Lithium is a gold standard treatment...
Figure 4. Prescribing of mood stabilisers by sex. A) Male and B) Female.
doi:10.1371/journal.pone.0028725.g004
Pharmacological interventions

7.6.1.2 When planning long-term pharmacological treatment to prevent relapse, take into account drugs that have been effective during episodes of mania or bipolar depression. Discuss with the person whether they prefer to continue this treatment or switch to lithium, and explain that lithium is the most effective long-term treatment for bipolar disorder.
Why are we so confident lithium works?
Placebo-controlled randomized trials

- Patients
- Placebo
- Medication

Randomized

Estimate of difference in outcome

Time $t$
**Figure 2: Network of all eligible comparisons for the network meta-analysis**

Each node (circle) corresponds to a drug included in the analysis, with the size proportional to the number of comparisons involving that drug. Each line represents direct comparisons between treatment nodes in the closed-loop network. ARP, PAL, and CBZ, were compared with the remaining treatment options.

**Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis**

Tomofumi Miura, Hisashi Noma, Toshi A Furukawa, Hiroshi Mitsuyasu, Shiro Tanaka, Sarah Stockton, Georgia Salanti, Keisuke Motomura, Satomi Shimano-Katsuki, Stefan Leucht, Andrea Cipriani, John R Geddes, Shigenobu Kanba
Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis

Emanuel Severus\textsuperscript{1}, Matthew J Taylor\textsuperscript{2}, Cathrin Sauer\textsuperscript{1}, Andrea Pfennig\textsuperscript{1}, Philipp Ritter\textsuperscript{1}, Michael Bauer\textsuperscript{1} and John R Geddes\textsuperscript{3}

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|c|c|c|}
\hline
 \textbf{Study} & \textbf{Events} & \textbf{Total} & \textbf{Events} & \textbf{Total} & \textbf{RR} & \textbf{95\%-CI} & \textbf{W(fixed)} & \textbf{W(random)} \\
\hline
Prien 1973 & 43 & 101 & 84 & 104 & 0.53 & [0.41; 0.67] & 18.7\% & 18.5\% \\
Kane 1982 & 1 & 4 & 5 & 7 & 0.35 & [0.06; 2.04] & 0.8\% & 1.5\% \\
Bowden 2000 & 28 & 91 & 36 & 94 & 0.80 & [0.54; 1.20] & 8.0\% & 13.5\% \\
Bowden 2003 & 18 & 46 & 49 & 70 & 0.56 & [0.38; 0.83] & 8.8\% & 13.7\% \\
Calabrese 2003 & 56 & 121 & 66 & 121 & 0.85 & [0.66; 1.09] & 14.9\% & 18.3\% \\
Amsterdam 2010 & 17 & 26 & 19 & 27 & 0.93 & [0.64; 1.35] & 4.2\% & 14.3\% \\
Weisler 2011 & 95 & 364 & 208 & 404 & 0.51 & [0.42; 0.62] & 44.6\% & 20.1\% \\
\hline
\textbf{Fixed effect model} & \textbf{753} & \textbf{827} & & & 0.61 & [0.54; 0.68] & 100\% & -- \\
\textbf{Random effects model} & & & & & 0.66 & [0.53; 0.82] & -- & 100\% \\
\hline
\end{tabular}
\caption{Risk Ratio}
\end{table}

Heterogeneity: I\textsuperscript{2}\textsuperscript{-}squared=68\%, tau\textsuperscript{-}squared=0.054, p=0.0046
WHEN DOES LITHIUM START WORKING?

... as a long-term treatment for bipolar disorder
Why think about timing?

Clinical importance

Informing basic science – better treatments in the future
Informed treatment decisions...
Basic science

Clinical practice
Why think about timing?

