**Lithium (Li) has been the first line treatment for bipolar disorder (BD) for the last five decades** [1,2]. In modern times, John Cade, an Australian physician, began the use of Li for psychiatric illnesses in 1949 [3]. Over the years, Li has demonstrated that it is an effective in preventing the recurrence of mood episodes, and as an enhancement strategy in major depressive disorder [4]. Li is the most efficient drug in reducing suicide tendency and mortality [5], which are very high among war veterans and patients with mood disorders [6]. In the last few years Li has been gaining attention as a therapeutic in several neurological disorders, such as schizophrenia, post-traumatic stress disorder, traumatic brain injury etc. However, one of the major factors limiting the more widespread use of Li treatment is its short- and long-term adverse effects on the kidney in a subpopulation of recipients. Up to 40% of patients receiving Li report various degrees of acute increase in urine production, so-called Nephrogenic Diabetes Insipidus (NDI) [7]. Long-term Li treatment (years to decades) has more severe side effects known as Chronic Kidney Disease (CKD), which is characterized by reduced glomerular filtration rate (GFR), interstitial nephritis, renal fibrosis, microcyst formation, which can ultimately lead to end-stage renal disease (ESRD). CKD occurs only in a small subpopulation of Li-treated patients with a 2.5-fold higher incidence compared to the general population [8].

Though Li is undoubtedly a lifesaver for many BD patients, the toxic effects on kidneys in some patients forces them to stop Li treatment, frequently resulting in a plunge back into the psychotic illness. This greatly impacts the patients’ quality of life, work productivity, and life expectancy. Some patients choose their short-term quality of life at the expense of deteriorating kidney function, especially those who respond only to Li as a psychotropic medication. The time renal complications are measurable according to the current standards, kidney damage might already have reached a ‘point of no return’, and withdrawal of Li does not improve kidney function, or in some patients does not even preclude the progression of CKD to ESRD. There are multiple open-ended questions that need to be addressed, but the following two questions require immediate attention:

**Who is at high risk of developing NDI and/or CKD?** Little is known about the predictors of Li-induced renal adverse effects. The dose, the length of treatment and age are certainly important, but not the only factors. In an effort to stratify the risk for renal insufficiency in these patients, Castro et al [9] showed that hypertension and diabetes are predictors, although by themselves these conditions increase the risk for renal insufficiency. Another novel risk factor that emerged from this study is schizophrenia. If we can develop a risk model that predicts, who will develop CKD after 10 or 20 years of Li treatment, a huge dilemma among many patients and doctors could be avoided and more patients could enjoy confidently the benefits of Li without worrying about its side effects. In addition, this understanding would reverse the slowly declining rate of Li prescriptions in many countries. However, this decline might be due to the fact that pharmaceutical companies are promoting drugs that are patented and, thus, are more profitable for them.

**When does Li-induced CKD develop?** Using the current biomarkers of renal function, by the time we realize that the kidney function is deteriorating, we may be already too late. The key is to find a biomarker that will reliably inform us about declining renal function before the renal reserve is exhausted. For example, the current gold standard marker - serum creatinine - shows a significant increase only when up to 50% of renal function may have already been lost. A biomarker in this regard may also help in the early diagnosis of CKD caused by other factors.

**Answering these questions is paramount for the safe use of Li not only for BD patients, but also for those who will benefit in the near future from its positive effect on a number of other neurological disorders. It is our responsibility as scientific community to allow those who need Li to enjoy its undoubted benefits, without worrying about the harmful side effects that may or may not occur decades down the line.**

**REFERENCES**


*Review Editor’s Comments | This review highlights the use and risk of Lithium. Lithium is very effective against BD and other neurological diseases, identifying biomarkers for CKD would be highly beneficial to patients in terms of safety and cost.*