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Lithium and the Kidney
An Updated Review

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Abstract

Despite the availability of alternative agents, lithium continues to be the standard against which all mood stabilisers, prescribed for acute and maintenance treatment of bipolar (and, to a lesser extent, unipolar) mood disorders, are compared. As a medication often used on a maintenance basis for a lifelong disorder, the potential for lithium to cause long term organ toxicity has generated appropriate concern. Foremost among these concerns are its renal effects.

Lithium adversely affects renal tubular function, causing polyuria secondary to a deficit in urine concentrating ability. This effect is probably progressive for the first decade of lithium therapy, i.e. it correlates with duration of lithium therapy. Although this effect of lithium is probably functional and reversible early in treatment, it may become structural and irreversible over time. In contrast, the effect of lithium on glomerular function is not progressive.

Conclusions in this area are hampered by the evidence that patients with psychiatric disorders who are not receiving lithium also show defects in certain aspects of renal function. Despite the generally sanguine data on glomerular function, a very small group of patients may develop renal insufficiency due to lithium (possibly in conjunction with other somatic factors) in the form of interstitial nephritis. However, for the vast majority of patients, the renal effects of lithium are benign.

Current strategies for minimising the renal effects of lithium include: (i) assiduously avoiding episodes of renal toxicity; (ii) monitoring serum lithium concentrations in order to achieve optimal efficacy at the lowest possible concentration; (iii) monitoring serum creatinine levels on a yearly basis, getting further medical evaluation when the serum creatinine level consistently rises above 140 mmol/L (1.6 mg/dl); and (iv) possibly administering lithium once a day.

Despite the availability of alternative agents, lithium continues to be the standard against which all mood stabilisers, prescribed for acute and maintenance treatment of bipolar (and, to a lesser unipolar) mood disorders are compared.[1] Given its longevity in the relatively young field of psychopharmacology, concerns about the long term adverse effects of lithium have been increasingly studied over the last decade.

Primary among these concerns has been the effect of lithium on renal function. The question of lithium-induced renal toxicity began with the 1977 report of renal biopsy abnormalities in a small group of lithium-treated patients.[2] Since then, a number of studies have evaluated renal function in lithium-treated patients. Because a series of papers published in 1987 to 1989 reviewed these studies in some detail,[3-5] this article will highlight studies published over the last decade while summarising the results of earlier studies. In examining those questions for which few studies have been published, both older and newer studies will be described. Additionally, this article will consider strategies to prevent and manage potential renal dysfunction associated with the use of lithium.

1. Effect on Renal Function

1.1 Effect on Tubular Function

Lithium is completely absorbed by the gastrointestinal tract, filtered completely by the glomeruli and then reabsorbed, primarily in the proximal tubule. It is likely that little if any reabsorption occurs in the loop of Henlé.[3,6,7] Lithium accumulates in the collecting tubule, the likely site of its capacity to alter renal water excretion. It has been conclusively shown that lithium interferes with the capacity of the cortical portion of the collecting tubule in the kidneys to generate cyclic adenosine monophosphate in response to antidiuretic hormone stimulation.[5] The consequence of this effect is to reduce the capacity of the kidneys to preserve free water, resulting in an impairment in renal concentrating ability and the production of an excessively dilute urine, defined as diabetes insipidus.[8] Clinically, this manifests in an obligate polyuria, with secondary thirst. Although other mechanisms may also contribute to the polyuria, it is the interference with antidiuretic hormone–induced antidiuresis that is the most important cause of lithium-induced polyuria.

1.1.1 Early Cross-Sectional Studies

A decade ago, reviews of earlier studies concluded that when evaluated in cross-sectional studies, lithium use was associated with a decrease in renal concentrating ability, manifested by decreased maximal urine osmolality.[3-5] The percentage of lithium-treated patients with this finding varied across studies as did the percentage decrease in maximal urine osmolality. Boton and colleagues[3] estimated that 54% of lithium-treated patients showed diminished renal concentrating ability (as defined by a maximal urine osmolality <800 mmol/kg) with 19% showing polyuria (defined by a 24-hour urine output >3 L/day). In contrast, Schou,[4] relying heavily on his own data, estimated mean concentrating ability to be decreased by only 7 to 10%. Additionally, most, but not all studies found an association between reduced maximal urine osmolality and duration of lithium treatment, implying a progressive deficit.

