Meta analysis of the effects of lithium usage on serum creatinine levels


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Review: Meta-analysis of the effects of lithium usage on serum creatinine levels
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Meta-analysis of the effects of lithium usage on serum creatinine levels

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Abstract

There is conflicting evidence concerning lithium’s effect on renal function. The aim is to clarify whether lithium affects kidney function and at what stage of treatment any effect may occur. Systematic review identified 23 studies split into three groups on which meta-analysis was performed to identify the following: A) lithium’s effect on renal function in cross-sectional case-control studies, B) studies of renal function before and after commencement on lithium, C) studies of longer term effect in those already established on lithium therapy. Group A showed a statistically significant increase of 5.7 μmol/L in creatinine in the study population compared with controls. Group B showed a non-statistically significant rise in creatinine (2.9 μmol/L) after a mean follow-up of 86 months. Group C showed a statistically significant increase in creatinine of 7.0 μmol/L over a mean duration of 64 months. An increase in creatinine of an average of 1.6 μmol/L/year on lithium was also identified in this group. Any lithium-associated increase in serum creatinine is quantitatively small and of questionable clinical significance. However, routine renal function monitoring of patients on lithium is essential.

Key words creatinine; glomerular filtration rate; lithium; meta-analysis; renal function

Introduction

Lithium has been used in the treatment of affective disorders for many years as a mood-stabilizing agent in bipolar affective disorder. However, there has been an increase in the number of available mood stabilizers recently, such as sodium valproate, carbamazepine, olanzapine and quetiapine, giving a wider range of treatment options for this condition.

Lithium’s effect on the kidney was first observed by Garrod in the nineteenth century, who noted polyuria and nocturia, with nephrotoxicity subsequently being reported in the late 1970s (Lindop and Padfield, 1975). Since this, there have been studies published that imply that renal dysfunction is a limitation on the effectiveness of lithium therapy (Johnson, 1998); however, it is not entirely clear to what extent clinically significant renal change occurs.

With treatment being guided partly by side-effect profile, a clear and updated review of studies on lithium’s effect on renal function is timely. Serum creatinine measurement is a quick, valid and reliable measure used to accurately estimate glomerular filtration rate (GFR) and therefore a easily useable marker for practicing physicians.

Method

This systematic review is drawn from a MEDLINE, PUBMED and PSYCHLIT search using the terms LITHIUM and RENAL FUNCTION or KIDNEY FUNCTION. All articles in English were then reviewed and papers then hand searched for any other studies that met the entry criteria set out below. Review articles or other articles, for example, those concerning case studies of less than 10 participants or animal studies, were not included in the analysis. Given that a number of these studies were more than a quarter of a century in age, a decision was taken that it would not be practicable to collect primary data from all the studies.

The remaining studies were divided into three groups. The first group enabled a cross-sectional comparison to be made between lithium users (cases) and age- and sex-matched control groups not on lithium (group A). The second group of studies

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focused on longitudinal assessment of renal function before and after commencement on lithium (group B). The final group of studies prospectively assessed renal function over time for those who were already established on lithium (group C).

The main outcome measure was the difference in serum creatinine levels between cases and control groups (group A) or over time (groups B and C). Some studies presented results for serum creatinine using mg/dL and therefore all results were converted to the SI measurement unit of μmol/L. The difference in mean creatinine between the lithium and control group (and 95% confidence intervals) was calculated for each study. The before and after studies were analysed as two independent samples because data on within-pair differences were not presented in the study reports. In three studies (Povlsen, et al., 1992; Walker, et al., 1982; Lokkegaard, et al., 1985), the standard deviation was not presented but was estimated from a formula using the range (Hozo, et al., 2005).

Serum creatinine is now a valid and recognised marker to be used in estimation of GFR as developed within the Modification of Diet in Renal Disease (MDRD) study (Levey, et al., 1999). Levey, et al. (1999) found that using serum creatinine in an equation along with factors for age, sex and ethnicity provided a more accurate value for GFR than measuring creatinine clearance or by using the Cockcroft and Gault (1976) formula.

