Clinical studies on long-term lithium treatment and kidney failure

Akademisk avhandling

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av

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This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Aiff, H; Attman, PO; Aurell, M; Bendz, H; Schön, S; Svedlund, J.
End-stage renal disease associated with prophylactic lithium treatment.
European Neuropsychopharmacology 2014; 24(4):540-4

II. Aiff, H; Attman, PO; Aurell, M; Bendz, H; Schön, S; Svedlund, J.
The impact of modern treatment principles may have eliminated lithium-induced renal failure.
Journal of Psychopharmacology 2014; 28(2):151-4

III. Aiff, H; Attman, PO; Aurell, M; Bendz, H; Ramsauer, R; Schön, S; Svedlund, J.
Effects of ten to thirty years of lithium treatment on kidney function.
Manuscript

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Clinical studies on long-term lithium treatment and kidney failure

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Background: Lithium enjoys the strongest evidence among today's mood stabilisers for long-term relapse prevention of bipolar disorders, and has been shown to reduce the risks of completed and attempted suicides. However, the benefits of lithium are restricted by its adverse side effects, the most serious being the progression of renal insufficiency to end-stage renal disease (ESRD). The risk of lithium-induced ESRD (Li-ESRD) was generally acknowledged in the 1970s. As a result of these findings, much stricter lithium treatment routines, intended to reduce the lithium burden on the kidneys, were introduced in Sweden in the early 1980s. However, the impact of these modern treatment principles remains unclear.

Aims of the thesis: To estimate the prevalence of lithium-associated ESRD (ESRD from all causes in lithium users), and to evaluate the role of lithium in the pathogenesis of ESRD; to test the hypothesis that modern lithium treatment routines have eliminated the risk of Li-ESRD (lithium classified as the sole or main cause of ESRD), and to study the prevalence and extent of kidney damage during the course of long-term lithium treatment in patients who started lithium treatment after 1980.

Patients and Methods: We used the Swedish Renal Registry to search for lithium-treated patients with ESRD among 2644 patients with chronic renal replacement therapy (RRT), either dialysis or transplantation, within two geographical areas in Sweden with 2.8 million inhabitants. The Swedish Prescribed Drug Register was used to estimate the number of lithium patients in the two regions. The prevalence date was December 31, 2010. We reviewed the medical records of patients with suspected Li-ESRD to verify the exposure to lithium treatment, the diagnoses of Li-ESRD according to specified criteria, and the date of starting the lithium treatment. Serum lithium and creatinine levels were retrieved for 4879 patients examined between January 1, 1981, and December 31, 2010. The estimated glomerular filtration rate (eGFR) was calculated according to the Revised Lund-Malmö equation and chronic kidney disease (CKD) stages were defined using the KDOQI guidelines. Only patients who started their lithium treatment during the study period and had at least ten years of cumulative treatment were included.

Results: The prevalence of ESRD patients with RRT in the lithium user population was 15.0‰ (95% CI 9.7-20.3) and the relative risk of ESRD with RRT in the lithium user population compared with the general population was 7.8 (95% CI 5.4-11.1). No patient with Li-ESRD started lithium treatment later than 1980. There was an annual increase in median serum creatinine levels already from the first year of treatment among 630 patients treated for more than ten years. About one third of those patients had CKD stage 3-5 (eGFR <60 mL/min/1.73m^2) and almost 5% reached CKD stage 4 or 5 (eGFR <30 mL/min/1.73m^2).

Conclusions: The thesis corroborates earlier findings that Li-ESRD is an uncommon but not rare condition and gives a reasonably well-founded estimate of its prevalence. Modern lithium treatment may have eliminated the risk of Li-ESRD, as no patient with Li-ESRD started lithium treatment later than 1980. The reduced risk of Li-ESRD is probably due to less lithium exposure with lower plasma levels and lithium discontinuance when indicated on the basis of monitoring of renal function. However, a substantial proportion of patients who are treated with lithium for more than a decade develop signs of renal dysfunction and it remains to be shown whether there is still a risk of progression to Li-ESRD, but at a slower pace than earlier. The results support continuous monitoring of kidney function during long-term lithium treatment.

Keywords: Affective disorders, Lithium, Adverse effects, Chronic Kidney failure
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