These conclusions, however, were confounded by evidence that patients with psychiatric disorders who had never been treated with lithium also demonstrated reduced maximal urine osmolality compared to a control group[9,10] or normative data derived elsewhere.[10] The relative contribution of the psychiatric disorder itself *vs* the effects of other nonlithium-psychotropic agents in explaining this finding is still unknown. Another study[11] found no difference in tubular function between lithium-treated patients and patients with psychiatric disorders not receiving lithium ('psychiatric control group'), but did not include a population control group, thereby precluding any clear interpretation of the results.

1.1.2 Early Longitudinal Studies

A few of the earlier studies used a longitudinal design to evaluate the potential progressive nature of tubule dysfunction in patients receiving lith-

ium.[12-17] Results were inconsistent with 2 out of 3 studies finding a progressive increase in 24-hour volume[12-14] and only 1 out of 4 studies[14-17] finding a progressive decline in maximal urine osmolality. However, with only 1 exception,[17] the length of time between examinations of renal function in these studies was 2 years or less. The only study with a longer time between examinations (mean = 4.7 years) found the largest progressive deficit in renal concentrating capacity from a mean of 713 to 573 mmol/kg.[17]

1.1.3 Recent Cross-Sectional Studies

Over the last decade, 7 new studies have evaluated lithium and renal tubular function.[18-24] The details of these studies are given in table I.

Of 3 studies using a cross-sectional design, 2[18,19] found clear deficits in maximal urine osmolality and/or increased 24-hour urine volume as compared with either population control participants[18] or psychiatric control participants.[19] The third study[20] provided few details, but found no abnormalities except for polyuria in 8% of the sample. Only 1 of these studies[18] found a correlation between total lithium exposure (as a marker of duration of lithium treatment) and diminished urine concentrating ability.

1.1.4 Recent Longitudinal Studies

Four longitudinal studies have re-examined renal tubular function in lithium-treated patients (table I).[21-24] The length of time between examinations ranged from 3 to 10 years. Only 1 out of 4 studies[21] showed a significant decrease in tubular function as defined by maximal urine osmolality. The reason for the disparity in results is unclear and cannot be explained by either length of follow-up or number of participants studied. However, significant loss of the sample at follow-up,[22-24] and/or refusal to participate in follow-up examination,[23] make the results of these studies tentative.

The studies of the effects of lithium on tubular dysfunction can be summarised as follows: most, but not all, the studies indicate that the use of lithium is associated with a diminished capacity to conserve free water as measured by 24-hour urine volume and/or maximal urine osmolality. The extent to which these changes are progressive and/or correlate with duration of lithium exposure is less clear. Most cross-sectional studies seem to show a correlation between duration of lithium treatment and decreased maximal urine osmolality. In contrast, the more recent longitudinal studies, examining patients with extended time between examinations (mean = 8 years) did not consistently find further progression of the tubular dysfunction over time. This may indicate that the progression of renal concentrating deficit occurs predominantly within the first few years of treatment and that, later (e.g. in the second and third decade of treatment), no further consistent changes are seen.

Aside from its effects on water balance, lithium may have other lesser tubular effects. It may cause a mild incomplete distal tubular acidosis in patients with and without reduced urine osmolality.[3] However, this effect is unlikely to be clinically relevant.[25]

1.1.5 Renal Function After Lithium Discontinuation

The potential reversibility of the effects of lithium on tubular function has been evaluated in a handful of studies by measuring renal function in patients who have discontinued lithium therapy for reasons other than renal dysfunction.[12,23,26-28] Details of these studies are given in table II.

Across studies, tubular dysfunction as measured by 24-hour urine volume and/or maximal osmolality either stayed constant or improved only somewhat after lithium discontinuation and remained abnormal compared with control populations. These results imply that at some point during lithium treatment, a functional, potentially reversible abnormality becomes structural and only minimally reversible. Results of renal biopsy studies (reviewed in section 2) are consistent with these clinical findings.

1.2 Effect on Glomerular Function

Most of the studies reviewed in section 1.1 also evaluated the effect of lithium on glomerular function. Glomerular filtration rate is determined either by measuring serum creatinine levels, endogenous creatinine clearance or by using alternative filtra-

tion markers such as ^{51}Cr–EDTA (^{51}chromium-ethylene diamine tetra acetic acid) clearance. Serum creatinine level measurement is a crude and often inaccurate measure of glomerular filtration rate since extrarenal creatinine excretion, the effect of muscle mass and other factors preclude a linear relationship between serum creatinine level and glomerular filtration rate.[29] Especially in the face of renal insufficiency, serum creatinine levels may show almost no change despite a significant decrease in glomerular filtration rate. Creatinine clearance is a more accurate measure of glomerular filtration rate. However, it too progressively overestimates glomerular filtration rate as glomerular function deteriorates. ^{51}Cr-EDTA clearance is the most accurate measure of glomerular filtration rate used in lithium studies.[30]

