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Letter to the Editor

Low-dose lithium adjunct therapy associated with reduced off-time in Parkinson's disease: A case series

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Dear Editor,

The basis for this case series stemmed from an unexpected observation over 2-years ago from a patient with Parkinson's disease (PD) and bipolar disorder.

This 59 year-old white male patient with PD for 10 years and bipolar disorder for 8 years inquired during a routine clinic visit if lithium could be improving his PD symptoms. The patient reported full resolution of off-time, which had been occurring for about 4–5 h/day, and no change in dyskinesias after his psychiatrist initiated lithium therapy for his bipolar disorder 5 months previously. There had been no change in his only PD medication, carbidopa/levodopa 25/100, 3 tabs every 2.5 h, since lithium therapy had been initiated. The trough serum lithium level at the time of this clinic visit was 0.37 mmol/L. A literature search was performed.

In 1982, Coffey et al. reported standard-dose lithium adjunct therapy (serum levels = 0.78–0.85 mmol/L) to reduce off-time by a mean 70% among 5 PD patients in a randomized, placebo-controlled crossover trial; [1] however, these 5 patients all eventually developed severe and disabling dyskinesias and 2 developed new visual hallucinations after 1–7 months of open-label, standard-dose lithium therapy [2]. Quinn & Marsden subsequently performed the only other randomized controlled trial using standard-dose lithium adjunct therapy in PD (serum levels = 0.5–1.2 mmol/L) and reported improved painful off-dystonia among all 7 PD patients studied; dyskinesias worsened in 4 and improved in 2 of these patients [3].

Based on these published data and the improvement in off-time without an increase in dyskinesias reported by the above bipolar patient receiving low-dose lithium (LowDL), 9 additional PD patients all receiving levodopa and experiencing bothersome off-time or depression were placed on open-label, LowDL (target serum level = 0.25–0.50 mmol/L) [4] and monitored for tolerability and subjective changes in symptoms. Lithium was initiated at 150 mg bid and trough morning serum lithium levels were monitored weekly during dose adjustment until the target range was achieved. Lithium dosing could be adjusted over time based on patients' subjective benefits and/or side effects. Renal function tests, thyroid stimulating hormone (TSH), and serum calcium were also monitored periodically according to standard-of-care practices. This work was reviewed by the University at Buffalo's Institutional Review Board and determined to constitute clinical care and not clinical research.

Five of the 10 patients (50%) have discontinued LowDL due to adverse events (Table 1). Two patients discontinued LowDL due to increased hand tremors, one after 4 days and the other after 6 months at a supratherapeutic lithium level of 0.62 mmol/L. The patient who discontinued LowDL after 4 days subsequently discontinued rasagiline adjunct therapy after 5 days also due to increased hand tremors suggesting that this may be an idiosyncratic adverse event for this patient. One patient discontinued LowDL after 5 months due to symptomatic hypothyroidism (TSH = 10.74). Two patients with Baseline (BL) dementia developed worsened visual hallucinations and new urinary incontinence, respectively, and discontinued LowDL.

None of the 9 patients receiving LowDL for 2–26 months (median 11 months) has reported any increase in dyskinesias.

The 6 patients who reported >2 h of off-time/day at BL and who continued LowDL for >4 days have reported a mean 75% decrease in subjective off-time (range 50–100%) beginning about 1–3 weeks after achieving the target serum lithium level and persisting for 5–26 months (Table 1). No patients have increased and 2 have decreased their dopaminergic medications. Two patients have reported increased off-time when their lithium doses were either discontinued or decreased and subsequently reported resolved off-time after resuming their original lithium doses (Table 1). All 6 patients have reported noticeably greater reductions in off-time at lithium serum levels ≥0.40 mmol/L than <0.40 mmol/L. The 5 patients remaining on lithium have been satisfied with LowDL adjunct therapy and have wished to continue it.

These cases suggests that LowDL therapy may reduce off-time in PD patients with motor fluctuations and, in contrast to the previous report using standard-dose lithium therapy [2], may not increase dyskinesias. Prevention of dopamine receptor supersensitivity by lithium may partially account for these associated clinical reductions in off-time [5]. It should be noted that large placebo effects are well known to occur in PD and the open-label nature of these clinical observations may simply represent this reality [6]. In addition, these observations did not include any formal research methodology such as specific subject eligibility criteria or formal assessments of off-time through the use of daily diaries. Thus, the reported subjective improvements in off-time among some of these patients should not be considered as evidence of efficacy until results from a randomized, double blind, placebo controlled clinical trial of sound design are available. Such a trial is currently being planned.

An important finding from this report is that none of the 9 patients receiving LowDL for 2–26 months (median 11 months) has reported any increase in dyskinesias and no such increases have been observed on routine clinical examinations. This is in sharp contrast to the marked increases in dyskinesias previously reported among all 5 PD patients receiving standard-dose adjunct lithium therapy for 1–7 months and suggests that long term adjunct LowDL has improved tolerability compared to standard-dose lithium [2]. On the other hand, LowDL was poorly

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Table 1
Summary of PD patients receiving low-dose lithium adjunct therapy ($n = 10$).

Age/sex	H&Y stage at BL	Years with PD at BL	Duration/most recent lithium serum level	Subjective effects
59yo/M*	3	10	26 months/ 0.50 mmol/L	100% reduction in off-time, which was lost 6 wks after stopping lithium and resumed 6–8 wks after resuming lithium.
56yo/F*	2	12	5 months/ 0.44 mmol/L	60% reduction in off-time. Discontinued lithium due to symptomatic hypothyroidism.
51yo/M*	1	9	19 months/ 0.60 mmol/L	100% reduction in off-time, which diminished on a lower lithium dose and resumed on the previous higher dose.
55yo/M*	2	11	12 months/ 0.46 mmol/L	50% reduction in off-time.
57yo/M*	2	10	4 days	Increased hand tremors and discontinued lithium.
54yo/F*	3	20	10 months/ 0.50 mmol/L	60% reduction in off-time.
68yo/F*	1	6	11 months/ 0.40 mmol/L	80% reduction in off-time. Improved depression.
75yo/F	4	10	2 months/ 0.50 mmol/L	BL dementia. No improvement in depression. Developed nocturnal urinary incontinence and discontinued lithium.
64yo/F	4	14	8 months/ 0.47 mmol/L	BL dementia. Improved depression but developed worsened visual hallucinations and discontinued lithium.
54yo/M	1	2	6 months/ 0.62 mmol/L	Developed hand tremors at supratherapeutic lithium level and discontinued lithium.

* >2 h/day of subjectively reported off-time at BL; H&Y: Hoehn & Yahr in "on" state.

tolerated by PD patients with BL dementia and in one non-demented PD patient when the serum lithium reached a supratherapeutic level of 0.62 mmol/L (Table 1). TSH should also be monitored no later than 3 months after initiation of LowDL, per standard-of-care recommendations, which likely would have prevented one patient from discontinuing LowDL due to symptomatic hypothyroidism identified 5 months after initiation of LowDL. In order to improve the tolerability of adjunct LowDL, such subject characteristics and monitoring parameters should be considered for any future clinical research on LowDL for potential symptomatic or disease-modifying [7] benefit in PD.

Considering that 2 separate reports have now associated adjunct lithium therapy with approximate 70% reductions in off-time in PD- which compares favorably with reductions seen with approved oral adjunct as well as surgical therapies- [8–10] and lithium is inexpensive, widely available and likely to be safe at low doses [4], further controlled clinical research appears merited using LowDL therapy in PD.

Conflicts of interest

None.

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