CASE REPORT

Successful management of persistent distressing neuropsychiatric symptoms by clozapine in a patient suffering from dementia with Lewy bodies

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SUMMARY

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementia associated with poor prognosis and high carers' burden. Neuropsychiatric symptoms worsen this prognosis and are a high source of distress for service users and their carers. However, there is currently insufficient evidence to support the pharmacological and non-pharmacological management of these symptoms. Acetylcholinesterase inhibitors are the first-line pharmacological option, but challenging risky behaviours may persist despite their use. Antipsychotic medications are indicated in such clinical scenarios, but there is very limited evidence to support the efficacy and safety of these medications for managing neuropsychiatric symptoms in DLB. Hence, we report an individual with DLB with severe distressing persistent visual hallucinations and agitation. After multiple treatment options had failed, clozapine was successfully initiated with substantial improvement in both clinical and functional outcomes. Further studies are warranted for evaluating the efficacy of clozapine in managing neuropsychiatric symptoms in DLB.

BACKGROUND

Dementia with Lewy bodies (DLB) is the second most common type of neurodegenerative dementia, accounting for 10%–20% of all dementias.¹ It is characterised by fluctuations in cognition, visual hallucinations, parkinsonism and rapid eye movement sleep behaviour disorder (RBD).² The condition is recognised as being under-researched and often misdiagnosed, leading to poor management.³

DLB is associated with a poorer prognosis than Alzheimer's disease, including accelerated cognitive decline, increased nursing home admission and shorter lifespan, as well as carrying higher healthcare costs and caregiver burden.⁴ The presence of neuropsychiatric symptoms is believed to contribute to this poor prognosis and has a major clinical impact on patients, carers and the healthcare system. However, current evidence to support treatment of neuropsychiatric symptoms is limited and largely based on expert opinion, as few randomised controlled trials in patients with DLB exist.⁵ There are some reports of beneficial effects of acetylcholinesterase inhibitors on neuropsychiatric symptoms, although there is yet no evidence to support the use of antipsychotics in DLB, especially in combination with acetylcholinesterase

inhibitors.^{6,7} Hence, we add evidence by reporting the management of challenging neuropsychiatric symptoms by clozapine in an individual with DLB.

CASE PRESENTATION

We present a 75-year-old visual artist, who lives with his partner of 35 years' duration. His medical history includes hypertension, constipation and prostatic hypertrophy but he was generally physically robust. Medications included sertraline, aspirin, cetirizine, finasteride, losartan and simvastatin. He had recently been treated for depression by his general practitioner, although there was no other significant history or family psychiatric history of note. The patient had an unremarkable history of substance use. His first contact with mental health services was in December 2014 due to memory impairment and word finding difficulties. An MRI scan at the time showed no significant atrophy or small vessel disease. At the time, his partner reported that the patient presented intermittent visual hallucinations in full consciousness and vivid dreams with being physically active during sleep for 4 to 5 years prior to the onset of memory problems. A diagnosis of probable Alzheimer's disease was made in April 2015 based on a Mini-Mental State Examination (MMSE) score of 23/30 and an Addenbrooke's Cognitive Examination (III) score of 59/100. He was commenced on donepezil, which was increased to 10 mg daily. An improvement in behaviour and word finding was noted despite the lack of objective evidence and he continued to work.

His condition deteriorated in late 2016 following a family holiday and he became increasingly anxious and voicing delusions of infidelity and vivid visual hallucinations. The patient later presented in February 2017 with severe agitation, suicidal ideation and distress from visual hallucinations. He spoke of seeing students in the house, two versions of his partner and interference with his artwork. A coarse resting tremor and jaw tremor, with a rather expressionless face, was observed. He was admitted to a psychiatric hospital. Notable risks included wandering, intermittent suicidal ideation and self-neglect from eating poorly due to suspicions that food was poisoned. During admission, he presented as anxious, distressed, frequently distracted and repeatedly responding to unseen stimuli. His partner reported that he was seeing

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objects, faces and cartoon characters, all from his paintings that added to his distress. There was severe receptive and expressive dysphasia. There were several instances of aggression towards staff members, particularly during medication administration and personal care, interventions that he perceived as threatening.

The patient was rediagnosed with a probable DLB in view of the trajectory of illness, history of fluctuating cognitive impairment, recurrent well-formed and detailed visual hallucinations, parkinsonism and RBD. Further investigations were requested to support this. Blood tests rendered normal results for full blood count, renal function, liver function, thyroid function, glucose, B₁₂, folate, C reactive protein and blood-borne viruses, while an ECG was unremarkable. Detailed brain imaging was performed (table 1). Dopamine transporter imaging using single-photon emission CT showed very marked reduced dopaminergic active transport (figure 1).