1.2.1 Earlier Studies

Examining the earlier studies published up to 1 decade ago, previous reviews[3-5] all shared the same conclusions: lithium treatment is generally not associated with a meaningful decrease in glo-

Table I. Recent studies evaluating tubular function in lithium-treated patients

Reference	No. of patients	Duration of lithium treatment		Serum lithium concentration		Control group	Results
		mean (y)	range (y)	mean (mmol/L)	range (mmol/L)		
Cross-sectional studies							
Conte et al.[20]	50	6.3	1.5-14	0.58	0.34-0.8	Unstated (? demographic controls)	4/50 patients with polyuria. Mean U_{max} (mmol/kg) = 950 ± 56 in 10 patients. All other values within normal limits
Bendz et al.[18]	142	19	15-29	0.64	0.20-1	Demographic controls	Mean U_{max} (mmol/kg) = 580 ± 205. 44% of patients had abnormal values. 12% of patients were ostenuric
Coskunol et al.[19]	107	4.5		0.76		Psychiatric patients	Mean U_{max} (mmol/kg) = 814 ± 170 (patients) *vs* 1042 ± 132 (controls) [p < 0.0001]. 24-h urine volume (ml/24-h) = 2194 ± 1434 (patients) *vs* 794 ± 346 (controls) [p < 0.0001]
Longitudinal studies							
Jorkasky et al.[22]	65 baseline; 51 (1y); 18 (3y)			0.68			Increased urine volume at 1y. Returning to baseline at 3y. No difference in U_{max} at 3y
Nilsson & Axelsson[21]	37	15.4 (7y between examinations)	8.9-20	0.56 at follow-up	0.30-0.85		U_{max} (mmol/kg) = 511 (range 164-946) at baseline and 397 (range 123-888) at follow-up (p < 0.0001)
Hetmar et al.[23]	46 at baseline; 27 at follow-up (19 receiving lithium)	8.1 at baseline; 19.5 at follow-up (10y between examinations)	1-14 at baseline; 11.5-23.5 at follow-up	0.8	0.5-0.98 at follow-up		U_{max} (mmol/kg) = 607 at baseline and 685 follow-up (NS). 24-h urine volume (ml/24-h): 3033 at baseline and 2917 at follow-up (NS)
Kallner et al.[24]	207 (50 patients re-examined after 5y)	12		0.61			U_{max} (mmol/kg) = 651 at baseline and 616 at follow-up (NS)

NS = nonsignificant differences; **U_{max}** = maximal urine osmolality.

Table II. Studies of lithium-treated patients who discontinued treatment

References	No. of patients	Time after lithium discontinuation	Tubular function	Glomerular function	Comments
Bucht & Wahlin[26]	87	3wk and 8wk	U_{max} (mmol/kg) = 517 ± 197 at baseline, 605 ± 202 at 3wk and 658 ± 181 at 8wk (p = 0.001)	Serum creatinine level (μmol/L) = 82 ± 16 at baseline), 78 ± 15 at 3wk and 78 ± 16 (NS)	U_{max} still lower than demographic controls (p = 0.001) Serum creatinine level higher in patients *vs* controls (p = 0.02 at 8wk)
Vestergaard & Amdisen[12]	37	Mean = 14mo	24-h urine volume (L) = 2.8 at baseline and 2.19 at follow-up (p < 0.02). U_{max} improved (p < 0.01) in post-lithium *vs* pre-lithium but still less (p < 0.01) than in 'never treated' group	Creatinine clearance (ml/sec) = 1.51 in controls *vs* 1.49 in lithium-treated patients (NS)	Urine volume post-lithium did not differ from 'never treated' group
Bendz et al.[27]	36	3mo	U_{max} (mmol/kg) = 674 at baseline *vs* 751 at follow-up (p < 0.001). 24-h urine volume (L) = 2.5 at baseline *vs* 1.9 at follow-up (p < 0.001)	Serum creatinine level (μmol/L) = 86.3 at baseline and 90.6 at follow-up (NS). ^{51}Cr-EDTA (ml/min/1.73m^2) = 80 at baseline *vs* 88 at follow-up (p < 0.05)	
Hetmar et al.[23]	8	Unknown	24-h urine volume (L) = 3101 at baseline *vs* 2981 at follow-up (NS). U_{max} (mmol/kg) = 704 at baseline *vs* 810 at follow-up (NS)	Creatinine clearance (ml/sec) = 1.44 at baseline *vs* 1.26 at follow-up (NS)	One patient discontinued lithium secondary to renal insufficiency
Bendz et al.[28]	13	5wk and 9wk	U_{max} (mmol/kg) = 645 at baseline *vs* 637 at follow-up (NS). 24-hour urine volume (L) = 3.8 at baseline *vs* 4.7 at follow-up (NS)	Serum creatinine level (μmol/L) = 103 at baseline *vs* 97 at follow-up (NS). GFR (ml/min/1.73m^2) = 69 at baseline *vs* 74 at follow-up (NS)	

