



## Letter to the editor: Dietary nitrates may reduce cardiorenal side-effects of lithium therapy in older subjects



### To the Editors

The habitual consumption of vegetable-derived dietary nitrates by persons 60 years or older may reduce certain pro-inflammatory effects of lithium therapy in this population.

In a large study of older bipolar patients who had been taking lithium for at least 15 years, [Tondo et al. \(2017\)](#) reported that these patients were at increased risk for reductions in glomerular filtration rate and other medical co-morbidities. While the dose of lithium declined significantly over time, the lithium serum concentrations remained stable. There were non-significant increases in body mass index (BMI). However, the patients had significant increases in serum glucose, blood urea nitrogen (BUN), and creatinine. The estimated glomerular filtration rate (eGFR) declined significantly over the period of study. The BMI changes appeared after the first year, glucose and eGFR from years 6–10, creatinine from years 16–20, and the blood urea nitrogen (BUN) from years 21–30. Reductions in eGFR and increases in creatinine emerged after age 55, and in subjects with 20 years or greater exposure to lithium. Other factors included age of illness onset, sex, drug co-treatments, medical co-morbidities, longer exposure to lithium, greater circulating BUN, and greater BMI. [Aprahamian et al. \(2014\)](#) treated 35 elderly patients experiencing mild cognitive impairment with lithium or placebo. Subjects receiving lithium had no significant changes in renal function after 4 years of lithium therapy. However, the lithium-treatment group had greater numbers of circulating neutrophils, higher levels of serum thyroid stimulating hormone (TSH), and weight gain. They experienced more adverse events which interfered with daily activities, and had higher incidences of diabetes mellitus and arrhythmia.

[de Sousa et al. \(2014\)](#) have reported that lithium treatment significantly increased plasma nitric oxide (NO) in young adults (mean age: 27.7 yrs.) with bipolar depression after 6 weeks of treatment. Similar studies of the effects of lithium on circulating levels of nitric oxide in older bipolar patients have not been reported. [Torregrossa et al. \(2011\)](#) reviewed several studies of aging men and women which observed that the constitutive production of nitric oxide is very significantly reduced during aging: “Clinical studies provide evidence that insufficient NO production is associated with all major cardiovascular risk factors, such as hyperlipidemia, diabetes, hypertension, smoking, and severity of atherosclerosis, and has a profound predictive value for disease progression including cardiovascular and Alzheimer’s disease ... It appears that aging interrupts NO signaling at every conceivable level from production to inactivation.” [Torregrossa et al. \(2011\)](#) also noted: “Endothelium-dependent vasodilation in resistance vessels declines progressively with increasing age. This abnormality is present in

healthy adults who have no other cardiovascular risk factors ... Endothelium-independent vasodilation does not change significantly with aging, demonstrating that the responsiveness to NO does not change, only the ability to generate it.”

[Van der Avoort et al. \(2018\)](#) reviewed the nitrate contents of several green leafy and root vegetables. [Omar et al. \(2016\)](#) noted that the effects of dietary nitrates from leafy green vegetables included vasodilation, improved endothelial function, enhanced mitochondrial efficiency, and reductions in the generation of reactive oxygen species. [Khambata et al. \(2017\)](#) reported that feeding nitrates to mice with accelerated atherosclerotic disease reduced systemic leukocyte rolling and adherence, circulating neutrophil numbers, and monocyte activation. [Radomski et al. \(1987\)](#) observed that endogenous nitric oxide inhibited human platelet adhesion to vascular endothelium, and [Radizon-Balicka et al. \(2017\)](#) reported that human platelets possess an endothelial-type nitric oxide synthetase which can limit the size of platelet aggregates.

In a 23-study meta-analysis, [Jackson et al. \(2018\)](#) reported that the oral inorganic nitrate/nitrite intake by human subjects was found to “significantly reduce resting blood pressure, improve endothelial function, reduce arterial stiffness, and reduce platelet aggregation.” [Raubenheimer et al. \(2017\)](#) gave nitrate-rich beet juice to healthy elderly males and females, and they observed significant decreases in systolic and diastolic blood pressures, decreases in the number of blood monocyte-platelet aggregates indicating reduced platelet activation, and a shift toward an anti-adhesive circulating granulocyte phenotype 3–6 hours later. Importantly, [Vanhatalo et al. \(2018\)](#) have reported that in older healthy subjects, dietary nitrate supplementation led to specific changes in the oral microbiome which were correlated with greater increases in plasma nitrites and reduced systemic blood pressure in older but not young participants. Both an anonymous reviewer of this report and (subsequently) the author JM have failed to find any studies of lithium treatment on the human oral microbiome. [Van der Avoort et al. \(2018\)](#) have recommended the habitual intake of green leafy vegetables as an alternative to inorganic nitrate supplementation. The regular intake of green leafy vegetables has also been associated with lower risks for primary open-angle glaucoma ([Kang et al., 2016](#)), and a slowing of aging-related cognitive decline ([Morris et al., 2018](#)).

[Bock et al. \(2018\)](#) observed that dietary nitrate reduced systolic and mean arterial blood pressures without affecting spontaneous cardiovascular baroreflex sensitivity in older adults. [Kemmner et al. \(2017\)](#) found that dietary nitrates significantly reduced the renal resistive index (a measure of intrarenal perfusion and hydrodynamics) and systemic blood pressure in elderly patients with chronic renal disease. [Lundberg et al. \(2018\)](#) and [Carlstrom and Montenegro \(2019\)](#) have proposed that clinical studies employing chronic dietary nitrate

Comment on: Lithium increases nitric oxide levels in subjects with bipolar disorder during depressive episodes ([de Sousa et al., 2014](#)).

<https://doi.org/10.1016/j.jpsychires.2019.04.025>

Received 18 February 2019; Received in revised form 20 April 2019; Accepted 25 April 2019

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treatment may reduce endothelial dysfunction and slow the progression of cardiorenal diseases such as hypertension.

In summary, increases in dietary nitrate consumption may reduce pro-inflammatory and cardio-renal risks in middle-aged and elderly patients taking long-term lithium therapy for the treatment of bipolar disorders.

#### Declaration of interests

None.

#### Funding source for current study

None.

#### Previous presentation/publication of data

None.

#### Acknowledgements

None.

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