### Statistical analysis

Chi-squared tests were used to formally test for heterogeneity between study estimates. The $I^2$ statistic was used to quantify the inconsistency between study estimates (Higgins, et al., 2003). $I^2$ values of greater than 50% indicate moderate heterogeneity, whereas values greater than 75% represent severe heterogeneity. Publication and selection bias was investigated by checking for asymmetry in funnel plots (Kirkwood and Sterne, 2003).

As heterogeneity was present, random-effect models were used to calculate pooled mean estimates (Dersimonian and Laird, 1986). Study-specific weights in the random-effects model were calculated and scaled to percentages. All statistical analyses were performed using STATA 9.0 (Stata Corporation, College Station, Texas, USA).

The results from group C were also analysed using meta-regression to investigate the association between the length of time to follow-up and mean change in creatinine measurements from baseline to re-testing.

### Results

Figure 1 displays the results for the nine cross-sectional studies that used age- and sex-matched controls. It shows moderate heterogeneity across the different studies ($\chi^2 = 19.33$, df = 8, $P = 0.013$, $I^2 = 59\%$). The analysis shows an association of higher creatinine in patients treated with lithium, amounting to 5.7 μmol/L (95% CI 1.7–9.9, $P = 0.005$). The mean duration of lithium use in the treated group was 76 months (range 38–141).

Figure 2 shows the results for six studies that measured serum creatinine before commencement of lithium and then various time points after beginning treatment. There is borderline statistically significant heterogeneity across these studies ($\chi^2 = 15.55$, df = 5, $P = 0.008$, $I^2 = 68\%$). Overall, there was a non-statistically significant ($P > 0.1$) increase in serum creatinine (2.9 μmol/L) at a mean follow-up period of 86 months (range 16.5–141).

Figure 3 shows the results for the eight studies that assessed the effect of lithium on renal function in people already established on lithium over time, with a mean follow-up period of 64 months (range 14–132). There is a severe degree of

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Control group</th>
<th>Lithium group</th>
<th>Treatment duration (months)</th>
<th>Difference in Serum Creatinine (mean Lithium group – mean control group)</th>
<th>Difference (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hullin, 1979</td>
<td>30 84 (15)</td>
<td>30 93 (29)</td>
<td>100</td>
<td>9 (-3.21)</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Walker, 1982</td>
<td>19 80 (20)</td>
<td>25 100 (20)</td>
<td>60</td>
<td>20 (8.32)</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Khandelwal, 1983</td>
<td>15 97 (18)</td>
<td>40 106 (19)</td>
<td>56</td>
<td>9 (-2.20)</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Decina, 1983</td>
<td>190 110 (19)</td>
<td>190 115 (21)</td>
<td>61</td>
<td>5 (1.9)</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Gelenberg, 1987</td>
<td>44 85 (16)</td>
<td>220 94 (20)</td>
<td>38</td>
<td>9 (2.15)</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Heitmar, 1987</td>
<td>53 87 (30)</td>
<td>46 99 (20)</td>
<td>96</td>
<td>10 (0.20)</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Coskunol, 1997</td>
<td>29 85 (17)</td>
<td>107 81 (14)</td>
<td>54</td>
<td>-4 (-10.3)</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Turan, 2002</td>
<td>10 78 (27)</td>
<td>10 75 (16)</td>
<td>15</td>
<td>-3 (-22.16)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Lepkičker, 2004</td>
<td>94 88 (14)</td>
<td>82 90 (17)</td>
<td>141</td>
<td>2 (-3.6)</td>
<td>17</td>
<td>17</td>
</tr>
</tbody>
</table>

**Figure 1** Forest plot of difference in creatinine (μmol/L) in lithium and control group in cross-sectional studies, ordered by year of publication. Test for heterogeneity $\chi^2 = 19.33$, df = 8, $P = 0.013$; $I^2 = 59\%$ (95%CI 13%, 80%); test for overall effect $Z = 2.80$, $P = 0.005$. *Standard deviation estimated from the range (Hozo, et al., 2005).
heterogeneity across the published studies ($\chi^2 = 28.41$, $df = 7$, $P \leq 0.001$, $I^2 = 75\%$). There is evidence of an increase in serum creatinine levels of 7.0 $\mu$mol/L over time ($P = 0.045$).