^{51}Cr-EDTA = ^{51}chromium-ethylene diamine tetra acetic acid; **GFR** = glomerular filtration rate; **NS** = nonsignificant differences; **U_{max}** = maximal urine osmolality.

merular filtration rate and, if a decrease is seen, it is typically mild and not clinically significant. In 1987, Boton et al.[3] estimated that glomerular filtration rate was reduced by an average of 15% across all published studies. Furthermore, this very mild decrease cannot necessarily be attributed to lithium alone since some patients had pre-existing renal disease, others had had lithium intoxication (a presumed risk for lithium-induced renal damage – see section 4) and many patients were taking other psychotropic medications with their own potential effects on renal function.

A second sanguine conclusion from the earlier reviews was that the majority of studies found no significant correlation between reduced glomerular filtration rate and duration of lithium therapy, implying that even if lithium-induced glomerular dysfunction existed, it was not progressive in nature. However, these conclusions were tempered (as were the studies on tubular function) by the acknowledgment that few studies had prospectively followed patients for long periods of time while they were receiving lithium, thereby precluding definitive conclusions on this question.

Since these earlier reviews, the same 7 studies[18-24] that examined tubular function also reported on glomerular function, 6 using creatinine or ^{51}Cr-EDTA clearance as a marker[18-20,22-24]

while 1 simply measured serum creatinine levels.[21] The findings of these studies are summarised in table III.

1.2.2 Recent Cross-Sectional Studies

Three studies used a cross-sectional design.[18-20] Conte et al.[20] found no tubular function abnormalities in 50 lithium-treated patients and no relationship between duration of lithium treatment and creatinine clearance; however, the study provided few details. Coskunol et al.[19] compared 107 lithium-treated patients to a psychiatric control population and found no significant difference between the 2 groups in terms of serum creatinine levels or creatinine clearance. Of note, patients with renal concentrating defects (maximum urine osmolality <700 mmol/kg) showed no differences in glomerular function compared with those with normal tubular function.

Bendz et al.,[18] evaluating 142 patients all of whom had been receiving lithium for at least 15 years, found that 21% of the sample showed significantly reduced glomerular filtration rate compared with a demographic population control group. Compared with patients whose glomerular filtration rates were within the normal range, those with diminished glomerular filtration rate had higher 24-hour urine volume (mean = 3850 ± 1900 *vs* 3050 ± 2000 ml/24h, $p < 0.05$), lower maximal urine osmolality (mean = 485 ± 233 *vs* 605 ± 191 mmol/kg, $p = 0.01$). Additionally, in earlier studies from the same research group, only 7% of patients

Table III. Recent studies evaluating glomerular function in lithium-treated patients

References	No. of patients	Duration of lithium treatment		Serum lithium concentration		Control group	Results
		mean (y)	range (y)	mean (mmol/L)	range (mmol/L)		
Cross-sectional studies							
Conte et al.[20]	50	6.3	1.5-14	0.58	0.34-0.8	Unstated (? demographic controls)	No abnormalities noted
Bendz et al.[18]	142	19	15-29	0.64	0.20-1	Demographic controls	GFR (ml/min) = 72 ± 17 (21% below normal)
Coskunol et al.[19]	107	4.5		0.76		Psychiatric patients	Creatinine clearance (ml/sec) = 1.44 ± 0.36 in lithium-treated patients *vs* 1.4 ± 0.34 in controls (NS)
Longitudinal studies							
Jorkasky et al.[22]	65 baseline; 51 (1y); 18 (3y)			0.68			No change in creatinine clearance in women. Decreased creatinine clearance (ml/min) in men: 107 ± 4 at baseline *vs* 80 ± 11 at 3y ($p < 0.04$)
Nilsson & Axelsson[21]	37	15.4	8.9-20.4 (7y between examinations)	0.56 at follow-up	0.30-0.85		Serum creatinine level (μmol/L) = 92 (60-153) at baseline *vs* 102 (70-192) at follow-up
Hetmar et al.[23]	46 at baseline; 27 at follow-up (19 patients receiving lithium)	8.1 at baseline; 19.5 at follow-up	1-14 at baseline; 11.5-23.5 at follow-up (10y between examinations)	0.8	0.5-0.98 at follow-up		Creatinine clearance (ml/sec) 1.44 ± 0.32 at baseline *vs* 1.17 ± 0.31 at follow-up ($p < 0.01$)
Kallner et al.[24]	207 (50 patients re-examined after 5y)	12		0.61			^{51}Cr-EDTA (ml/min) = 74 ± 14 at baseline *vs* 73 ± 15 at follow-up (NS)

