How practical clinical trials can inform our use of lithium in bipolar and other mood disorders

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Disclosures (past 12 months)

- Consultant
  - Janssen (Johnson & Johnson)
  - Alkermes

- Research Support
  - Palo Alto Health Sciences
Complex Clinical Case

- 40 year old woman with bipolar I disorder
  - Depressed in teens, treated with SSRIs
  - First hospitalized for manic episode age 22
  - Treated initially with divalproex sodium 1500 mg and olanzapine 20 mg
  - Depressed after discharge, started on venlafaxine 225 mg with partial effect, bupropion 300 mg added, zolpidem for insomnia
  - Gained 15 kg, stopped divalproex and olanzapine after 9 months, stayed on antidepressants
Complex Clinical Case

- 40 year old woman with bipolar I disorder
  - Manic episode, age 24, not hospitalized while home after graduating from college
  - Divalproex sodium 1500 mg and risperidone 3 mg started, antidepressants not stopped
  - Mania resolved after 2 months
  - Lamotrigine 25 mg started, titrated to 50 mg, but continued depressed more often than not
  - Some periods of euthymia, never more than for 2 or 3 months at a time, spends most of time depressed.
Complex Clinical Case

- 40 year old woman with bipolar I disorder
  - Trials of:
    - Quetiapine up to 150 mg (too sedating to increase)
    - Paroxetine up to 60 mg
    - Lurazidone 60 mg, improved depression; depression returned after 4 months, increased to 120 mg with no benefit
  - 1/2 to 1 pack per day smoking; cannabis most nights "for sleep"
  - No hospitalization for mania, but periods of mixed symptoms
  - No recent suicide attempts
  - Intermittent work history, often sick from work
  - BMI 29
  - QIDS-SR$_{16}$ 12, YMRS 5
How do we decide how to treat bipolar disorder?
Prescribing patterns for bipolar disorder in US

Lithium & Bipolar Disorder

- Cade 1949
- FDA approved 1970
  - ~50th country to approve its use
- Declining use, especially in US
- Firmly established for maintenance treatment
- Potential to prevent suicide
Efficacy vs Effectiveness

- Need for guidance for the care of actual patients
- Efficacy sacrifices generalizability for internal validity
  - Increases assay sensitivity
- Effectiveness sacrifices internal validity for generalizability
Three Effectiveness Studies

- BALANCE (Bipolar Affective disorder: Lithium/ANti-Convulsant Evaluation)
- LiTMUS (Lithium Treatment Moderate-Dose Use Study for Bipolar Disorder)
- Bipolar CHOICE (Clinical and Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder)

BALANCE

A randomized open-label comparison of combination lithium plus divalproex sodium vs monotherapy
BALANCE

Active run-in

Randomized Phase

Up to 8 weeks

2 years

Time to first intervention for mood episode

lithium or
divalproex or
lithium +
divalproex
Active run-in phases

Useful in trials when adherence is a problem i.e. primary prevention, BPD

- Screen for adherence – both drug and non-drug
- Screen for clinical response
- Screen for tolerability
- Enhance clinical applicability
Drug doses

- Lithium – 0.4 to 1.0 mmol
- Divalproex – target 1250mg, dose established during run-in
- No blood levels
Sites

- 4 countries (UK, US, France, Italy)
- 90% UK
- 41 sites
Design issues

- Open design – potential for
  - Ascertainment bias
  - Performance bias

- Active run-in:
  - Effects on generalizability

- Drug dosing
  - Optimize vs clinically typical
BALANCE

Outcomes

- Time to new treatment or hospitalization
- Secondary outcomes
  - Time to hospitalization
  - Time to first use of new medication
  - Time to first episode of depression
  - Time to first episode of mania
  - Time to switch from allocated treatment
- No mood/severity measures
Characteristics of participants

- 459 patients with Bipolar I Disorder entered run-in
- 129 withdrew before randomization
  - 30% couldn’t tolerate drugs
  - 30% withdrew consent for various reasons
- 330 patients randomized – 110 in each group
- Equal men and women
- Mean age 43 years
- Median 2 hospital admissions (range 0-30)
- 75% previous long-term drug therapy
Primary Outcome – New Treatment/Hospital Admission

