Using the CKD-EPI Formula in a Longitudinal Observational Study to assess Renal Safety of Drug Therapy:

The Effect of Lithium Maintenance Therapy for Affective Disorders on estimated Glomerular Filtration Rate (eGFR) – a Population Cohort (2000-2011)

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Background
Lithium is an evidence based treatment and the gold standard in the maintenance therapy of Bipolar Affective Disorders.

Since Hestbech (1977) reported ‘chronic renal lesions following long-term treatment with lithium’ there has been an ongoing debate about the effect of Lithium on renal function and whether it leads to chronic kidney disease (CKD) or even end-stage renal disease (ESRD).

Two meta-analyses [Paul 2010; McKnight 2012] point out the poor quality of available data and the need for large scale epidemiological studies that control for confounders.

Until recently there was no simple tool available to estimate GFR reliably above 60 ml/min/1.73m², as the widely used MDRD formula is associated with negative bias.

Aims
The aim was to examine the effect of Lithium maintenance therapy on renal function via the CKD-EPI formula.

We used record linkage of population based datasets available via the University of Dundee’s Health Informatics Centre (HIC).

Methods
Design: observational cohort study in Tayside (Scotland) of patients newly commenced on Lithium therapy (incidence exposure) or comparator drugs (Quetiapine/Olanzapine /Semisodium Valproate)

Primary outcome variable: eGFR via CKD-EPI formula with the parameters serum creatinine, age and sex (Levey 2009)

Longitudinal analysis: via a random coefficients model (PROC MIXED; SAS 9.2) for repeated measures; a propensity score (to remain on lithium for at least six months) was calculated for each patient to reduce confounding.

Modelling: stepwise forward; variables chosen acc. to clinical relevance, statistical significance and collinearity diagnostics. The model fit was checked via Akaike’s Information Criterion (AIC).

Results
1,120 patients (437 males [39%] and 683 females [61%]); aged 18-64 (mean 43 ±11.7) were included (305 lithium; mean exposure 55 months [range 6-144]; 815 comparator drugs) providing 13,963 estimated Glomerular Filtration Rate (eGFR) values over a 12 year period (2000-2011) from the population database.

Results – contd
Mean adjusted decline in eGFR was 1.5 ml/min/1.73m² per year (SE 4.2 ml/min/1.73m²) for the combined groups in keeping with Paul’s estimates for patients already established on long-term Lithium therapy (Paul 2010). The magnitude of exposure*time interaction in a simple random coefficient model (including variables age, sex, baseline eGFR, exposure, time and exposure*time interaction) and its significance level (p = 0.48) suggest no effect of lithium on rate of eGFR decline.

Results – contd

<table>
<thead>
<tr>
<th>Lithium</th>
<th>Comparators</th>
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<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>hypertension (baseline)</td>
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<td>CVD (baseline)</td>
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<td>Diabetes (baseline)</td>
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<td>Renal disorder (baseline)</td>
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<td>ACE-Inhibitors (FU)</td>
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<td>NSAIDs (FU)</td>
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<td>41.0</td>
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<tr>
<td>Loop Diuretics (FU)</td>
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<td>10.5</td>
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<tr>
<td>Thiazides and related (FU)</td>
<td>21</td>
<td>6.9</td>
</tr>
</tbody>
</table>

Discussion / Limitations
• Generalizability: Majority of Pxs slow-release lithium carbonate preparations; no data on race (nearly exclusively Caucasian)
• 90% of lithium levels <0.8 mmol/L; mean Lithium level 0.56 mmol/L (STD 0.11, range 0.24-1.0) lower than early studies
• Model overestimates effect of co-drugs/underestimates effect of co-morbidities (hospital admission based ICD 10 codes)
• Model needs testing on datasets other than derivation data

Conclusions
This population based analysis suggests
• no effect of Lithium maintenance therapy on eGFR
• co-morbidities and co-medication are the key drivers for a deteriorating renal function rather than lithium toxicity

Our findings should be taken into account when considering discontinuation of Lithium therapy due to assumed ‘chronic lithium toxicity’. We consider the latter a modern medical myth.

Previous concepts (duration of therapy and cumulative dose being the major determinants of ‘chronic toxicity’ [Bendz 2010; Bocchetta 2013; Nolin & Himmelwahr 2010]) may be the result of study design problems, associated bias and confounding.

Our approach of using the CKD-EPI formula in an observational longitudinal dataset may be applicable to other research questions in renal drug safety.

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