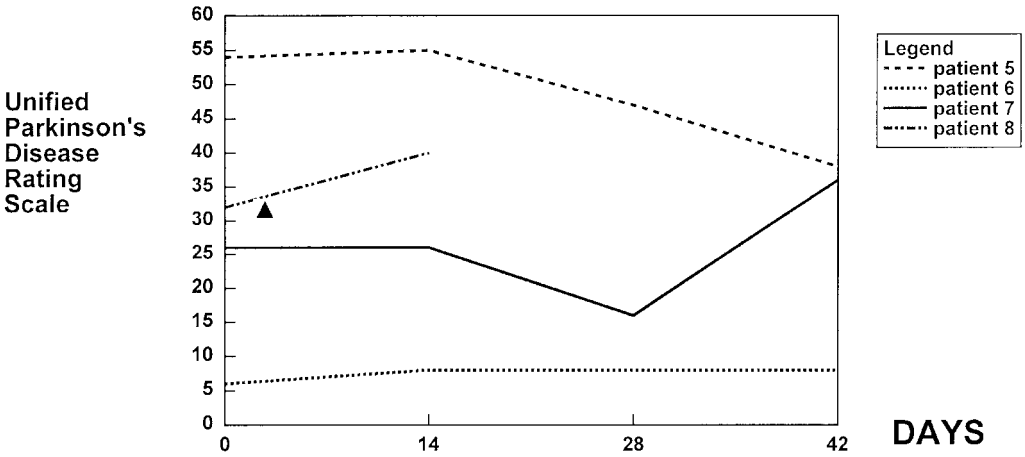

Fig. 4. UPDRS for patients 5–8 during the study period; arrowhead shows when olanzapine was discontinued

moderately severe cognitive impairment as rated by MMSE.

The responses to olanzapine were disappointing considering its selective affinity for mesolimbic pathways and its theoretical advantage over more conventional neuroleptics. This may be explained by the high dopamine receptor occupancy by even low doses of olanzapine in DLB patients whose dopaminergic systems are already severely depleted. The worsening of confusion and psychosis observed in four patients on olanzapine (case 3 with dose of only 10 mg daily) may be intrinsic to DLB but on the other hand may be due to the strong muscarinic receptor affinity of olanzapine. It has been shown that DLB patients with particularly severe cholinergic deficits are more likely to hallucinate (Perry *et al.*, 1990b).

Two patients (cases 2 and 3) had concomitant severe depressive symptoms needing treatment with an antidepressant and some of their improvement could be attributed to the antidepressant rather than the olanzapine.

Overall, 37.5% of patients experienced significant worsening of their symptoms (neuroleptic

Table 1.

Case	Age	Sex	MMSE baseline/ after olanzapine	Residence	Sensitivity to neuroleptics	Other diagnosis	Response to olanzapine	Outcome
1	76	M	15/15	Home	Thioridazine	—	Stopped	Long-stay ward
2	83	F	†	Nursing home	Sulpiride	PD depression	2.5 mg some improvement	Nursing home
3	79	M	15/16	Home	No	ICHD depression	2.5 mg some improvement	Home
4	83	F	12/12	Home	Thioridazine	—	Stopped	Residential home
5	74	M	16/16	Home	Risperidone	—	2.5 mg improvement	EMI nursing
6	84	F	17/18	Home	*	—	7.5 mg improvement	Home
7	83	M	19/14	Home	Risperidone Haloperidol	—	7.5 mg some improvement	Nursing home
8	89	M	†	Home	*	PD	Stopped	EMI nursing

*Never received neuroleptics.
†Untestable.

sensitivity) on olanzapine. This figure is similar to the 39% recently reported by Ballard *et al.* (1998) in response to a range of neuroleptics in DLB patients, and to the original reports of 57% neuroleptic sensitivity rates in DLB cases coming to autopsy (McKeith *et al.*, 1992a,b). At the time of the study only 5 mg tablets were available, so that smaller doses could only be given with great difficulty. Recently, a 2.5 mg tablet has become available in the UK and the use of smaller doses deserves further evaluation.

This study further stresses the importance of judicious prescribing of neuroleptics in patients with DLB. Our results suggest that olanzapine, at the doses we used, should only be given with great caution to patients with DLB. Other classes of drugs such as benzodiazepines, antidepressants and sociopsychological methods should be considered first. Finally, alternative treatment strategies such as use of cholinesterase inhibitors may ultimately prove to be safer and more effective in the management of psychosis and behavioural disturbance in DLB.

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