^{51}Cr-EDTA = ^{51}chromium-ethylene diamine tetra acetic acid; **GFR** = glomerular filtration rate; **NS** = nonsignificant difference.

who had taken lithium for 6 years had a reduced glomerular filtration rate[27,31] (compared with 21% in the more recent study of patients who had taken lithium for a mean of 19 years), implying that the longer duration of lithium treatment was associated with reduced glomerular function (although at a subclinical level.)

1.2.3 Recent Longitudinal Studies

Of the 4 longitudinal studies published within the last decade, all showed declines in creatinine clearances over time[22-24] or an increase in serum creatinine levels.[21] One study[22] found this decrease occurred only in men, but this study had the shortest follow-up time of 3 years. However, since glomerular filtration rate normally decreases over time as a normal consequence of aging, 2 of the studies adjusted the changes in creatinine clearance for age.[23,24] With this statistical adjustment, the change in glomerular function virtually disappears. Thus, the longitudinal studies show no overall trend towards progressive glomerular dysfunction beyond that seen with normal aging.

1.2.4 Other Glomerular Effects

An unusual (only a total of 21 cases have been reported to date) but well recognised renal complication of lithium therapy is nephrotic syndrome, typically associated with biopsy proven minimal change disease and manifested by high serum creatinine levels, lithium toxicity and heavy proteinuria.[32,33] Acute renal failure is often present.[32] Typically, the nephrotic syndrome disappears within weeks after lithium discontinuation, although treatment with corticosteroids is occasionally needed. Reinstitution of lithium therapy after the resolution of nephrotic syndrome results in the re-emergence of the glomerular disease.[32]

1.2.5 Renal Function After Lithium Discontinuation

The studies (both from the last decade and previously) in which patients who discontinued lithium were re-evaluated found no significant changes in glomerular function after short term discontinuation (see table II).[12,23,26-28] Creatinine clearances are generally comparable between those patients who continued lithium and those who discontinued the drug and within individuals after they discontinued lithium. In 1 study, however, patients who discontinued lithium showed a significant increase in ^{51}Cr-EDTA while serum creatinine levels did not change.[27]

2. Biopsy Studies of Lithium-Treated Patients

The first renal biopsy study of lithium-treated patients was that of Hestbech et al.[2] who found chronic, not acute, abnormalities consisting of focal nephron atrophy and/or interstitial fibrosis, tubular dilatation and cyst formation in 13 out of 14 renal specimens. Of the 14 patients, 10 had had at least 1 episode of lithium intoxication and 8 out of 14 had had a biopsy taken in the context of lithium toxicity. Because of this selection bias, it was initially unclear whether these findings reflected changes that might be seen in patients who had not had at least 1 episode of lithium toxicity.

A second study from the same research group,[34] however, examined renal biopsy specimens from 14 patients receiving lithium treatment selected on the basis of polyuria and/or decreased creatinine clearance and in whose history no other cause of renal disease could be ascertained. They found similar morphological changes consistent with chronic interstitial nephritis in this group. Renal concentrating ability showed an inverse correlation with biopsy abnormalities while glomerular function was relatively preserved.

Subsequent studies[35-39] have generally supported the findings of a chronic interstitial nephritis with relative preservation of glomeruli in lithium-treated patients. Most investigators have found the lesions to be nonspecific, seen in a number of other renal diseases.[34] One set of unique acute reversible renal lesions associated with lithium, characterised by cytoplasmic swelling with glycogen deposits in the distal convoluted tubules and collecting ducts has been suggested by 1 group.[38,40,41] The relationship between these lesions and the chronic changes seen in other studies in unclear.

Whether the chronic interstitial changes found in patients with mood disorders treated with lithium can be definitively attributed to the prescribed medication is still unknown since similar lesions have been found in patients with psychiatric disorders who were not treated with lithium.[37,40] Since most of these patients were treated with other psychotropic medications such as antipsychotics, it is as yet unclear whether it is the underlying psychiatric disorder or other medications that may be associated with interstitial abnormalities.