TREATMENT

Symptoms persisted despite the use of non-pharmacological strategies including cognitive stimulation, use of arts materials and carer and multidisciplinary team education and training. Donepezil was stopped and rivastigmine was initiated and titrated up to 3 mg two times a day. The patient was discharged to a private care home, although frequent visual hallucinations, agitation and physical aggression prompted readmission 1 month later. These episodes of aggression occurred on attempted engagement by care home staff and perceived threat from others. Cognition also progressively deteriorated from an initial MMSE score of 8/30 to not being able to complete this on discharge. Rivastigmine was converted to transdermal patch form and was increased to a dose of 9.5 mg daily for 2 weeks before titration to a maximum dose of 13.3 mg daily. Due to the persistence and distress caused by visual hallucinations, the decision was made in conjunction with his family to commence clozapine. Parkinsonian symptoms at the time included bradykinesia, slight stiffness and resting tremor. Quetiapine and aripiprazole were discussed as possible alternatives, although clozapine was preferred due to a lower propensity for worsening parkinsonian symptoms, and due to its efficacy in managing psychotic symptoms in Parkinson's disease. This was initiated at a dose of 6.25 mg daily and later a maintenance dose of 6.25 mg two times a day. Blood monitoring was performed in the presence of his partner. The patient responded within less than a week with a virtual full remission of his agitation and notably, he started drawing again. His hallucinations became less frequent but crucially, they did not impact his mood or behaviour. Although his cognition continued to decline, levels

Figure 1 Dopamine transporter imaging using single-photon emission CT with marked reduction of striatal ioflupane binding, bilaterally, in keeping with a diagnosis of probable dementia with Lewy bodies.

of agitation, distress and the frequency and severity of hallucinations significantly improved with few adverse effects (table 2).

OUTCOME AND FOLLOW-UP

His family attributed the improved presentation to clozapine, and they wanted to maintain it as long as possible. There was a reduction in carer's burden, with his partner reporting she was able to engage with the patient, who was considerably less agitated. A best interest meeting was held in August 2017 with a final decision to discharge home in September 2017 with his partner and live-in carers. Community mental health follow-up and regular blood tests continued. The patient has remained largely settled at home, although episodes of agitation have resulted in an increase of clozapine to a total daily dose of 18.75 mg in combination with rivastigmine, after 6 months since the initiation of clozapine. He still lives at home with the same care arrangements.

DISCUSSION

There is currently no robust evidence for the treatment of neuropsychiatric symptoms in DLB and treatment has generally been guided based on the evidence in Parkinson's disease. Dopaminergic antiparkinsonian drugs can worsen neuropsychiatric symptoms and so optimising medication is an initial priority. Antipsychotic use in patients with DLB is restricted due to their blockade of dopamine D₂ receptors which can induce dyskinesia and other extrapyramidal side effects. Second generation antipsychotics such as clozapine and quetiapine are considered safer in these populations because of their lower affinity for D₂ receptors.⁸ Many clinicians choose to use these without a clear evidence base. A small randomised controlled trial of quetiapine in DLB was negative.⁹ Two double-blind placebo-controlled studies in mixed Parkinson's disease and Parkinson's disease dementia cohorts showed good efficacy of low-dose clozapine in reducing visual hallucinations and psychotic symptoms.^{10 11} A review in PubMed and Embase, conducted with the search terms 'Clozapine and Lewy', identified three case reports written in English on the treatment of DLB with clozapine. One case reported an individual with diffuse DLB who responded well to clozapine, while another demonstrated improvement in DLB symptoms with an increased dose of clozapine in conjunction with levodopa.^{12 13} However, the third reported two patients with DLB who demonstrated extreme sensitivity to clozapine

Table 1 Investigations performed prior to commencing clozapine

Investigation	Result
MRI head	Minor, generalised cerebral and cerebellar volume loss within the spectrum of normal for age. No focal, lobar atrophy to suggest any specific neurodegenerative process. Minor small vessel ischaemic change in the hemispheric deep white matter.
Dopamine transporter imaging using single-photon emission CT (figure 1)	Uptake deficits in both striata. Quantitation confirms symmetrically very low specific ratios. Background activity is increased. Specific ratios in the left striatum 0.38 and right striatum 0.54. The findings are those of very marked reduced dopaminergic active transport. This would be in keeping with a diagnosis of a Parkinson's plus syndrome or very severe Parkinson's disease.

Table 2 Assessments performed prior to commencing clozapine and on discharge from hospital 4 months later