Li+Va vs Va  HR 0.59 p=0.002
Li+Va vs Li  HR 0.82 p=0.27
Li vs Va     HR 0.71 p=0.05
Time From Randomization to First Treatment for Mania

At risk (events):

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
<th>27</th>
<th>30</th>
<th>33</th>
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<tbody>
<tr>
<td>Combination</td>
<td>110</td>
<td>108</td>
<td>95</td>
<td>91</td>
<td>84</td>
<td>75</td>
<td>68</td>
<td>59</td>
<td>25</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lithium</td>
<td>110</td>
<td>96</td>
<td>89</td>
<td>79</td>
<td>71</td>
<td>66</td>
<td>59</td>
<td>49</td>
<td>19</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Valproate</td>
<td>110</td>
<td>90</td>
<td>79</td>
<td>73</td>
<td>68</td>
<td>59</td>
<td>51</td>
<td>37</td>
<td>15</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Time From Randomization to First Treatment for Depression

At risk (events):

<table>
<thead>
<tr>
<th></th>
<th>Combination</th>
<th>Lithium</th>
<th>Valproate</th>
</tr>
</thead>
<tbody>
<tr>
<td>110 (11)</td>
<td>99 (9)</td>
<td>88 (7)</td>
<td>81 (4)</td>
</tr>
<tr>
<td>88 (7)</td>
<td>81 (4)</td>
<td>76 (3)</td>
<td>70 (2)</td>
</tr>
<tr>
<td>76 (3)</td>
<td>70 (2)</td>
<td>62 (2)</td>
<td>51 (1)</td>
</tr>
<tr>
<td>62 (2)</td>
<td>51 (1)</td>
<td>24 (0)</td>
<td>2 (0)</td>
</tr>
<tr>
<td>51 (1)</td>
<td>24 (0)</td>
<td>2 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>24 (0)</td>
<td>2 (0)</td>
<td>1 (0)</td>
<td>0</td>
</tr>
<tr>
<td>2 (0)</td>
<td>1 (0)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Time to 25% depressed (months) (95% CI)
Combination: 9.6 (5.8 to 17.1)
Lithium: 12.0 (6.0 to 19.9)
Valproate: 5.2 (3.1 to 10.1)
Numbers needed to treat (NNT)

- Combination vs valproate 6
- Combination vs lithium 20
- Lithium vs valproate 10
BALANCE Conclusions

- Combination therapy with lithium plus divalproex sodium is more likely to prevent relapse than monotherapy with valproate monotherapy.

- Lithium monotherapy is more likely to prevent relapse than monotherapy with valproate monotherapy.

- This relative benefit appears to be irrespective of baseline severity of illness and is maintained for up to two years.
Methodological Issues

BALANCE

- VPA blood levels not measured, doses modest
- Only 21-33% of subjects received antipsychotics, antidepressants, or other mood stabilizers at randomization
- Sample was markedly enriched for mania
  - Most patients had recent mania/mixed states episodes (60%), whereas depression is typically 2-3 times as common in BP I
- Employed an open label design that did not appear to manage pre-randomization selection bias
- BP II were excluded
LiTMUS

- NIMH funded trial following STEP-BD
- Compare strategies of treatment
  - Lithium plus optimized treatment (OPT)
  - OPT without lithium
- 6 month primary outcomes
  - CGI-BP-S over the entire 6 months
  - Necessary clinical adjustments
- Open treatment
- Blinded assessments for CGI-BP-S

Nierenberg et al., Clinical Trials 2009; 6: 637–648
Optimized Treatment (OPT) in LiTMUS

- TIMA Guideline informed care
  - Texas Implementation of Medication Algorithm
- Manage comorbid conditions
- Manage symptoms
  - Anxiety
  - Insomnia
- Change as necessary
- Monitored by assigned investigator
LiTMUS Outcomes

- Co-primary outcomes
  - CGI-BP Overall Severity
  - Necessary Clinical Adjustments (NCAs)

- Secondary outcomes
  - Mood metrics
  - Quality of life
  - Suicide measures
LiTMUS Participants

- 283 adults with BPI or BPII
- Require change in treatment
  - Can enter in any mood state except recovered
- CGI-BP-S $\geq 3$ (Mild)
- Can have been on lithium in the past
- Willing to be randomized
Lithium Use in LiTMUS