3. Lithium-Induced Renal Insufficiency

The general conclusion that lithium does not cause progressive renal insufficiency (as measured by decreased glomerular filtration rate) does not preclude the possibility that a small percentage of lithium-treated patients might show progressive renal failure. As an example, Løkkegaard et al.[42] found very few low glomerular filtration rate values among lithium-treated patients, but 2 of their original sample were excluded from the study because of low glomerular filtration rates following lithium intoxication.

Another study of patients treated with lithium for at least 10 years noted that 3 out of 19 (16%) had a plasma creatinine level of 140 mmol/L or greater.[43] Lithium was discontinued in 2 of these patients due to renal insufficiency. In a third study, despite the conclusion of a 'well preserved glomerular filtration rate over 20 years', 2 patients developed progressive renal insufficiency requiring lithium discontinuation.[23] Biopsies in both cases showed changes consistent with tubulointerstitial nephritis. Finally, 3 out of 82 patients (4%) treated with lithium showed evidence of renal insufficiency as defined by a serum creatinine level of above 185 mmol/L (2 mg/100ml).[44] Renal biopsy in 2 patients (the third patient refused biopsy) showed tubular and interstitial fibrosis.

Additionally, 5 documented cases of patients with progressive renal failure that required maintenance haemodialysis associated with lithium treatment have been reported.[44-46] For the 4 patients from whom biopsy specimens were obtained, the classic changes already described in association with lithium treatment–induced interstitial fibrosis, tubular atrophy, focal sclerosis and acquired renal cystic disease were seen. No other major risk factors for interstitial nephritis, such as paracetamol (acetaminophen) abuse, recurrent urinary tract infections, renal stones, etc., were present in any of these patients. Only 1 of the patients had reported acute lithium intoxications.[46] All 5 patients had been exposed to lithium for at least a decade. Furthermore, the biopsy findings were all similar and consistent with lithium-induced changes seen in other human and animal studies.

Despite these case reports and case series, there is no direct causal evidence implicating lithium. Additionally, in some of the patients, other comorbid medical disorders, such as hypertension,[43] mitral valve insufficiency,[23] hyperuricaemia,[44] and hyperparathyroidism,[43] were present, suggesting the possibility that lithium plus these other disorders may have conferred the risk for renal insufficiency. Compounding the problem is the unknown rate of spontaneous renal insufficiency in the general population. Thus, the rate of renal failure in lithium-treated patients is probably very small, occurring in only a small group of vulnerable patients possibly due to other medical, unknown familial or environmental factors.

4. Risk Factors for Lithium-Induced Renal Changes

Factors other than duration of lithium therapy itself have been proposed as enhancing the risk of either tubular dysfunction or diminished glomerular filtration rate. They are: concomitant use of other medications, episodes of lithium intoxication, pre-existing somatic disorders and the lithium treatment regimen (i.e. once daily *vs* multiple dose strategies.)

Many,[11,18,25,47-48] but not all,[12,17,42] studies have found that concomitant use of other psychotropic medications, especially antipsychotics, is associated with higher rate of tubular dysfunction. In 1 study, patients taking lithium plus antipsychotics showed higher urine volume but normal

proximal tubular function, suggesting that the defect was due to a lowered fractional resorption of water in the distal nephron.[48] In the same study, patients treated with lithium plus antidepressants did not show alterations in renal tubular function compared with those treated with lithium alone. In contrast, there is much less evidence that adjunctive treatment with antipsychotics is associated with diminished glomerular filtration rate.[12,48]

It is generally assumed that episodes of lithium intoxication increase the long term risk of renal damage[1,15] although definitive data are lacking.

Pre-existing somatic disorders which may independently diminish renal function enhance the risk for lithium-induced renal effects. As an example, Bendz et al.[18] found that lithium-treated patients taking medications for somatic conditions had lower glomerular filtration rate and lower maximal urine osmolality. Similarly, as noted in section 3, some patients who have developed lithium-induced renal insufficiency have also had active medical disorders. By themselves, these medical disorders would be unlikely to cause the interstitial fibrosis seen, but they may have contributed to the renal effects of lithium.

