Emerging Treatments in Bipolar Disorder: Fall 2015 Update

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Disclosures

“My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:”

- **Scientific Advisory Board**: Psybrain, Genomind
- **Consultation**: Genomind, RID Ventures, Perfect Health
- **Advisor**: Perfect Health
Overview

• FDA approvals and relevance to bipolar disorder
• Recent large bipolar treatment trials
• rTMS and ketamine update
• Emerging bipolar depression treatments
FDA new approvals, 2015

- **Brexpiprazole** (MDD, schizophrenia):
  - *No bipolar disorder trials in clinicaltrials.gov* – Otsuka, shame on you!
  - 2 pivotal trials as MDD add-on (Thase JCP 2015 x2)
    - Akathisia, weight gain
  - 2 studies as add-on to SSRI/SNRI in irritable MDD
    - N=55 open-label (completed 7/14)
    - N=25 single-blind fMRI (ongoing)

Source: clinicaltrials.gov, accessed 8/2015
FDA new approvals, 2015

- **Flibanserin** (hypoactive sexual desire disorder in premenopausal women)
  - HT1A agonist, HT2A antagonist
  - Ineffective in MDD but (+) in mouse antidepressant model (Kennedy J Sex Med 2010, Borsini Psychopharm 2001)
  - AE’s seen in >5% in continuation: somnolence, fatigue, nasopharyngitis, upper respiratory tract infection, dizziness, headache, nausea, and sinusitis
  - In 52-week continuation (n~1723)
    - One report of SI, no reports of mania (Jayne J Sex Med 2012)
  - No published evidence in bipolar disorder, no ongoing bipolar trials

Source: clinicaltrials.gov, accessed 8/2015
FDA new approvals, mid-late 2014

- **Suvorexant** (insomnia) – orexin receptor antagonist
  - CYP450 3A4 substrate...beware grapefruit juice, fluvoxamine

- One adjunctive study planned (n=100) in treatment-resistant insomnia in bipolar disorder

- In meta-analysis, 3/2809 with primary insomnia experienced SI; no reported mania

- *No published evidence in bipolar disorder*, one adjunctive study planned (n=100) in treatment-resistant insomnia in bipolar disorder

What’s new in bp depression?

- Large studies
  - Lurasidone (FDA approval)
  - Armodafinil (maybe – not FDA-approved)

- Smaller studies
  - Levothyroxine
  - Pregnenolone
  - Pioglitazone

- Works in progress
  - rTMS
  - Ketamine (s-ketamine?)
Lurasidone RCT’s

Loebel AJP 2014 x2; mean lurasidone dose 62.7mg, monotherapy, 66.3mg add-on to Li or VPA
Similar benefit in 20-60 and 80-120
Primary AE: nausea, headache, akathisia, and somnolence
Armodafinil add-on (n=150mg vs pbo)

Calabrese JCP 2014 (n=433 bipolar 1 depressed); Ketter JAD 2014
But adjunctive trial #2 did not separate from placebo...

Change in IDS-C30: $-20.8 \pm 0.99$ vs $-19.4 \pm 0.99$ – i.e., very large placebo response

Frye Int J Neuropsychopharm 2015; n=399; HA 15% versus 8%
Summary of NNT for bipolar depression interventions

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment</th>
<th>NNT (95% CI)</th>
<th>Side Effect</th>
<th>NNH (95% CI)</th>
<th>Benefit vs. Harm</th>
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<tbody>
<tr>
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<tr>
<td>Tohen et al., 2003</td>
<td>Olanzapine + fluoxetine</td>
<td>4 (3–8)</td>
<td>≥7% weight gain</td>
<td>6 (4–10)</td>
<td>Cli overlap</td>
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<tr>
<td>Calabrese et al., 2005;</td>
<td>Olanzapine</td>
<td>6 (5–9)</td>
<td>Sedation/somnolence</td>
<td>5 (4–5)</td>
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<td>Thase et al., 2006</td>
<td>Quetiapine</td>
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<tr>
<td>Loebel et al., 2014a</td>
<td>Lurasidone</td>
<td>5 (4–8)</td>
<td>Akathisia</td>
<td>15 (10–33)</td>
<td>Benefit-harm</td>
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<td>Loebel et al., 2014b</td>
<td>Lurasidone (adjunctive)</td>
<td>7 (4–24)</td>
<td>Nausea</td>
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<tr>
<td>Tohen et al., 2003</td>
<td>Olanzapine (olanzapine + fluoxetine trial)</td>
<td>12 (7–63)</td>
<td>≥7% weight gain</td>
<td>6 (5–7)</td>
<td>Cli overlap</td>
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<td>Tohen et al., 2012</td>
<td>Olanzapine (international trial)</td>
<td>11 (6–1130)</td>
<td>≥7% weight gain</td>
<td>5 (4–6)</td>
<td>Cli overlap</td>
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<td>Calabrese et al., 2008;</td>
<td>Lamotrigine</td>
<td>12 (8–41)</td>
<td>Sedation/somnolence</td>
<td>37 (NS)</td>
<td>NC</td>
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<td>Geddes et al., 2009</td>
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<tr>
<td>Sidor and MacQueen, 2011</td>
<td>Antidepressants (adjunctive)</td>
<td>29 (NS)</td>
<td>TEAS</td>
<td>200 (NS)</td>
<td>NC</td>
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<td>McCreary et al., 2010</td>
<td>Paroxetine</td>
<td>46 (NS)</td>
<td>TEAS</td>
<td>56 (NS)</td>
<td>NC</td>
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<tr>
<td>Calabrese et al., 2014</td>
<td>Ammodafinil (adjunctive)</td>
<td>9 (5–43)</td>
<td>Anxiety</td>
<td>29 (17–107)</td>
<td>Cli overlap</td>
</tr>
</tbody>
</table>