Figure 4 shows the results from meta-regression analysis performed on group C. This shows an increase in creatinine of an average of 1.6 $\mu$mol/L/year on lithium (95% CI 0.9–2.3, $P < 0.001$).

**Discussion**

The main finding from this meta-analysis is one of a small non-statistically significant rise in serum creatinine in the first years of lithium treatment that becomes statistically significant with increasing duration of treatment. When compared with control patients, an association between lithium usage and higher serum creatinine was showed. However, the interpretation of these results is made more difficult by the moderate to severe degree of heterogeneity. Caution should be used in attempting to draw conclusions from the published data.

There are various strengths and weaknesses in this meta-analysis. Strengths include that by separating the studies into groups we addressed not only whether impairment of kidney function occurs but also attempted to identify at what stage of lithium treatment any impairment may begin and also whether there is any potential progressive decline over time; that the studies included were derived from a literature search spanning four decades from 1979 to 2004; that most of the studies included either had a large number of subjects or a lengthy follow-up period and that the use of serum creatinine as a marker for renal impairment is a strength given its ease of use in routine clinical practice and its incorporation into a widely used formula for the estimation of GFR (Levey, et al., 1999).

Weaknesses include the limited number of trials published; poor retention of subjects in some studies, resulting in the potential for those whose lithium was stopped due to renal failure to be misclassified; and that the published data did not include follow-up periods beyond 10 years.

**Table 1**

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Baseline mean (sd)</th>
<th>Follow-up mean (sd)</th>
<th>Follow-up (months)</th>
<th>Difference in Serum Creatinine</th>
<th>Difference (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jensen, 1984</td>
<td>13 88 (11)</td>
<td>13 85 (14)</td>
<td>16.5</td>
<td>-3 (-13.6)</td>
<td>11</td>
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<tr>
<td>Lokkegaard, 1985</td>
<td>142 93 (37)</td>
<td>142 90 (32)</td>
<td>120</td>
<td>-3 (-11.5)</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Hetmar, 1986</td>
<td>46 90 (12)</td>
<td>46 97 (19)</td>
<td>97</td>
<td>7 (1.4)</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Schou, 1988</td>
<td>39 87 (11)</td>
<td>194 92 (13)</td>
<td>48</td>
<td>5 (1.8)</td>
<td>21</td>
<td></td>
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<tr>
<td>Povlsen, 1992</td>
<td>53 87 (10)</td>
<td>10 99 (10)</td>
<td>96</td>
<td>12 (5.19)</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Leppikifer, 2004</td>
<td>114 91 (15)</td>
<td>82 90 (17)</td>
<td>141</td>
<td>-1 (-5.4)</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2** Forest plot of difference in creatinine ($\mu$mol/L) in before and after studies of lithium, ordered by year of publication. Test for heterogeneity $\chi^2 = 15.55$, $df = 5$, $P = 0.008$; $I^2 = 68\%$ (95% CI 24%, 86%); test for overall effect $Z = 1.32$, $P = 0.19$. $^a$Standard deviation estimated from the range (Hozo, et al., 2005). $^b$Mean and standard deviation estimated from the median and range (Hozo, et al., 2005).

**Table 2**

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Baseline mean (sd)</th>
<th>Follow-up mean (sd)</th>
<th>Follow-up (months)</th>
<th>Difference in Serum Creatinine</th>
<th>Difference (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson, 1984</td>
<td>23 84 (15)</td>
<td>23 97 (44)</td>
<td>24</td>
<td>13 (-6.32)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>De Paulo, 1986</td>
<td>40 97 (16)</td>
<td>40 92 (17)</td>
<td>14</td>
<td>5 (-12.2)</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Hetmar, 1987</td>
<td>46 97 (19)</td>
<td>32 99 (20)</td>
<td>24</td>
<td>2 (-7.11)</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Waller, 1988</td>
<td>28 84 (16)</td>
<td>28 83 (16)</td>
<td>56</td>
<td>3 (-9.7)</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Muir, 1989</td>
<td>18 87 (42)</td>
<td>9 90 (30)</td>
<td>18</td>
<td>3 (28.34)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Hetmar, 1991</td>
<td>46 97 (20)</td>
<td>19 118 (40)</td>
<td>120</td>
<td>22 (7.37)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Kallner, 1995</td>
<td>50 86 (24)</td>
<td>50 101 (20)</td>
<td>120</td>
<td>15 (6.24)</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Bendz, 2001</td>
<td>137 84 (17)</td>
<td>86 96 (17)</td>
<td>132</td>
<td>12 (7.17)</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3** Forest plot of difference in creatinine ($\mu$mol/L) for prospective group previously established on lithium, ordered by year of publication. Test for heterogeneity $\chi^2 = 28.41$, $df = 7$, $P \leq 0.001$; $I^2 = 75\%$ (95% CI 50%, 88%); test for overall effect $Z = 2.01$, $P = 0.045$. 