One medical disorder that deserves special attention in this regard is hyperparathyroidism since lithium treatment is associated with an increased risk for hypercalcaemia and hyperparathyroidism.[43,49,50] One study found a higher rate of isostenuria with lithium-treated patients with hyperparathyroidism compared with those with normal parathyroid levels.[49] The course of the lithium-associated hypercalcaemia after lithium discontinuation is variable. However, given the association with hypercalcaemia and renal dysfunction, serum calcium levels should be monitored in lithium-treated patients.

The greatest controversy regarding risk factors surrounds the potential association between the lithium treatment regimen and changes in renal function. Studies examining this question are of 2 types. In 1 group of studies, renal function of patients treated with different lithium regimens (typically once daily *vs* 2 and/or 3 times daily) were evaluated retrospectively. In the second group of studies the change in renal function – typically maximal urine osmolality or 24-hour urine volume – was measured after patients had been switched from 1 regimen to another.

The 2 series of studies[51-56] (5 of these papers[51-55] came from the same research centre) using the first paradigm in which patients treated with different regimens are evaluated retrospectively found differences with patients treated with once daily doses, typically showing lower urine volume. Consistent with this finding, animal studies demonstrate clearly that rats treated with lithium at a relatively constant concentration show reduced renal concentrating ability and greater tubular and interstitial scarring on biopsy specimens compared to rats treated with a regimen producing high peak alternating with low trough lithium concentrations.[57] These 2 conditions mimic the difference between multiple daily dosages *vs* once daily administration in humans. Furthermore, higher 24-hour urine volume correlates best with minimal serum lithium concentration, as opposed to maximal lithium concentration or 12-hour levels.[57] All these lines of evidence suggest that in order to minimise lithium-induced tubular and interstitial effects, it is important that there be some portion of the day when serum (really tubular) lithium concentrations are low, allowing regeneration of renal tubular cells.

These findings, however, must be tempered by 2 methodological points. First, participants in the human studies were assigned nonrandomly to the 2 treatment conditions. Secondly, partly due to the lower lithium clearance at night[58] (and the greater load of lithium during this time in the once daily dosage group), in order to maintain the same serum lithium concentration, those treated with twice daily lithium require higher daily lithium doses (typically 20% higher)[59] thus introducing an important confound. No studies have yet compared once *vs* twice daily regimens with similar total daily lithium doses.

In contrast, studies in which patients have been switched from 1 lithium regimen to another have

generally not shown changes in tubular function.[60-62] The exception to this is a recent study in which urine volume decreased when patients were switched from multiple daily doses to once daily administration but only in those patients who had been treated with lithium for 5 years or less.[63] Since the changes in tubular function may be irreversible over time (as evidenced by the lack of changes in maximal urine osmolality in the lithium discontinuation studies noted in section 1.1.5 and 1.2.5), switching may only be effective (if at all) relatively early in the course of treatment.

An extension of the regimen in which lithium is given as a larger load at less frequent intervals is the paradigm of administering 1.5 times the daily dose every other day.[64] This would clearly produce a low trough concentration just before the dose was administered every 48 hours. In a random assignment study of once daily *vs* every other day lithium, those treated with every other day lithium showed only a trend (not statistically significant) towards less polyuria/polydipsia compared with the daily treated group.[65] However, despite the random assignment to the 2 groups in the study, those treated with every other day lithium had had significantly more lithium exposure before the trial (mean = 10 years *vs* 3 years, $p < 0.05$), making the results of the trial more difficult to conclusively interpret.

5. Management and Prevention Strategies

Given the data reviewed in section 1 to 4, it is important to look at what clinical strategies may be employed to diminish the tubular dysfunction associated with lithium, causing polyuria and an excessively dilute urine in many patients and interstitial nephritis in a rare few.

First, of course, patients receiving lithium should have demonstrated a need for this treatment by their diagnosis, symptom pattern and evidence of benefit. As noted in section 1.1.1, distal tubular function probably correlates with duration of lithium therapy whereas any decrease in glomerular filtration rate is unlikely to be time dependent in the majority of lithium-treated patients. Whether abnormalities in urinary concentrating capacity can be minimised by lowering the serum lithium concentration has not been demonstrated in clinical studies. However, measurements of distal reabsorption of water indicate a strong correlation with serum lithium concentration, suggesting that lower concentrations are associated with enhanced lithium-sensitive tubular function.[66]

There is no consensus as to the optimal monitoring schedule of renal function in lithium-treated patients. With increasing cost-consciousness in healthcare, measuring creatinine clearances and measurements of 24-hour urine volume and/or maximal urine osmolality seems excessive as routine screening procedures. Although measurement of serum creatinine levels is a rather crude method of monitoring glomerular function since significant loss of renal function can occur before serum creatinine levels increase, it remains the simplest, least expensive and most reasonable screening tool. Recommendations on how frequently serum creatinine levels should be measured in lithium-treated patients range from every 3 months to every year.[1,5,67-69]

