Doing the Impossible Task of Practicing Evidence Based Psychiatry: Treating Bipolar Depression as an Example

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### Disclosure Statement

<table>
<thead>
<tr>
<th>Employee Of</th>
<th>Massachusetts General Hospital</th>
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<tbody>
<tr>
<td>Consultant For</td>
<td>Abbott Laboratories, Astra Zeneca, Basilea, BrainCells Inc., Bristol-Myers Squibb, Eli Lilly &amp; Co., Genaissance, GlaxoSmithKline, Innapharma, Janssen Pharmaceutica, Jazz Pharmaceuticals, Merck, Novartis, PGx Health, Pfizer, Sepracor, Schering-Plough, Shire, Somerset, Takeda, Targacept</td>
</tr>
<tr>
<td>Stockholder In</td>
<td>Appliance Computing, Inc. (MindSite); Brain Cells, Inc.</td>
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<tr>
<td>Grant Support From</td>
<td>Bristol-Myers Squibb, Cederroth, Cyberonics, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica, Lichtwer Pharma, Eli Lilly, NARSAD, NIMH, Pfizer, Shire, Stanley Foundation, Wyeth-Ayerst</td>
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<tr>
<td>Honoraria From</td>
<td>MGH Psychiatry Academy in the past 3 years (Prior to 3 years ago, honoraria from Bristol-Myers Squibb, Cyberonics, Forest Pharmaceuticals, GlaxoSmithKline, Eli Lilly, Shire, Wyeth-Ayerst)</td>
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<tr>
<td>Category</td>
<td>Details</td>
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<tr>
<td>Other Income</td>
<td>MBL Publishing for services as Editor-in-chief of CNS Spectrums; Slack Inc. for services as Associate Editor of Psychiatric Annals; Editorial Board, Mind Mood Memory, Belvior Publications</td>
</tr>
<tr>
<td>Patents and Copyrights</td>
<td>Patent pending for combination of buspirone, bupropion, melatonin for mood disorders; Copyright joint ownership with MGH for Structured Clinical Interview for MADRS and Clinical Positive Affect Scale</td>
</tr>
<tr>
<td>Additional Honoraria</td>
<td>ADURS, University of Pisa, University of Wisconsin at Madison, University Texas Southwest at Dallas, Health New England and Harold Grinspoon Charitable Foundation and Eli Lilly and AstraZeneca, American Soc Clinical Psychopharmacology and Zucker Hillside Hospital and Forest and Janssen, Brandeis University</td>
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</table>
Outline

• Evidence-Based Medicine (EBM)
  – Basics
  – Strengths and limitations
  – Critical Appraisal and quality of evidence
  – Challenges to Implementation

• EB treatment of Bipolar Depression
Boston Society of Medical Observation est. 1835 at the Massachusetts General Hospital

- Oliver Wendell Holmes
- George C. Shattuck Jr.
- Henry Ingersoll Bowditch
- James Jackson Jr.
- CG Putnam
- Pierre Charles Alexandre Louis

–Numerical method disproved bloodletting

Louis PCA. Researches on the effects of blood-letting in some inflammatory diseases, and on the influence of tartarised antimony and vesication in pneumonitis. Am J Med Sci 1836;18:102-1 1
“[Physicians] were not prepared to discard therapies 'validated by both tradition and their own experience on account of somebody else's numbers.'”


Strengths of EBM

• Better than the alternatives
• Provides scientific foundation for clinical practice
• Increases probability that effective and safe treatments will be given
• Decreases probability that ineffective or unsafe treatments will be given
Limitations of EBM

• Quality of evidence rarely evaluated
  – Studies of groups have limited information for the care of individual patients
  – Registration trials may not inform care
  – Investigators have varying incentives
  – Subjects differ from patients
  – Outcomes not clinically relevant
  – Raters display bias

• Difficult to implement
…”evidence-based” should not be understood to be synonymous with “best practice”…

Randomization reduces bias….but not completely

• Selected patients
  – Invitation bias: Invited to become research participants
  – Volunteer bias: Selected participants agree

• Research participants
  – Milder forms of the disorder
  – Less susceptible to the worst outcomes

• Observer biases
  – Response and side effects uncover concealment of randomization
Explanatory vs. Pragmatic Trials

Explanatory
Does the intervention change the target outcome?

Pragmatic
Does the intervention work when used in clinical practice?