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side effects being excluded; a broad range of follow-up periods studied, with fewer long-term studies being published; the use of different laboratory tests for measuring serum creatinine and the fact that serum creatinine was not the primary outcome measure for most of the studies. There is also a significant degree of heterogeneity across the three groups of studies analysed ($I^2 = 59, 68$, and $75\%$ in groups A, B and C, respectively); however, approximately $25\%$ of all published meta-analyses have an $I^2$ value of greater than $50\%$ (Higgins, et al., 2003).

Does lithium lead to increased creatinine levels compared with controls (group A)?

This analysis compares subjects on lithium with an age- and sex-matched control group. There are a number of inherent differences in the designs of these studies including the length of time patients had been on lithium; presence of control-group diagnosis and concurrent medication usage. All studies set out with different primary aims, raising the question of comparability. Heterogeneity was moderate ($I^2 = 59\%$), with a statistically significant ($P = 0.005$) increase in creatinine levels of $5.7\ \mu$mol/L in patients taking lithium when compared with control patients that were age- and sex-matched.

The largest study in this group is by Decina, et al. (1983), who clearly set out with the primary aim to use creatinine as a measure of glomerular renal function. They concluded that lithium patients had a significantly higher creatinine concentration than controls even when weight, sex, age and arterial blood pressure were allowed for.

Khandelwal, et al. (1983) took a much broader look at both tubular and glomerular function, and although some obvious effects on renal concentrating capacity were noted, no effect was shown in GFRs. Similarly, Hullin, et al. (1979); looking at GFR and renal concentrating capacity, found no evidence of deterioration of GFR associated with lithium.

Another entirely different approach was undertaken by Walker, et al. (1982). In this article, the primary outcome measure was histological change associated with lithium treatment, whereas change in creatinine in patients on lithium was a secondary measure. Renal biopsy showed a specific acute reversible change in the tubule in all subjects on lithium and also the presence of a chronic non-specific interstitial nephropathy in all patients who were either receiving lithium or who were pre-lithium treatment but deemed clinically appropriate for lithium therapy to be given.

Gelenberg, et al. (1987) looked at gender differences and discovered no significant differences between creatinine levels and, therefore, glomerular function. However, they did suggest women have a poorer concentrating capacity, which raises the potential for a higher risk of renal toxicity from lithium. It remains unclear whether this represents a gender difference in vulnerability to lithium or a physiological sex difference in tubular functioning.

Coskunol, et al. (1997) and Turan, et al. (2002) showed non-significant findings that seemed to favour lithium, that is, a trend towards lower creatinine levels with lithium treatment. This result is of course counter-intuitive.

Is there any change in creatinine levels associated with early lithium treatment (group B)?

Analysis of these studies suggested potential significant heterogeneity. Overall, a small, non-statistically significant, increase in serum creatinine was shown (2.9 $\mu$mol/L). Of the six studies included in the analysis, three detected no significant change in plasma creatinine and the other three a statistically significant increase in plasma creatinine.