No simple, inexpensive test of tubular function is available. Asking patients routinely about polyuria is surely the simplest probe. Measurement of 24-hour urine volume is clearly more accurate if the patient is organised and compliant enough to cooperate. Asking about thirst is also useful since, in 1 study, it strongly negatively correlated with maximal urine osmolality.[18]

Another obvious method of minimising the risk of renal dysfunction from lithium is to assiduously avoid episodes of lithium intoxication. Although the data suggesting this as a major contributing factor are based almost exclusively on anecdotes, common sense suggests this approach. Additionally, lithium intoxications are mostly preventable.[70] Lithium intake should be reduced or transiently discontinued in the face of gastrointestinal episodes resulting in diarrhoea, vomiting or dehydration. When other medications known to decrease lithium clearance and to increase lithium

concentrations are added to a patient's regimen such as thiazide diuretics, ACE inhibitors, some nonsteroidal anti-inflammatory drugs, lithium concentrations should be checked and dosages monitored accordingly.[71] A corollary of this is that lithium-treated patients should have individualised dose titration and monitoring to assure optimal benefit at the lowest possible dosage and serum concentrations.

The data presented in section 4 on whether once daily lithium administration is associated with less tubular dysfunction compared to a multiple dose regimen cannot be easily translated into clinical recommendations given the disparate results among studies. Furthermore, in light of the differences in lithium clearance between the 2 regimens, it is still unclear whether, in comparison to those treated with divided doses, patients on once daily regimens should be treated with a lower dosage (to maintain the same lithium concentration) or the same dosage but with a higher concentration. A reasonable current recommendation would be that patients who can tolerate once daily lithium and find it an easier regimen should be allowed to use this regimen since no studies have suggested any benefit from administration of multiple daily doses.

Preliminary data have suggested the utility of potassium supplements in diminishing lithium-induced renal effects. In animal studies, supplemental potassium reduces polyuria, hypo-osmolality and lithium-induced structural abnormalities.[72,73] Potassium may reverse lithium-induced polyuria by increasing the fractional reabsorption of water in the distal tubule by reversing the antidiuretic hormone effects of lithium.[74] The results of 1 small open case series[75] support this approach by demonstrating that adjunctive potassium significantly decreased 24-hour urine volume from 3856ml (±926) to 2618ml (±994) and increased urine osmolality from 239 mmol/kg (±89) to 361 mmol/kg (±127). Suggested dosages of adjunctive potassium are 20 to 60 mmol/day taken in the form of supplements or by increasing dietary intake. It has also been proposed that amiloride, the potassium-sparing diuretic may have similar salutary effects.[76] Despite these intriguing preliminary data, it is premature to recommend supplemental potassium on a routine basis for lithium-treated patients.

Finally, the timing of lithium discontinuation in the presence of increasing serum creatinine levels ('creeping creatinines')[77] or decreasing creatinine clearance is still a matter of clinical judgment. At least 2 authors[44,69] have suggested that serum creatinine values consistently above 140 mmol/L (1.6 mg/dl) should trigger a medical evaluation. There is no consensus as to the creatinine clearance values below which lithium should be discontinued. Given the generally weak correlation between tubular and glomerular dysfunction, however, even marked polyuria does not hold the same significance. Lithium discontinuation for symptomatic polyuria should be decided only on the basis of distress, not physiological markers.

6. Conclusion

After 30 years of use in treating mood disorders, the long term risks of lithium have become more clear. Lithium unquestionably causes renal tubular damage, initially on a functional basis, progressing to structural damage over time. In the vast majority of patients, the tubular damage is unassociated with significant changes in glomerular filtration rate. Clinically important glomerular dysfunction from lithium is rare and is unrelated to the duration of lithium therapy.

Thus, for the vast majority of treated patients, the effects of lithium on renal function do not lead to serious morbidity. For those patients who are benefited by lithium, the risk-benefit ratio is overwhelmingly in favour of continuing treatment. Because a few patients show either slowly increasing serum creatinine levels and a rare few progress to lithium-induced chronic renal failure, however, monitoring of renal function in lithium-treated patients is still recommended. The tubular dysfunction may be minimised by once daily administration, avoiding episodes of lithium toxicity and possibly adjunctive potassium treatment. Whether these measures will minimise the risk of the rare

cases of lithium-induced chronic renal failure is still unclear.

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