- Start low, increase to 600 mg for 8 weeks
- Adjust as needed thereafter
- Within limits of tolerability and safety
- Any other clinically indicated medications (OPT)
CGI-BP Overall Severity (Observed Cases)

Clinical Global Impression - Bipolar Disorder (CGI-BP) Overall Severity Score

- Li + OPT (n = 140 → 115)
- OPT (n = 142 → 122)

Between-Group p = NS

Study Week
Necessary Clinical Adjustments (NCAs) (All Cases)

Between-Group p = NS

Study Week

Necessary Clinical Adjustments Per Month

OPT (n = 142)

Li + OPT (n = 141)
LiTMUS Secondary Hypotheses
Li+OPT > OPT Improvement Over 6 Months

- Mood metrics
  - Clinical Global Impression for Bipolar Disorder (CGI-BP)
    - Depression Severity
    - Elevation Severity
  - Montgomery-Asberg Depression Rating Scale (MADRS)
  - Young Mania Rating Scale (YMRS)
  - Clinician Administered Rating Scale for Mania (CARS-M)
  - Quick Inventory of Depressive Symptoms (QIDS-SR$_{16}$)

- Quality of life
  - Quality of Life Enjoyment & Satisfaction Questionnaire (Q-LES-Q)

- Suicidality
  - Modified Scale for Suicidal Ideation (MSSI)
Use of Atypical Antipsychotics

p=0.028

Atypical Antipsychotic

\[
\begin{align*}
\text{Li+OPT} & \quad 48.3 \\
\text{OPT} & \quad 62.5
\end{align*}
\]
LiTMUS Conclusions

- No statistically significant Li+OPT versus OPT differences
  - Primary outcomes
  - Secondary outcomes
- Use of lithium associated with less exposure to atypical antipsychotics
Bipolar CHOICE

- Strategy with Li or Quetiapine

- Co-primary outcomes
  - CGI-BP Overall Severity
  - Necessary Clinical Adjustments (NCAs)

- Secondary outcomes
  - Time to discontinuation
  - Framingham Cardiac Risk Score
  - LIFE-RIFT
  - Bipolar Inventory of Symptoms Scale (BISS)
Li Dose and Levels

- N=240
- Mean maximum tolerated dose = 1007.5 mg
- Median dose 900 mg
- Mean (SD) blood Li levels
  - Week 2 0.5 (0.3)
  - Week 16 0.6 (0.3)
  - Week 24 0.6 (0.4) mEq/L
- Monotherapy 23.8%
QTP

- N = 242
- Mean (SD) dose = 344.9 (170.6) mg
- Median dose 300 mg
- Monotherapy 27.3%
Clinical Global Impressions- Efficacy Index (CGI-EI)

- Marked—vast improvement of all symptoms
  - No side effects

- Unchanged or worse symptoms
  - Side effects outweigh therapeutic effect

Randomized treatment group:
- Li+APT (N=240)
- QTP+APT (N=242)

Study week
Necessary Clinical Adjustments
Time to Discontinuation

![Graph showing survival probability over months for two treatment groups: Li+APT (N=240) and QTP+APT (N=242).](image)
Response at 6 Months

CGI-BP severity ≤ 2 for at least 8 weeks

p = 0.14
Monotherapy at 6 Months
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Estimated 6-month difference (Li+APT) – (QTP+APT)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean [95% CI]</td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-EI difference</td>
<td>0.06 [-0.16, 0.29]</td>
<td>0.59</td>
</tr>
<tr>
<td>NCAs/month</td>
<td>0.07 [-0.07, 0.21]</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-BP severity</td>
<td>0.10 [-0.10, 0.31]</td>
<td>0.31</td>
</tr>
<tr>
<td>CGI-BP depression</td>
<td>0.10 [-0.10, 0.31]</td>
<td>0.32</td>
</tr>
<tr>
<td>CGI-BP mania</td>
<td>0.00 [-0.16, 0.16]</td>
<td>0.99</td>
</tr>
<tr>
<td>BISS: overall</td>
<td>0.94 [-2.10, 3.99]</td>
<td>0.54</td>
</tr>
<tr>
<td>BISS: depression</td>
<td>0.71 [-1.60, 3.01]</td>
<td>0.55</td>
</tr>
<tr>
<td>BISS: mania</td>
<td>-0.22 [-1.55, 1.11]</td>
<td>0.75</td>
</tr>
<tr>
<td>CHRT</td>
<td>-0.61 [-2.37, 1.14]</td>
<td>0.49</td>
</tr>
<tr>
<td>FRS</td>
<td>-0.43 [-0.94, 0.09]</td>
<td>0.11</td>
</tr>
<tr>
<td>FISER: frequency</td>
<td>-0.33 [-0.65, -0.00]</td>
<td>0.05</td>
</tr>
<tr>
<td>FISER: intensity</td>
<td>-0.36 [-0.65, -0.07]</td>
<td>0.01</td>
</tr>
<tr>
<td>FISER: impairment</td>
<td>-0.36 [-0.61, -0.11]</td>
<td>0.01</td>
</tr>
<tr>
<td>Q-LES-Qa</td>
<td>-0.45 [-4.07, 3.17]</td>
<td>0.81</td>
</tr>
<tr>
<td>LIFE-RIFT</td>
<td>-0.14 [-0.84, 0.57]</td>
<td>0.70</td>
</tr>
</tbody>
</table>
CHOICE Summary