Assessment	Prior to commencing clozapine	On discharge
Mini-Mental State Examination (MMSE) ²⁰	8/30	Unable to provide information*
Neuropsychiatric Inventory Questionnaire ²¹	Delusions: 12/12 Hallucinations: 12/12 Agitation/aggression: 12/12 Depression/dysphoria: 12/12 Anxiety: 12/12 Elation/euphoria: 4/12 Apathy/indifference: 1/12 Disinhibition: 6/12 Irritability/lability: 8/12 Motor disturbance: 12/12 Night-time behaviours: 4/12 Appetite and eating: 12/12 Total: 106/144	Delusions: 1/12 Hallucinations: 3/12 Agitation/aggression: 1/12 Depression/dysphoria: 1/12 Anxiety: 2/12 Elation/euphoria: 0/12 Apathy/indifference: 6/12 Disinhibition: 2/12 Irritability/lability: 1/12 Motor disturbance: 1/12 Night-time behaviours: 3/12 Appetite and eating: 3/12 Total: 24/144
North-East Visual Hallucinations Interview ²²	Total severity: 48/90 Distress: 18/18	Total severity: 24/90 Distress: 6/18
Cohen-Mansfield Agitation Inventory ²³	Physical/aggressive: 21/77 Physical/non-aggressive: 53/70 Verbal/aggressive: 10/21 Verbal/non-aggressive: 17/35	Physical/aggressive: 12/77 Physical/non-aggressive: 17/70 Verbal/aggressive: 3/21 Verbal/non-aggressive: 7/35
Simpson-Angus Extrapyramidal Side Effects Scale ²⁴	12/40	10/40

*The MMSE could not be completed, because the patient's communication deteriorated to the point that he could not engage in meaningful assessment.

with an increase in confusion and behavioural symptoms.¹⁴ None of these has reported a combination of antidementia drugs and clozapine.

The possible therapeutic effect of clozapine may be due to blockade of the 5-HT_{2A} receptor.¹⁵ Pimavanserin, a selective serotonin 5-HT_{2A} inverse agonist, yet to be approved in Europe, has shown promise in significantly reducing psychotic symptoms in patients with Parkinson's disease without dementia.¹⁶ More recently, pimavanserin has also shown some efficacy in patients with Alzheimer's disease psychosis.¹⁷

In addition to an increased sensitivity to antipsychotics characterised by motor and cognitive deterioration, there are several other limitations to the use of clozapine in DLB. These include orthostatic hypotension, the risk of inducing agranulocytosis and myocarditis, and the need for regular blood monitoring, which may prove difficult to acquire in severe DLB. As an anticholinergic, clozapine has the potential effect of inhibiting the effects of acetylcholine increase in the synapse resulting from rivastigmine. The high anticholinergic burden and sedative properties of clozapine may also contribute to cognitive deficits.¹⁸ However, there are suggestions that the N-methyl-D-aspartate (NMDA) and M₄ agonistic properties of clozapine may enhance cognition and compensate for deficits due to anticholinergic burden.¹⁹ In this case, clozapine appeared to have no cognitive benefit, and could have even contributed to further cognitive deterioration.

As the patient's cognition deteriorates, his compliance with clozapine blood monitoring becomes difficult. We are mindful that as the prescription of clozapine in DLB remains off label, clozapine monitoring services may not allow further administration in case of missed blood tests. The patient's partner agrees that the risk of re-emergence of his challenging behaviour and subsequent transition to institutional care overrides the risk of haematological adverse effects. Consequently, we are identifying a potential gap in clozapine monitoring policy that requires further discussion.

This case demonstrates the successful use of clozapine in reducing levels of agitation, aggression and the frequency and severity of hallucinations in DLB. Where discharge to a specialist

nursing home was felt to be the most suitable initial setting, further improvement in functional outcome and quality of life following clozapine initiation has now made a safe discharge home with partner and carers possible. Finally, clozapine was used safely without any adverse effects or worsening of parkinsonian symptoms.

Clozapine is a potential option for managing symptoms of DLB where non-pharmacological and first-line pharmacological strategies have been unsuccessful. Further understanding of DLB is crucial for optimising its management. The possibility of a placebo-like effect cannot also be ruled out. This case prompts the need for further research, particularly larger case series and placebo-controlled trials, to investigate the safety and efficacy of clozapine for managing neuropsychiatric symptoms in DLB.⁶

Patient's perspective

The patient's next of kin has kindly provided the following comment:

"The change in (him) shortly after his first dose of Clozapine was profound...

He could concentrate... And was back to a 'real' world...

His communication levels were increased because he was free from the incessant hallucinations he had been experiencing...

His hallucinations went from 95%–100% of his waking time to around 5%

This made him become much more responsive... Calmer... Less agitated... Less aggressive and confused...

Things he had previously stopped doing he managed again:

He began to draw... Looked at his art-books... Watched TV...

Managed to feed himself...

Became more responsive to visitors and family.

The medication made him a much more manageable, peaceful, contented man and subsequently he was discharged home.

I'm not really sure how to say this appropriately but:

'(He) became (him) again'..."

Learning points

- Neuropsychiatric symptoms in dementia with Lewy bodies (DLB) are associated with poor prognosis, poor quality of life and high carers' burden.
- Clozapine is a potential option for managing symptoms of DLB where non-pharmacological and first-line pharmacological strategies have been unsuccessful.
- We report an individual with DLB, who demonstrated substantial improvement in levels of agitation, distress and hallucination frequency after commencing clozapine, and maintained the gains after 6 months of follow-up.
- Clozapine in combination with high-dose rivastigmine was well tolerated.

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