CI – confidence interval; NC – not calculated (at least one 95% CI is NS); NNH – number needed to harm for specific side effect compared with placebo; NNT – number needed to treat for response compared with placebo; NS – non-significant (infinite/discontinuous) confidence interval; TEAS – treatment-emergent affective switch.
But depression RCT’s may overstate benefit in real-world patients

• But quetiapine-XR performs less well in bipolar with comorbid anxiety...

• n=100 bipolar I/II with comorbid GAD
  • Modal dose 276mg

• No difference vs placebo; effect size 0.19 favored quetiapine XR

• “data from relatively ‘pure’ bipolar patients may not be generalizable to a highly comorbid population.”

Gao JCP 2014
rTMS for depression

Figure 1. rTMS for Depression, Results of the Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Hedges' $g$</th>
<th>$P$ Value</th>
<th>Hedges' $g$ and 95% CI</th>
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<td>Rossini et al.10 2005</td>
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<td>Herwig et al.2 2007</td>
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<td>.135</td>
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<td>Poulet et al.4 2004</td>
<td>-0.157</td>
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<tr>
<td>Hausmann et al.11 2004</td>
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<td>.352</td>
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<tr>
<td>Garcia-Toro et al.13 2001^a</td>
<td>0.129</td>
<td>.754</td>
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<td>Garcia-Toro et al.20 2006</td>
<td>0.682</td>
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<td>Garcia-Toro et al.26 2006</td>
<td>0.734</td>
<td>.098</td>
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<td>Fitzgerald et al.17 2003</td>
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<td>Fitzgerald et al.17 2003</td>
<td>0.615</td>
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<tr>
<td>Avery et al.40 1999</td>
<td>1.200</td>
<td>.121</td>
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<td>Hopfner et al.22 2003</td>
<td>-0.442</td>
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<td>Hopfner et al.22 2003</td>
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<td>Kauffmann et al.31 2004</td>
<td>1.407</td>
<td>.021</td>
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<td>Klein et al.37 1999</td>
<td>0.560</td>
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<td>Anderson et al.32 2007</td>
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<tr>
<td>Garcia-Toro et al.32 2001</td>
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<td>.002</td>
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<tr>
<td>Padberg et al.49 1999</td>
<td>0.355</td>
<td>.509</td>
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<td>Padberg et al.49 1999</td>
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<td>George et al.45 2000</td>
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<td>Janual et al.31 2006</td>
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<td>Loo et al.40 2003</td>
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<td>Buchholz Hansen.33 2004</td>
<td>-0.172</td>
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<td>Herwig et al.36 2003</td>
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<td>O'Reardon et al.8 2007</td>
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<td>.126</td>
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<td>Koerselman et al.25 2004</td>
<td>0.108</td>
<td>.762</td>
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<td>Boutros et al.41 2002</td>
<td>0.299</td>
<td>.483</td>
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<td>Manes et al.33 2001</td>
<td>0.336</td>
<td>.401</td>
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<td>Mosimann et al.36 2004</td>
<td>0.152</td>
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<td>Fitzgerald et al.29 2006</td>
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<td>Bortolomasi et al.24 2007</td>
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<td>Berman et al.44 2000</td>
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<tr>
<td>Weighted effect size, mean</td>
<td>0.545</td>
<td>.000</td>
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</tbody>
</table>

^a Add-on therapy.