- First randomized comparative effectiveness trial of Li vs QTP
  - Both with APT

- Most patients improved
  - But few became asymptomatic

- No large differences in outcomes

- Clinical implications
  - Acceptability of side effects
**BALANCE**

- BP I
  - Mostly recently manic
  - Maintenance design
  - Less polypharmacy
  - Combination therapy better than valproate alone, lithium better than valproate
  - No support for valproate monotherapy

**LiTMUS/CHOICE**

- BP I & BP II
  - Primarily recently depressed
  - Subacute treatment design
  - Wide polypharmacy
    - More with complex care
  - No differences on primary outcomes
  - Lower side effect burden (perhaps) in Li groups
**Li+: Lithium for Suicidal Behavior in Mood Disorders**

- VA CSP-590 funded by Department of Veterans Affairs
- Does lithium prevent suicide attempts in all mood disorders?
- Enriched design: Suicide attempt/hospitalization in past 6 months
- Large sample: 1862 subjects over 29 sites
  - "Real world" population with complex disorders
- 1 year follow up
- Lithium vs. placebo added to usual care
Li+: Lithium for Suicidal Behavior in Mood Disorders

- Lithium dosed to minimal level of 0.6 mEq/l or placebo
- Blinded lithium levels
- No more than 6 lifetime suicide attempts
- eGFR > 60
- Substance use disorders not an exclusion
- Monitoring in addition to enhanced care
- Powered to detect 37% relative difference in rate between groups
Li+: Lithium for Suicidal Behavior in Mood Disorders

- Study ended due to futility
  - Lithium group did not have fewer suicide attempts at projected rate
- Results not analyzed yet
- Why did study fail?
  - Enhanced care
  - Visits in addition to enhanced care
  - Doesn’t work?
Stratifying Risk for Renal Insufficiency Among Lithium-Treated Patients: An Electronic Health Record Study

Victor M Castro¹,², Ashlee M Roberson¹, Thomas H McCoy¹, Anna Wiste¹, Andrew Cagan¹,², Jordan W Smoller¹, Jerrold F Rosenbaum¹, Michael Ostacher³ and Roy H Perlis⁎,¹

¹Center for Experimental Drugs and Diagnostics, Psychiatric and Neurodevelopmental Genetics Unit, Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA; ²Partners Research Information Systems and Computing, Partners HealthCare System, One Constitution Center, Boston, MA, USA; ³Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA

Figure 1 Calibration curve for renal failure model, testing data set. The curve compares the proportion of individuals in each risk quintile with observed renal failure, to the proportion predicted to develop renal failure.
Modeling lithium-associated renal insufficiency

- Goal: can we predict who is at greatest risk for renal failure with lithium?
- ICD9 code or laboratory-confirmed glomerular filtration rate below 60 ml/min
- N=1445 adult lithium-treated patients with renal insufficiency
- Matched by risk set sampling 1:3 with 4306 lithium-exposed patients without renal insufficiency
Who develops renal failure?

