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Published in:
Bipolar Disorders

DOI:
[10.1111/bdi.12977](https://doi.org/10.1111/bdi.12977)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Nielsen, R. E., Kessing, L. V., Nolen, W. A., & Licht, R. W. (2021). A skewed perspective: A reply to Kovvuru et al. *Bipolar Disorders*, 23(1), 86-87. <https://doi.org/10.1111/bdi.12977>

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A skewed perspective – A reply to Kovvuru et al

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Thanks to Kovvuru et al¹ for granting us insight into the perspective of nephrology's view on lithium regarding its potential nephrotoxicity. Renal side-effects of long-term lithium exposure are well-known, and we concur with the proposed patient-centered approach when determining if a patient with observed impairment of renal function should discontinue or continue lithium treatment, and in the latter case whether the lithium dose should be reduced. In this difficult decision, indications for continued lithium treatment should be carefully evaluated, in particular the original indication and the subsequent potential benefits of the treatment, as well as other previous treatment attempts, in the given patient. In light of this, the risk associated with lithium discontinuation should be considered before choosing which path to take. Beyond the established evidence for the prophylactic efficacy of lithium, there are data, although conflicting, demonstrating that lithium discontinuation carries an additional risk of subsequent refractoriness with respect to recurrence prevention, even years after discontinuation. If lithium discontinuation is chosen, a slow tapering of lithium, where possible, is generally recommended.

In their publication Kovvuru et al¹ describe the risk of renal dysfunction after prolonged lithium exposure and conclude that it is heavily predominant. In our recent review on lithium exposure and renal impairment we discussed the methodological strengths and weaknesses of several recent large observational studies on the matter.² First, randomized clinical trials (RCTs) are the golden standard for evaluating causality between an intervention and an outcome due to the random and thereby most often even distribution of known and unknown confounders between treatment arms. However, RCTs usually have a relatively short duration of follow-up and small sample sizes. As a result, RCTs are not optimal for detecting and evaluating rare side effects occurring after years of treatment.

When utilizing an observational study design the risk of selection bias and confounding increases, and methodological approaches to minimize such errors need to be applied; eg case-control design, use of propensity score models or use of multivariate regression analysis. In the case of lithium and possible renal impairment, the risk of surveillance bias is high, as patients who are exposed to lithium systematically undergo repeated monitoring of renal function resulting in the likely risk that non-symptomatic renal impairment is being diagnosed to a larger degree in lithium-exposed patients than in controls.² To minimize the effects of surveillance bias, and thereby minimize the risk of skewing results between exposed and non-exposed, an outcome measure with symptoms severe enough for all or almost all patients with renal impairment to be diagnosed must be used, with end-stage renal disease (ESRD) being preferred in most studies.² The Swedish cohort studies thus utilized ESRD as outcome measure and interviewed ESRD patients regarding their lithium exposure and showed that the proportion of ESRD in lithium exposed patients was higher than that in the general population.² In these studies, variables associated with an increased risk of ESRD including other medications, physical co-morbidities and psychiatric disorders, as well as lithium treatment duration and cumulative dosage were not taken into account.² Furthermore, there was no adjustment for changes in prescription patterns of lithium over the years perhaps resulting in an inflated prevalence rate of ESRD in lithium exposed patients, and finally, the design carried an inherent risk of recall bias.²

In 2015, Kessing et al published a nationwide study on the association between number of lithium prescriptions and rates of chronic renal disease taking into account the above mentioned caveats.³ By means of the Danish healthcare registers, two cohorts were defined: (1) the general population and (2) patients diagnosed with bipolar disorder. All patients with a known previous renal

dysfunction were excluded from both cohorts. Adjusting for other variables, such as number of anticonvulsant prescriptions, number of antipsychotic prescriptions, number of antidepressant prescriptions, calendar year, bipolar diagnosis, age, gender, employment status, and prescriptions for other medications (including medications for physical disease), the rates of possible chronic kidney disease (CKD), definite CKD, and ESRD were estimated.³ Survival analyses did not reveal an increased rate of ESRD with an increasing number of lithium prescriptions. However, the rate of definite kidney disease was increased with an increasing number of prescriptions. Furthermore, ESRD and definite kidney disease were more frequent in patients with a bipolar diagnosis and in patients taking other medications, whereas female gender was protective.³ Based on an additional analysis of the dataset from this study, Kessing et al.⁴ reported that treatment with lithium was continued in a large proportion of patients after an initial diagnosis of chronic renal disease without increasing the risk of developing ESRD compared to those patients who had their lithium discontinued. However, it should be noted that, presumably, the patients who were continued on lithium were carefully selected based on their renal function and that their kidney function was closely and continuously monitored throughout treatment. Unfortunately, serum lithium levels were not available for analysis.⁴

In general, when less severe forms of renal impairment than ESRD were investigated, lithium exposure was associated with an increased incidence of renal impairment.² In studies utilizing ESRD as outcome measure, results varied. Notably, increased rates of ESRD associated with lithium exposure were observed in studies involving patients exposed to lithium over earlier decades, whereas studies involving patients exposed to lithium over the recent two to three decades did not find an increased rate of ESRD.² Treatment recommendations regarding optimal serum lithium levels in maintenance

treatment have changed over the decades from initial recommendations ranging from 0.8 to 1.2 mmol/L to newer recommendations ranging from 0.6 to 0.8 mmol/L,⁵ which likely accounts for this difference.

We would propose that the lack of difference regarding the risk of ESRD between lithium exposed and non-exposed participants in some studies might be a result of improvements in the methodology of study designs. The results are probably also due to improved renal monitoring with lithium discontinuation in patients with early signs of renal impairment, as well as a focus on recommended lower lithium serum levels during maintenance treatment.

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REFERENCES

1. Kovvuru K, Kanduri SR, Thongprayoon C, Cheungpasitporn W. Lithium and nephrotoxicity: Nephrology's perspectives. *Bipolar Disord*. 2020;22(4):331-333.
2. Nielsen RE, Kessing LV, Nolen WA, Licht RW. Lithium and renal impairment: A review on a still hot topic. *Pharmacopsychiatry*. 2018;51:200-205.
3. Kessing LV, Gerds TA, Feldt-Rasmussen B, Andersen PK, Licht RW. Use of lithium and anticonvulsants and the rate of chronic kidney disease. *JAMA Psychiatry*. 2015;72:1182.
4. Kessing LV, Feldt-Rasmussen B, Andersen PK, Gerds TA, Licht RW. Continuation of lithium after a diagnosis of chronic kidney disease. *Acta Psychiatr Scand Published Online First*. 2017;136(6):615-622. <https://doi.org/10.1111/acps.12820>
5. Nolen WA, Licht RW, Young AH, et al. What is the optimal serum level for lithium in the maintenance treatment of bipolar disorder? A systematic review and recommendations from the ISBD/IGSLI Task Force on treatment with lithium. *Bipolar Disord*. 2019;21:394-409.