Clinical importance

Informing basic science – better treatments in the future
Serendipitous clinical finding

Mechanism clarified

Range of treatments developed

Safer? Better tolerated? Easier to use?
Cascading underlying effects...
We used to expect delay in action for most of our medications

But lots of factors contribute to a particular patient improving or not…

We do have tools to clarify the medication-specific effects
Placebo-controlled randomized trials

Patients

Randomized

Medication

Placebo

Multiple Estimates of difference in outcome

Outcomes from multiple time points
Antipsychotic action

Figure 2. Mean improvement in standardized baseline scores in patients taking antipsychotic drugs vs placebo over time. Error bars represent SEM.

Delayed-Onset Hypothesis of Antipsychotic Action
A Hypothesis Tested and Rejected

Ofer Agid, MD; Shitij Kapur, MD, PhD, FRCPC; Tamara Arenovich, MSc; Robert B. Zipursky, MD, FRCPC
Arch Gen Psychiatry. 2003;60:1228-1235

Is there rebound psychosis on withdrawal of antipsychotic medication in schizophrenia?

Taylor & Yim. Schizophrenia Research 2018;201:430-431
SSRI action

Early Onset of Selective Serotonin Reuptake Inhibitor Antidepressant Action

Systematic Review and Meta-analysis

Matthew J. Taylor, MRCPsych; Nick Freemantle, PhD; John R. Geddes, MD; Zubin Bhugwagar, DPhil

Arch Gen Psychiatry, 2006;63:1217-1223
Molecular basis of lithium action: integration of lithium-responsive signaling and gene expression networks
RH Lenox and Le Wang
Molecular Psychiatry (2003) 8, 135–144
EXPERT REVIEW

Lithium in the treatment of bipolar disorder: pharmacology and pharmacogenetics

M Alda

After decades of research, the mechanism of action of lithium in preventing recurrences of bipolar disorder remains only partially understood. Lithium research is complicated by the absence of suitable animal models of bipolar disorder and by having to rely on in vitro studies of peripheral tissues. A number of distinct hypotheses emerged over the years, but none has been conclusively supported or rejected. The common theme emerging from pharmacological and genetic studies is that lithium affects multiple steps in cellular signaling, usually enhancing basal and inhibiting stimulated activities. Some of the key nodes of these regulatory networks include GSK3 (glycogen synthase kinase 3), CREB (cAMP response element-binding protein) and Na⁺-K⁺ ATPase. Genetic and pharmacogenetic studies are starting to generate promising findings, but remain limited by small sample sizes. As full responders to lithium seem to represent a unique clinical population, there is inherent value and need for studies of lithium responders. Such studies will be an opportunity to uncover specific effects of lithium in those individuals who clearly benefit from the treatment.

Molecular Psychiatry (2015) 20, 661–670; doi:10.1038/mp.2015.4; published online 17 February 2015

What we do not know

● How long does it take for lithium to exert its prophylactic effect?
When does lithium start working?

some clues that full effects take time to develop
(observational data)
Lithium Maintenance Treatment of Depression and Mania in Bipolar I and Bipolar II Disorders

Leonardo Tondo, M.D., Ross J. Baldessarini, M.D., John Hennen, Ph.D., and Gianfranco Floris, M.D.

Mortality vs general population - lithium duration

Mortality vs general population - lithium duration

<table>
<thead>
<tr>
<th>time (months)</th>
<th>mortality ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>12</td>
<td>1.0</td>
</tr>
<tr>
<td>24</td>
<td>1.0</td>
</tr>
<tr>
<td>36</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 1

Mortality of patients with continuous lithium treatment for less than six months

<table>
<thead>
<tr>
<th>n</th>
<th>Observed deaths</th>
<th>Expected deaths</th>
<th>Ratio observed/ expected</th>
<th>95% confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>118</td>
<td>2</td>
<td>0.105</td>
<td>19.047</td>
<td>2.30-68.78</td>
</tr>
</tbody>
</table>

A further sample of 118 patients with affective disorders who were treated for less than six months. We calculated the mortality rate and compared it with the mortality rate of the general population.
Timing of onset of lithium relapse prevention in bipolar disorder: evidence from randomised trials

Matthew J. Taylor

Summary
Lithium is widely prescribed, but the timing of key effects remains uncertain. The timing of onset of its relapse prevention effects is clarified by placebo-controlled randomised trials (3 studies, \( n = 1120 \)). Lithium reduced relapse into any mood episode over the first 2 weeks of treatment (hazard ratio 0.40, 95% CI 0.16–0.97). Fewer manic relapses were evident within the first 4 weeks, however, early effects on depressive relapse were not demonstrated. There is an early onset of lithium relapse prevention effects in bipolar disorder, particularly against manic relapse. Full effects against depressive relapse may develop over a longer period.