<table>
<thead>
<tr>
<th></th>
<th>Univariate, Odds Ratio</th>
<th>Adjusted Odds Ratio</th>
<th>p-value</th>
<th>[95% Conf. Interval]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male</td>
<td>0.68</td>
<td>0.57</td>
<td>&lt;.001</td>
<td>0.48 - 0.67</td>
</tr>
<tr>
<td>Race/ethnicity, white</td>
<td>1.63</td>
<td>1.53</td>
<td>&lt;.001</td>
<td>1.21 - 1.94</td>
</tr>
<tr>
<td>Age (per decade)</td>
<td>1.80</td>
<td>1.55</td>
<td>&lt;.001</td>
<td>1.45 - 1.65</td>
</tr>
<tr>
<td>Charlson index (Log10)</td>
<td>2.68</td>
<td>1.46</td>
<td>&lt;.001</td>
<td>1.31 - 1.64</td>
</tr>
<tr>
<td>Insurance, private</td>
<td>1.01</td>
<td>1.29</td>
<td>0.006</td>
<td>1.08 - 1.53</td>
</tr>
<tr>
<td>Lifetime hypertension</td>
<td>4.74</td>
<td>2.62</td>
<td>&lt;.001</td>
<td>2.18 - 3.16</td>
</tr>
<tr>
<td>Lifetime smoking</td>
<td>1.79</td>
<td>1.27</td>
<td>0.01</td>
<td>1.06 - 1.53</td>
</tr>
<tr>
<td>Lifetime diabetes mellitus</td>
<td>3.16</td>
<td>1.17</td>
<td>0.166</td>
<td>0.94 - 1.46</td>
</tr>
<tr>
<td>Any schizophrenia/schizoaffective</td>
<td>1.72</td>
<td>1.63</td>
<td>&lt;.001</td>
<td>1.31 - 2.03</td>
</tr>
</tbody>
</table>

N=3834
Do other treatments influence risk with lithium?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Univariate, Odds Ratio</th>
<th>Adjusted for Clinical Model, Odds Ratio</th>
<th>Fully adjusted for clinical model plus other treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Odds Ratio    p-value  [95% Conf. Interval]</td>
</tr>
<tr>
<td>Once-daily dosing</td>
<td>0.86</td>
<td>0.79</td>
<td>0.80          0.003  0.69                      0.93</td>
</tr>
<tr>
<td>Extended release (versus immediate/citrate)</td>
<td>0.90</td>
<td>1.09</td>
<td>1.13          0.164  0.95                      1.36</td>
</tr>
<tr>
<td>Concomitant first-generation antipsychotic</td>
<td>1.55</td>
<td>1.40</td>
<td>1.48          0.004  1.14                      1.94</td>
</tr>
<tr>
<td>Concomitant second generation antipsychotic</td>
<td>0.67</td>
<td>0.87</td>
<td>0.95          0.472  0.81                      1.10</td>
</tr>
<tr>
<td>Concomitant SSRI/SNRI</td>
<td>0.73</td>
<td>0.67</td>
<td>0.68          &lt;0.001  0.58                      0.80</td>
</tr>
</tbody>
</table>
Does lithium toxicity increase risk?

- Based on maximum recorded lithium level (N=2,650)
- At least one level exceeding 1.2 mEq/L prior to first recorded renal insufficiency

=> *increased risk for renal insufficiency* (OR 1.72, 95% CI 1.38-2.14).
Can we use the model to predict renal failure with lithium?

Figure 1  Calibration curve for renal failure model, testing data set. The curve compares the proportion of individuals in each risk quintile with observed renal failure, to the proportion predicted to develop renal failure.

359/483 (74%) cases in top 2 risk quintiles; overall N=1917; AUC=0.81

Castro Neuropsychopharm 2016
How can we use such a model to predict renal failure with lithium?

- Prior higher levels – avoid toxicity!
- Hypertension
- Diabetes
- Smoking
- Divided dosing
- Age, female, schizoaffective/schizophrenia, first-generation antipsychotics
Critical issues in Li use

- What study design can best inform care?
  - Outcomes important to patients

- Are the patients enrolled as subjects in these trials typical?

- Refractory patients are likely to remain refractory, so what can inform their care?

- Does lithium prevent suicide?

- How should lithium best be used? Or not?
Return to Complex Clinical Case

- 40 year old woman with bipolar I disorder
- Is lithium missing?
- Do antidepressants add benefit (or harm)?
- Dosing should be targeted to evidence
- Make sure harms are not outweighed by benefit
  - Ethics of side effects + no benefit