Jensen and Rickers’s (1984), small ($n = 13$) study with a short follow-up (mean of 16.5 months), detected no significant change in renal function in patients on lithium. Lokkegaard, et al. (1985) tried to approach the issue of long standing lithium therapy by taking a cohort of 142 patients who had been treated with lithium for more than 5 years (mean 10 years lithium duration). Overall, their findings are in line with those discussed above, that is, no significant change was detectable in plasma creatinine. However, a separate analysis of GFR showed a slight but significant reduction. Unfortunately, quantitative data were not presented in this study, but the authors suggested that it took 17 years or more for the regression line, time against GFR, to reach the lower reference limit. Thus, this study highlights the potential for shorter studies to miss this longer term effect.

In a more recent study, Lepkifker, et al. (2004) found that there was no statistically significant increase in serum creatinine in the majority of lithium takers; however, they also noted that 21% of people taking lithium long term develop renal insufficiency. The majority of these patients showed a sharp rise in serum creatinine after 11–15 years of treatment on a background of slowly creeping creatinine levels. This finding would be in keeping with those of Lokkegaard, et al. (1985).
Schou and Vestergaard (1988) started with a large cohort of patients, but over the 7-year follow-up period, there was a substantial drop-out rate. Therefore, we used the serum creatinine measurements of a subgroup of 39 patients who had received continuous lithium therapy for 4 years. In the main outcome analysis, lithium did not lead to significant reduction of glomerular function. A borderline statistically significant rise in serum creatinine was detected.

The remaining two studies, Hetmar, et al. (1986) and Povlsen, et al. (1992), show a statistically significant rise in serum creatinine measurements in the first few years of lithium treatment. This difference cannot be accounted for on the basis of differences in subject age or follow-up periods between studies.

A further study that addressed renal function in early lithium treatment by Smigan, et al. (1984) was not included due to an apparent error in the published results. The units of measurement used corresponded to non-physiological values for serum creatinine when converted to μmol/L. Overall, this study suggested a non-progressive decline on GFR during the first year of lithium therapy.

**Does long-term lithium treatment lead to increased creatinine (group C)?**

In combining studies in this area, the initial aim was to detect any change in creatinine levels over time in patients on long-term lithium treatment. The pooled data suggested a 7.0 μmol/L increase in creatinine, which reached statistical significance (P = 0.045). Heterogeneity between the studies in this section was severe, which suggests it is inappropriate to combine these studies. Similar to studies in groups A and B, there is concern regarding high drop-out rates and a wide range of study lengths and patient numbers. This obvious difference in parameters and study design can, of course, account for some of the heterogeneity.

Johnson, et al. (1984), De Paulo, et al. (1986), Hetmar, et al. (1987) and Muir, et al. (1989) represent four small, short-term studies, all concluding that lithium treatment led to no significant change in creatinine levels. These studies spanned a maximum of only 2-year follow-up, which represents a short-term follow-up period. However, Waller, et al. (1988) published similar findings in a longer 5-year study, in which they found no evidence of elevation of serum creatinine or reduction in creatinine clearance.

Opposite findings were showed in the other three studies in this section Hetmar, et al. (1991), Kallner and Petterson (1995) and Bendz, et al. (2001). Bendz, et al. (2001) conducted a large study of 149 patients over 8–12 years. Follow-up rates were poor, but results highlighted a significant increase in serum creatinine and suggest a decrease in GFR with increasing lithium treatment over time that would be more than expected from age alone.

Kallner and Petterson (1995) studied a cohort of 207 patients treated with lithium for between 1 and 30 years. Renal function tests were available for 50 patients treated for more than 15 years with lithium. A slight but statistically significant increase in serum creatinine was detected by this group over the 10-year follow-up period. However, age adjusted GFR changed only little with increasing treatment duration.

Using the same population from a previous study by the same group (Hetmar, et al., 1986), Hetmar, et al. (1991) conducted a smaller study over a similar period in which creatinine was found to increase significantly, whereas GFR decreased significantly; however, this change was dependent on increasing age.

Heterogeneity among the studies in this group was severe. Much of this can be explained when referring to Figure 4. Regression analysis showed an increase of 1.6 μmol/L of creatinine per year of follow-up. Shorter studies thus detected no significant changes in renal function, whereas those with longer term follow of 10 years or more seemed to identify a small, statistically significant change. The clinical significance of these findings is discussed below.