Thinking about and with evidence

• Phronesis
  – Practical wisdom
  – Practical reasoning
  – Thoughtful weighing of different types of evidence

• “Personalization”
  – What is most salient?

The Practice of Autonomy
Patients, Doctors, and Medical Decisions

Carl E. Schneider
Implementation of Evidence Based Decision Making

- Literature (Nomothetic Evidence)
- Clinical Experience (Organize & Quantify)
- Clinical Culture (Stories)
- Patient (Ideographic Information)
- Iterative Feedback (Measurement Based Care)
- Shared Decision Making
Bipolar Depression
## Do Antidepressants Work for Bipolar Depression?

<table>
<thead>
<tr>
<th>Study/Subcategory</th>
<th>Antidepressant N of Subgroup/ Total N</th>
<th>Placebo n of Subgroup/ Total N</th>
<th>Risk Ratio (fixed) ± 95% CI</th>
<th>Weight (%)</th>
<th>Risk Ratio (fixed)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mendlewicz et al. 1980 (33)</td>
<td>20/39</td>
<td>7/19</td>
<td>13.14</td>
<td>1.88</td>
<td>1.01 – 3.51</td>
<td></td>
</tr>
<tr>
<td>Himmelhoch et al. 1982 (32)</td>
<td>20/28</td>
<td>4/31</td>
<td>5.30</td>
<td>5.54</td>
<td>2.15 – 14.23</td>
<td></td>
</tr>
<tr>
<td>Cohn et al. 1989 (31)</td>
<td>30/60</td>
<td>5/29</td>
<td>9.41</td>
<td>2.90</td>
<td>1.26 – 6.69</td>
<td></td>
</tr>
<tr>
<td>Tohen et al. 2004 (29)</td>
<td>46/86</td>
<td>137/370</td>
<td>72.14</td>
<td>1.44</td>
<td>1.14 – 1.83</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>213</td>
<td>449</td>
<td>100.0</td>
<td>1.86</td>
<td>1.49 – 2.30</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>123</td>
<td>153</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Olanzapine ± Fluoxetine in Bipolar Depression

MADRS Change from Baseline vs Week

* P < .05 vs PBO
† P < .05 vs OLZ

Olanzapine (n=351)
Placebo (n=355)
OFC (n=82)

Tohen M et al. Arch Gen Psychiatry 60:1079-1088. 2003
Bipolar I Depression
Lamotrigine Monotherapy

Randomised trials comparing lamotrigine with placebo stratified by baseline severity of Hamilton Rating Scale for Depression (17-item version).

<table>
<thead>
<tr>
<th>Style</th>
<th>Risk ratio (95% CI)</th>
<th>Number of events</th>
<th>Weight, %</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Lamotrigine, n/N</td>
<td>Placebo, n/N</td>
<td></td>
</tr>
<tr>
<td>HDRS &lt; 24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCA100223</td>
<td>0.98 (0.66–1.47)</td>
<td>25/57</td>
<td>13.3</td>
</tr>
<tr>
<td>SCA30924</td>
<td>1.17 (0.80–1.72)</td>
<td>32/65</td>
<td>13.0</td>
</tr>
<tr>
<td>SCA40910</td>
<td>0.97 (0.67–1.41)</td>
<td>34/86</td>
<td>16.1</td>
</tr>
<tr>
<td>SCAA2010</td>
<td>1.07 (0.76–1.50)</td>
<td>31/56</td>
<td>14.7</td>
</tr>
<tr>
<td>SCAB2001</td>
<td>1.27 (0.78–2.05)</td>
<td>20/35</td>
<td>7.3</td>
</tr>
<tr>
<td>Subtotal</td>
<td>1.07 (0.90–1.27)</td>
<td>142/299</td>
<td>64.4</td>
</tr>
<tr>
<td>HDRS ≥ 24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCA100223</td>
<td>1.63 (1.07–2.49)</td>
<td>34/54</td>
<td>9.2</td>
</tr>
<tr>
<td>SCA30924</td>
<td>1.33 (0.80–2.21)</td>
<td>24/66</td>
<td>8.8</td>
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<tr>
<td>SCA40910</td>
<td>1.34 (0.80–2.23)</td>
<td>21/47</td>
<td>7.8</td>
</tr>
<tr>
<td>SCAA2010</td>
<td>1.22 (0.72–2.07)</td>
<td>20/47</td>
<td>7.7</td>
</tr>
<tr>
<td>SCAB2001</td>
<td>2.75 (1.08–6.99)</td>
<td>11/28</td>
<td>2.2</td>
</tr>
<tr>
<td>Subtotal</td>
<td>1.47 (1.16–1.87)</td>
<td>110/242</td>
<td>35.6</td>
</tr>
<tr>
<td>Overall</td>
<td>1.21 (1.06–1.40)</td>
<td>252/541</td>
<td>100.0</td>
</tr>
</tbody>
</table>

