CASE REPORT

High dose rivastigmine in the symptom management of Lewy body dementia

Joseph Marwan Nour,¹ Leonidas Chouliaras,² Lilian Hickey³¹Oxford University Clinical Academic Graduate School (OUCAGS), Oxford University Hospitals NHS Foundation Trust, Oxford, UK²Department of Psychiatry, Oxford Health NHS Foundation Trust, Oxford, UK³Older Adults Mental Health, Oxford Health NHS Foundation Trust, Oxford, UK**Correspondence to**
Dr Joseph Marwan Nour,
josephnour@gmail.com

Accepted 14 November 2016

SUMMARY

A man presented in late 2004 at the age of 65 with a decline in memory. He was diagnosed with Lewy body dementia and started on 3 mg rivastigmine a day, which made a marked clinical improvement. He lived with the illness for 10 years, over which time the dose of acetylcholinesterase inhibitors (ChEI) he took rose to two 9.5 mg rivastigmine patches and 7.5 mg donepezil, significantly above British National Formulary (BNF) limits. He demonstrated clear clinical response to ChEI and showed improvements in alertness and functioning. He did not exhibit life-threatening cardiac side effects and his death in 2014 was not related to the ChEI.

were aspirin 150 mg, levothyroxine 50 µg, ramipril 5 mg; atenolol 50 mg; simvastatin 40 mg and glyceryl trinitrate spray when required.

TREATMENT

He was diagnosed with LBD and started on the ChEI rivastigmine at a dose of 3 mg daily in December 2004 (see [figure 1](#)). The rivastigmine had a clear effect on his mental state and day-to-day functional ability. As expected, the beneficial effects of the rivastigmine began to diminish as the neurodegenerative disease took its course. In just under 2 years, the dose of rivastigmine was gradually increased to 12 mg (BNF maximum oral dose) and held there for nearly two more years, at which point his mental state and cognitive function had once again deteriorated.

He and his wife noticed a clear benefit in quality of life, with a rapid improvement in attention, verbal fluency, alertness and reactivity after each rivastigmine dose increment. At each point in his illness when his cognitive function declined, they both argued forcefully for a trial increment in his antidementia medication, pointing out the clear benefits which had been evident at the last increment.

At this stage, there was no evidence that the patient lacked mental capacity to decide on his treatment and he participated regularly in discussions regarding the risks and possible benefits from high dose cholinesterase inhibitors. The dose of his antedementia medications over time can be seen in [figure 1](#).

The maximum tolerated oral dose was 22.5 mg in five divided doses of 4.5 mg. At this point, there was an observable difference in his mental state and myoclonic jerks if a dose was given late.

In late 2012, he was switched to two 9.5 mg rivastigmine patches, mainly for progressive decline in his swallowing. The maximum dose for the patches in the BNF is 13.3 mg per 24 hours, so this too was above BNF limits. Later, 5 mg donepezil was added and in April 2014, the donepezil was further increased to 7.5 mg and memantine 5 mg was also added for the alleviation of hallucinations. The initiation of another ChEI agent was highly unusual, and the authors do not advocate combining different ChEI in clinical practice.

The decision to further increase ChEI doses came about following robust lobbying by the family at a point where the patient lacked capacity to make decisions about his treatment. At each dose increment, the decision took place in a structured clinical interview (a 'best interests meeting') with

BACKGROUND

This case demonstrates therapeutic benefit of using acetylcholinesterase inhibitors (ChEI) above their BNF maximum doses when tolerated for a patient with advanced Lewy body dementia (LBD). It suggests the benefit of timely 'best interests' decision-making in the disease, where higher dose ChEI may offer further stabilisation for patients, but that each patient's best interest assessment is unique and must be undertaken with great care.

CASE PRESENTATION

This patient presented to psychiatric services in late 2004 at the age of 65. He was a retired psychiatric nurse who was reporting of depressive symptoms with a gradual decline in his memory. He had lost interest in his job, become less competent with technical equipment and found he was forgetting the names of his former colleagues in social settings. These changes had been ongoing over the previous 2 years, and his wife had noted increased fatigue, changes in character and loss of confidence in himself.

He was experiencing vivid dreams and would occasionally hit out and shout during sleep. He was experiencing occasional visual illusions and hallucinations, which he described 'as if something was running around the room'. His speech was soft, lacking impact and had a dysarthric quality. He also demonstrated mild facial masking suggestive of Parkinson's disease but did not present with bradykinesia, tremor, rigidity or postural instability. Also of note were symptoms of fluctuating myoclonus in his left arm. His medical history included hypothyroidism, angina and chronic back problems. On examination, he scored 29/30 on the Mini Mental State Examination (MMSE) and 16/36 on the Hopkins Verbal Learning Test. His CT head was unremarkable. His daily medications at the time

CrossMark

To cite: Nour JM, Chouliaras L, Hickey L. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-217240

Figure 1 Doses of antideementia medication prescribed from point of diagnosis.

his family, who argued in favour of further antideementia medication to reduce hallucinations and improve his alertness and engagement in family life. The risk of sudden cardiac death was made abundantly clear; however, this was offset by the evidence of meaningful increases to the patient's quality of life following each previous increment in ChEI. He died in June 2014 from causes unrelated to the antideementia medication.