Overall, within the broad spectrum of studies and outcomes, a common message is clear – changes in renal function are often associated with age, episodes of toxicity and concurrent illness rather than time on lithium or dose.

**Conclusion**

Renal insufficiency is clearly a very important potential clinical side effect of lithium. This is reflected in the inclusion of renal monitoring in the guidelines for lithium prescribing that have been published [British National Formulary (BMJ, 2006), American Psychiatric Association, British Association of Psychopharmacology, Maudsley prescribing guidelines]. However, as this review shows, there is limited good robust published evidence to support a significant rise in serum creatinine. This is particularly important for today’s clinicians given the emergence of other mood stabilizers and a trend away from using lithium, particularly in the United States, with Blanco, et al. (2002) showing a statistically significant decline (P = 0.001) in lithium prescriptions from approximately 50 to 30% during the 1990s in bipolar outpatients. It may be that the recent decrease in publication of articles relating to lithium and renal function found here represents a trend away from usage of lithium.

The majority of published literature shows a reduction in renal concentrating capacity in the early stages of treatment. The significance and reversibility of this effect on tubular function remain unclear. Volume depletion is a cause of reversible decline in renal function and a risk factor for lithium toxicity. Episodes of lithium toxicity have been linked with subsequent deterioration in glomerular function (Johnson, 1998; Walker, 1993) but lithium use itself has no effect on glomerular function if levels are kept within treatment range (Johnson, 1998).

The effect of changes in dosing regimes and a lowering of the recommended therapeutic range may potentially be lowering the risk of renal impairment further by limiting the potential for renal toxicity (Gitlin, 1999).
In these studies, any lithium-induced decrease in renal function is quantitatively small. This change is probably clinically insignificant. However, recent studies of patients with early chronic kidney disease have identified that small changes in serum creatinine near the normal range can signify more significant changes in renal function than were previously envisaged. For instance, in those with small muscle mass such as an 80-year-old female, a creatinine that changes reproducibly over time from 80 to 90 μmol/L reflects a fall in GFR of perhaps just over 10% from 64 mL/min (45–83 mL/min) to 56 mL/min (39–73 mL/min) (Levey, et al., 1999). This has to be interpreted carefully as intra-individual day-to-day variation in serum creatinine can be just as high as this reflecting meat meals and hydration status etc. (Preiss, 2006).

National Institute for Clinical Excellence (NICE) guidelines on Chronic Kidney Disease published in September 2008 define disease progression as ‘a decline in GFR of >5 mL/min/1.73 m²’ within 1 year or less, or >10 mL/min/1.73 m² within 5 years using a minimum of 3 GFR estimations’ (NICE, 2008). These guidelines can be used to interpret the clinical importance of the statistically significant changes in serum creatinine seen in groups A and C.

In group A, the change in serum creatinine of 5.7 μmol/L represents an approximate 7 mL/min/1.73 m² fall in estimated glomerular filtration rate (eGFR) in the treatment group. As the average duration of lithium use was 6.3 years, this does not represent a clinically significant fall in eGFR based on the above guidelines. Group C showed a 7.0 μmol/L rise in creatinine over time; this is a fall of approximately 9 mL/min/1.73 m². The mean time to follow-up was 5.3 years in this group. However, given the severe heterogeneity showed between the studies in group C, caution must be used when attempting to derive meaningful clinical observations from this data.

These small changes in renal function cannot be disregarded. Lepkifker, et al. (2004) identified a potential subgroup of long-term lithium (>15 years) users at risk of developing renal impairment, suggesting a figure as high as 21%. Unfortunately, no studies published to date investigating lithium usage and serum creatinine have a mean follow-up period of more than 15 years. Any lithium-associated changes in renal function have to be weighed against the mental health benefits associated with lithium prophylaxis.

It is evident from this meta-analysis that renal monitoring programmes for patients on lithium are important. Although the identified changes in serum creatinine are small and of limited clinical significance, we advocate a cautious approach. Routine renal function monitoring of all patients taking lithium is required to identify the minority at risk of a decline in renal function.

There is a clear need for a large community-based study of lithium’s usage, its monitoring and its long-term effects on renal function.

References