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Li+LTG vs. Li+Plbo (MMRM)

MADRS

Van der Loos et al.
J Clin Psych 2009

* p=0.031
** p=0.006
## LTG vs. Olanzapine/Fluoxetine

<table>
<thead>
<tr>
<th></th>
<th>LTG</th>
<th>OFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response %</td>
<td>59.7</td>
<td>68.8</td>
</tr>
<tr>
<td>Time to Response days*</td>
<td>23.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Suicidal behavior %*</td>
<td>3.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

### OFC
- CGI, MADRS, YMRS (effect sizes ~ .25)
- Somnolence, sedation, increased appetite, weight gain, elevated total cholesterol and triglycerides

Quetiapine in Bipolar Depression

Intent-to-Treat; LOCF

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mood Stabilizer + Antidepressant (N = 179)</th>
<th>Mood Stabilizer + Placebo (N = 187)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient remission</td>
<td>32 (17.9)</td>
<td>40 (21.4)</td>
<td>0.40</td>
</tr>
<tr>
<td>Durable recovery (primary outcome)</td>
<td>42 (23.5)</td>
<td>51 (27.3)</td>
<td>0.40†</td>
</tr>
<tr>
<td>Transient remission or durable recovery</td>
<td>74 (41.3)</td>
<td>91 (48.7)</td>
<td>0.23</td>
</tr>
<tr>
<td>Treatment-effectiveness response</td>
<td>58 (32.4)</td>
<td>71 (38.0)</td>
<td>0.27</td>
</tr>
<tr>
<td>Treatment-emergent affective switch</td>
<td>18 (10.1)</td>
<td>20 (10.7)</td>
<td>0.84</td>
</tr>
<tr>
<td>Discontinuation of study medication</td>
<td>22 (12.3)</td>
<td>17 (9.1)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

* The study used an equipoise-stratified design, which allowed for the analysis of data stratified by the acceptance or rejection of enrollment into randomized psychosocial treatment study of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Outcomes are defined in Table 1.

† The P value for the main effect of treatment on the primary outcome of durable recovery, adjusted for acceptance or rejection of enrollment into randomized psychosocial treatment study of the STEP-BD, was 0.25.
Practice Based Evidence
No benefit with antidepressants for bipolar depression with manic symptoms

“[Physicians] were not prepared to discard therapies 'validated by both tradition and their own experience on account of somebody else's numbers.'”


Treatment-Resistant Bipolar Depression: Lamotrigine Added Might Help

1-year recovery rate for intensive group, 105/163 [64.4%]; for CC, 67/130 [51.5%];
log-rank $\chi^2(1) = 6.20$, $p = 0.013$; hazard ratio (HR) = 1.47; 95% CI = 1.08-2.00
EB Treatment of Bipolar Depression

• Psychopharmacology
  – Optimize lithium or valproate or carbamazepine
  – OFC
  – QTP
  – LTG
• Psychotherapy
  – CBT
  – IPT
  – FFT
Treating Bipolar Depression

• If antimanic med present:
  – Wait and do nothing (for how long?)
  – Add an antidepressant? (if it doesn’t work, when should it be stopped? What if someone is partially improved?)
  – Add an FDA approved med (which one? For how long? What about metabolic syndrome?)
    • Olanzapine/Fluoxetine Combination
    • Quetiapine
    • Modafinil? Pramipexole? Riluzole? NAC?
    • Lamotrigine?
    • Psychotherapy
Complications

• BP I or BP II
• Comorbid psychiatric conditions etc.
  – Subthreshold manic symptoms
  – Easily triggered into mania/hypomania/irritability
  – Anxiety
  – ADHD
  – Substance abuse
  – Chaotic life situation
  – Poor concordance
  – Relapse and recurrence
  – Persistent nonresponse to interventions
Summary

• EBM easier said than done
  – Complex
  – Dynamic
  – Iterative
  – Impossible

• Bipolar Depression
  – Few evidence based options
  – Many questions