Declaration of interest
M.J.T. reports personal fees from Sunovion, Otsuka, Lundbeck, outside the submitted work.

Keywords
Bipolar affective disorders; mood stabilisers; randomized controlled trial.

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Euthymic bipolar

three RCTs identified
Total participants randomized: 1120
Data up to 76 weeks from randomization
Placebo-controlled randomized trials

Euthymic patients

Lithium

placebo

Multiple Estimates of difference in risk of relapse

Outcomes from multiple time points
<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard ratio</th>
<th>HR</th>
<th>95%–CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Between weeks 0 and 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowden et al (2003)*</td>
<td>0.27</td>
<td>(0.03–2.24)</td>
<td></td>
</tr>
<tr>
<td>Calabrese et al (2003)*</td>
<td>0.13</td>
<td>(0.02–0.82)</td>
<td></td>
</tr>
<tr>
<td>Weisler et al (2011)*</td>
<td>0.59</td>
<td>(0.34–1.03)</td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td>0.40</td>
<td>(0.16–0.97)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 28%$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Between weeks 2 and 4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowden 2003</td>
<td>0.85</td>
<td>(0.35–2.06)</td>
<td></td>
</tr>
<tr>
<td>Calabrese 2003</td>
<td>0.46</td>
<td>(0.24–0.90)</td>
<td></td>
</tr>
<tr>
<td>Weisler 2011</td>
<td>0.68</td>
<td>(0.36–1.28)</td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td>0.62</td>
<td>(0.41–0.93)</td>
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<tr>
<td>Heterogeneity: $I^2 = 0%$</td>
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<tr>
<td><strong>Between weeks 4 and 7</strong></td>
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<td></td>
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<tr>
<td>Bowden 2003</td>
<td>0.32</td>
<td>(0.09–1.12)</td>
<td></td>
</tr>
<tr>
<td>Calabrese 2003</td>
<td>0.74</td>
<td>(0.37–1.50)</td>
<td></td>
</tr>
<tr>
<td>Weisler 2011</td>
<td>0.56</td>
<td>(0.34–0.90)</td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td>0.57</td>
<td>(0.39–0.84)</td>
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<tr>
<td>Heterogeneity: $I^2 = 0%$</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Between weeks 7 and 15</strong></td>
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<td></td>
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</tr>
<tr>
<td>Bowden 2003</td>
<td>0.44</td>
<td>(0.17–1.13)</td>
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</tr>
<tr>
<td>Calabrese 2003</td>
<td>0.83</td>
<td>(0.54–1.28)</td>
<td></td>
</tr>
<tr>
<td>Weisler 2011</td>
<td>0.57</td>
<td>(0.36–0.89)</td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td>0.66</td>
<td>(0.48–0.91)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 12%$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Between weeks 15 and 76</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowden 2003</td>
<td>0.52</td>
<td>(0.29–0.95)</td>
<td></td>
</tr>
<tr>
<td>Calabrese 2003</td>
<td>0.85</td>
<td>(0.57–1.27)</td>
<td></td>
</tr>
<tr>
<td>Weisler 2011</td>
<td>0.27</td>
<td>(0.18–0.41)</td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td>0.50</td>
<td>(0.24–1.03)</td>
<td></td>
</tr>
</tbody>
</table>
Rapid effects on manic relapse?

Delayed effects on depressive relapse?

Rapid effects on manic relapse
When does lithium start working?

Lithium is working to reduce relapse rates within the first fortnight.

Early effects seen for manic relapse in particular.

Full benefits for depressive relapse may take longer.