DISCUSSION

Anticholinesterase inhibitors in LBD

ChEIs are used to alleviate the symptoms of cognitive decline and psychotic symptoms in LBD.^{1 2} The main side effects are gastrointestinal disturbances, and these were reported as the main reasons to exit early trials. Other, more life-threatening side effects include the risk of bradycardias and heart block and it is these that worry clinicians about increasing doses beyond BNF maximums. In 2000, McKeith and colleagues¹ conducted a placebo-controlled double-blind, multicentre study in 120 patients with LBD over 20 weeks, with a 3-week rest period at the end. They observed a marked benefit of rivastigmine, but also a significant increase in side effects. However, the side effect profile was mostly deemed acceptable given the benefits. Of note, the maximum duration of titration from 0 to 12 mg was only 8 weeks, which is very fast compared to Mr X, where the same increase in dose was carried out over almost 2 years. The rate of dose increase could explain why high dose rivastigmine was tolerated relatively well in the reported case compared to in these early studies.

Above BNF rivastigmine doses in Alzheimer's disease

Regarding above-BNF doses of ChEI in dementia, there are no studies currently looking at LBD. There have, however, been a small number of reports in Alzheimer's disease (AD). As ChEIs are also used to battle the cognitive decline in AD,^{3 4} the same doses and side effect profiles are noted. Interestingly, there are two case reports on above BNF dose rivastigmine prescription in AD. In Greece, a 72-year-old lady was accidentally treated with 36 mg rivastigmine patches daily for 4 months.⁵ The authors noted that during that period they observed a dramatic improvement in cognitive function and neuropsychiatric symptoms of the patient, which disappeared when the dose was reduced back to the 12 mg recommended BNF maximum allowed dose. With informed consent, they increased the dose to 20 mg rivastigmine daily and again observed an improvement. The authors of that

study suggested that the observed dose-dependent effects of rivastigmine were related to possible effect on inhibition of butyrylcholinesterase along with acetylcholinesterase inhibition at high doses.⁵

Another case study reported a 77-year-old man with AD who's treatment was titrated up to 12 mg rivastigmine over 5 months. His MMSE rose from a low of 27 to 30, and he was continued with 12 mg for 6 months. At this point, his MMSE dropped to 21, and the dose was titrated up to 18 mg, which again showed a profound improvement in cognitive function. The cycle repeated 6 months later, and he was prescribed 22.5 mg a day at the time of publication.⁶

Farlow *et al*⁷ conducted a randomised double-blind study in 2010 looking at the effectiveness and tolerability of high doses of donepezil in AD. They took 1467 people with moderate-to-severe AD who had been taking 10 mg/day donepezil for greater than 12 weeks. They trialled 23 mg a day in half of these and monitored cognitive outcomes and tolerability. Thirty per cent of patients in the high-dose group withdrew from the study compared with 18% in the standard dose group, and 74% of patients in the high dose group reported adverse drug effects compared with 64% in the standard dose group. Of the most severe side effects, the most common were nausea, dizziness and vomiting. The authors report an improvement in cognitive function at the higher dose, which they noted that was more pronounced in those with more severe disease.

CONCLUSIONS

We have presented the case of a man with LBD who demonstrated exquisite responsiveness to the effects of ChEI and who tolerated and benefitted immensely from being prescribed above BNF doses of these medications. In the context of doses of this strength being trialled in AD, there is evidence to suggest that an increase in maximum BNF allowed dose of rivastigmine might be considered for patients with LBD, however further research and clinical trials are needed to validate that. For patients currently at the higher end of pharmacological management of their LBD symptoms, and especially those with few comorbidities and those who have demonstrated good tolerance of ChEIs, as well as strong clinical benefits, clinicians may consider trialling higher doses, however in parallel should always ensure safety and tolerability.

We hope that this case report will inspire others to report their own experiences with prescribing ChEIs in LBD. Larger

trials surveying the safety and efficacy of high doses of ChEIs as well as offering selection criteria for patients who would benefit are urgently required to further establish that.

Learning points

- ▶ For patients with Lewy body dementia on maximum doses of acetylcholinesterase inhibitors, consider trialling above BNF doses if safe and tolerated. Robust, informed consent or formal 'best interests' meeting are crucial to this decision.
- ▶ Always titrate doses up slowly, in small increments.
- ▶ Monitor pulse and ECG for bradycardia regularly.

Contributors All authors contributed to and approved the paper.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 McKeith Ian, Del Ser T, Spano P, *et al.* Efficacy of rivastigmine in dementia with lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet* 2000;356:2031–6.
- 2 Reading PJ, Luce AK, McKeith IG. Rivastigmine in the treatment of parkinsonian psychosis and cognitive impairment: preliminary findings from an open trial. *Mov Disord* 2001;16:1171–4.
- 3 Rogers SL, Farlow MR, Doody RS, *et al.* A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's Disease Donepezil Study Group. *Neurology* 1998;50:136–45.
- 4 Rösler M, Anand R, Cicin-Sain A, *et al.* Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial commentary: another piece of the Alzheimer's Jigsaw. *BMJ* 1999;318:633–40.
- 5 Politis AM, Theleritis C, Passa M, *et al.* Improvement of cognitive dysfunction with high-dose rivastigmine. *Psychosomatics* 2010;51:89–90.
- 6 Shua-Haim JR, Pass M. High dose rivastigmine (Exelon) for an Alzheimer's disease patient: a case report. *Int Psychogeriatr* 2003;15:312–13.
- 7 Farlow MR, Salloway S, Tariot PN, *et al.* Effectiveness and tolerability of high-dose (23 Mg/d) versus standard-dose (10 Mg/d) donepezil in moderate to severe Alzheimer's disease: a 24-week, randomized, double-blind study. *Clin Ther* 2010;32:1234–51.

Copyright 2016 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow