# Barry Blackwell: The Lithium Controversy. A Historical Autopsy

## Gordon Johnson's comment on Janos Rado's (January 25, 2018) final comment



**July 5, 2018**

**Uncertainty concerning lithium's effects on renal function are widespread and may adversely effect clinical management. As Rado notes lithium is the drug of first choice in long term prophylactic treatment in bipolar disorder requiring clinical and laboratory monitoring.**

**Thirst and increase of urine volume(polyuria)are two of the most frequently reported side effects.These changes are attributed to decreased responsiveness of the renal tubules to the antidiuretic hormone. This impairment of urinary concentrating ability is considered a reversible pharmacological-effect. Polyuria has been reported in upto 50% of patients; with polyuria greater than 3 litres per 24 hours in 20% of patients on long-term lithium therapy (Boton et. al 1987). Such increased urine volume carries a potential risk of toxicity to the patients because of sodium depletion, excessive fluid loss or reduced fluid intake.Progressive impairment may occur in some patients leading to a diabetes insipidus syndrome.**

**In 5to 10% of patients the impairment of concentrating ability may be irreversible or only partly reversible upon lithium discontinuation(Bendz 1983).**

**In contrast, glomerular function remains relatively unscathed(Johnson et al. 1984). There is an inverse correlation between maintenance plasma lithium levels and urinary concentrating ability and plasma levels should be kept at the lowest level**

**consistent with adequate therapeutic effect.As renal tubular concentrations of lithium may be 10-20 times that in plasma what are moderate differences in plasma level will be considerably amplified at the tubular level.**

**Rado reports a case study in a patient with irreversible diabetes insipidus associated with lithium maintenance treated in a cross over study with high dose pitressin analogue alone and in combination with indomethacin or calcitonin. Excessive doses of desmopressin alone had an antidiuretic effect with decreased urine volume and increased osmolality the nonsteroidal drug indomethacin enhanced the effect while calcitonin abolished it.**

**The mechanisms involved remain unexplained. No adverse effects were noted. The diabetes insipidus persisted followinglithium discontinuation and remained unchanged overthreeyears. A small improvement in glomerular filtration was noted. This also remained unchanged over the three years.**

**This is an interesting report of effective treatment paradigm in severe lithium-induced diabetes insipidus and warrant s further investigation.**

**Risk factors associated with impaired renal function in patients on lithium are:**

**1 Current or previous episodes of lithium intoxication**

**2Lithium dose and plasma levels**

**3 Concomitant psychotropic medication**

**4 Cardiovascular disease**

**5. Age decline inGFR**

**There is no consistent evidence that differences in lithium preparations or dosage regimens effect renal function differentially. The clinical benefits obtained in the majority of patients far outweigh the identifiable risks of renal impairment.**

**References:**

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**Johnson G. Lithium early development, toxicity and renal function Neuropsychopharmacology 1998; 19:200-5**

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