Abbreviation: rTMS = repetitive transcranial magnetic stimulation.
rTMS update

• Approved for MDD (not bipolar disorder) based on 510(k) status – ‘similar to existing devices’

• Still minimal bipolar data
  – N=11 bp 1 or 2 subjects, depressed despite 1+ acute treatments (Dell’Osso Bipolar Disord 2009)
    • open-label, 3 weeks
    • Remission in 4/11, Response in 6/11
  – At 1 year, acute remission predicts maintenance of response. Absence of acute rTMS response predicted the absence of subsequent response in the long-term. (Dell’Osso J ECT 2011)
  – N=17 bp 1 or 2 subjects (Rapinesi 2015)

• No apparent increase in manic/mixed states (Xia IJNP 2008)
Maintenance benefit with rTMS

- After 4 wk of acute rx (=20 treatments)...
- Randomize to another 3 months, or none.
- N=8 BP1, 7 BP2 (and 9 MDD) – all had not responded despite at least 2 treatments in current episode.

Rapinesi Front Neuro 2015
Ketamine for bp depression

N=15 (replicates n=18 study); ketamine 0.5 mg/kg IV over 40’

Zarate Biol Psych 2012
Effects by bipolar subtype

Zarate Biol Psych 2012
Challenge with ketamine is maintenance of benefit

• N=20 patients with TRD:
  – Up to 6 infusions over 12 days
  – “Among responders, median time to relapse after the last ketamine infusion was 18 days”
  – Murrough Biol Psych 2013

• Other failed strategies
  – Riluzole, lamotrigine, memantine, ...

• Alternative: different route of administration?
Alternative ketamine formulations

• Intramuscular
  – Eg, Cusin 2012 case report, and others
    • Some benefit with weekly use

• Intranasal (bioavailability ~45%)
  – Eg, Lapidus Biol Psych 2014
    • N=20 patients with MDD
    • Ketamine 50mg x1
    • Similar efficacy to IV
Alternative ketamine formulations

• Sublingual liquid (bioavailability ~30%, vs ~17% oral) –
  – Eg, Lara IJNP 2013:
    • N=26 MDD/BPD patients treated up to 6 months (majority ~4 weeks) – 10mg SL q2-3d
    • 20/26 improved (77%); no SAE’s
    • Nb only 2 bipolar I’s
Moderate, but sustained response with continuous treatment. Less mood swings, impulsivity and irritability. Gradual improvement in sleep and suicidal ideas.
Emerging somatic therapies

• Low-frequency magnetic stimulation
  – Depressed patients with either BPD (n = 41) or major depressive disorder (n = 22).
  – Single, 20-minute treatment
Other weird and (maybe) wonderful options...
Levothyroxine as adjunctive therapy in bipolar depression

- Multicenter (UCLA, 4 German hospitals), 6-week, fixed dose (300 μg/d) trial conducted from 2004 to 2009
- Assess efficacy and tolerability of levothyroxine adjunctive to continuing treatment with mood stabilizer and/or antidepressant medication
- Investigate gender differences in treatment response
- Of 74 patients enrolled in the study, 62 were randomized
- Primary efficacy measure: mean change in Hamilton Depression Rating Scale (HDRS)
- Sponsored by Charite University, Berlin, Germany
- Collaborator: Stanley Medical Research Institute

Stamm JCP 2014
No serious adverse event occurred during the study. In the levothyroxine group, the study was discontinued in 3 patients due to adverse events (mild thyrotoxicosis, exanthema, and switch into mania in 1 patient each).
Pregnenolone for bp depression

- N=80 bipolar, depressed
- Pregnenolone (steroid hormone precursor) up to 500mg/d vs placebo, 12 week double-blind RCT
- Significant improvement in depressive symptoms vs placebo; remission rates significantly greater in the pregnenolone group (61%) compared with the placebo group (37%) by IDS-SR but not HDRS.
- Change in neurosteroid levels as biomarker?

Brown Neuropsychopharm 2014
Pioglitazone as lithium add-on in bipolar 1 depression

- N=44 bipolar 1 depressed, double-blind RCT
- Lithium target level 0.6-0.8
- Pioglitazone 30mg qd

- Significant improvement in HAM-D (p<0.01) at week 2, 4, and 6; no worsening in YMRS

- Well-tolerated

Zeinoddini Depress Anx 2015
Cognition in bipolar disorder

- Impaired cognition common among bipolar patients
- Typical deficits executive function, attention, verbal learning (see, e.g., Arts Psychol Med 2008)
- Deficits more severe during mood episodes but may persist during euthymia
- Significant contributor to functional impairment (Bowie AJP 2010)

- Key first step: minimize meds with potential for cognitive impairment
- Useful tool: http://clearer.mghcedd.org (Castro BMJ 2014)
Pramipexole for residual cognitive symptoms

- n=50; target 1.5mg QD
- only statistically significant side effect of pramipexole vs. placebo was restlessness.
- greater benefit (p<0.03) in euthymic (vs residual depressed) patients

Burdick JCP 2012
Interventions for cognition

- Double-blind RCT of n=43 euthymic bipolar patients
- Erythropoietin 40,000 IU vs saline weekly x 8wk
- Improvement in sustained attention, complex information processing speed (learning/attention/executive) at 9wk, sustained at 14wk.
- No change in mood symptoms
- ??

Miskowiak JCP 2014
Another cognition option?

Table 3. Differences Between WSE and Placebo From Baseline to End of Study: ANCOVA

<table>
<thead>
<tr>
<th>Test</th>
<th>N</th>
<th>Change From Baseline</th>
<th>Difference From Placebo</th>
<th>P Value</th>
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<tbody>
<tr>
<td></td>
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<td>LS Mean (SE)</td>
<td>95% CI</td>
<td>LS Mean (SE)</td>
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<td><strong>Auditory Digit Span</strong></td>
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<tr>
<td>Span backward</td>
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<tr>
<td>WSE</td>
<td>24</td>
<td>0.73 (0.19)</td>
<td>0.34 to 1.11</td>
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<td>0.17 (0.18)</td>
<td>-0.19 to 0.516</td>
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<tr>
<td>Span forward</td>
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<tr>
<td>WSE</td>
<td>24</td>
<td>0.13 (0.18)</td>
<td>-0.23 to 0.48</td>
<td>-0.26 (0.24)</td>
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<td>Placebo</td>
<td>29</td>
<td>0.39 (0.16)</td>
<td>0.07 to 0.71</td>
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<td><strong>Flanker Test</strong></td>
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<td>Neutral RT</td>
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<tr>
<td>WSE</td>
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<td>-34.51 (11.32)</td>
<td>-56.96 to -12.05</td>
<td>-33.18 (15.41)</td>
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<td>-1.33 (10.45)</td>
<td>-22.07 to 19.40</td>
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<td>Congruent RT</td>
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<td>WSE</td>
<td>24</td>
<td>-34.67 (10.82)</td>
<td>-56.14 to 13.20</td>
<td>-21.97 (14.73)</td>
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<td>WSE</td>
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<td>-14.64 (14.53)</td>
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<td>-7.99 (13.41)</td>
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<td><strong>Penn Emotional Acuity Test</strong></td>
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<td>Response rating</td>
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<tr>
<td>WSE</td>
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<td>0.08 (0.04)</td>
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<td>WSE</td>
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<td>0.50 (0.54)</td>
<td>-0.58 to 1.57</td>
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</tbody>
</table>

Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval, LS = least squares, NA = not applicable, RT = response time in milliseconds, SE = standard error, WSE = standardized extract of Withania somnifera.

N=60 bipolar 1/2/NOS patients, RCT double-blind  
*Withania somnifera* – medicinal plant from Ayurvedic medicine  
250mg qd x1wk, then 250mg bid – well-tolerated

Chengappa JCP 2013
Cognitive remediation RCT in euthymic bipolar disorder

- 12 weeks, rater-blinded RCT, n=40 in ITT

- NO BENEFIT on primary and secondary cognitive measures

- Subjective benefit on sharpness/mental acuity at 12 and 26 weeks (but unblinded...)

- Another study with D-cycloserine and remediation is ongoing...

Demant PLOS One 2015; see also Breitborde BMC Psychol 2014
In sum...

• Our patients need and deserve better.
Hope or hype? Gadgets...

Hope or hype? Gadgets...

- Web-based interventions:
  - MoodSwings.net.au: in addition to psychoeducation/community, adding CBT-like interactivity = improvement in mood measures (Lauder JAD 2015)

- Mobile devices: Depp JAD 2015 (benefit at 12 wk, not sustained at 14wk after d/c)
Hope or hype? Gadgets...

• **BUT** – internet-based prevention program failed in large RCT (n=233) (Barnes JAD 2015)

• No benefit from daily monitoring in RCT (n=78); ?more sustained depressive sx in monitoring group (p=0.066) (Faurholt-Jepsen Psychol Med 2015)
And if all else fails...

Sailing Can Improve Quality of Life of People with Severe Mental Disorders: Results of a Cross Over Randomized Controlled Trial

Carta Clin Pract Epi Mental Health 2014
Progress toward diagnostic tools

• We do not need biomarkers to diagnose depression (if you must, consider PHQ-9)
• It would be helpful to distinguish a first depression as bipolar versus unipolar
  – Earlier onset, presence of bp family history; informativeness of symptoms (other than hypomania/mania) is not consistent
• It would be even more helpful to identify optimal treatment
Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia Working Group of the Psychiatric Genomics Consortium*
Emerging Treatments in Bipolar Disorder: Fall 2015 Update

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