Long-term Treatment in Bipolar Disorder: Fall 2016 Update

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Disclosures

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

Roy H. Perlis, MD, MSc

- **Scientific Advisory Boards (Consulting):** Genomind, Psybrain, Perfect Health
- **Patents/Royalties:** Bracket (formerly Concordant Rater Systems)
Overview

• Diagnostic update
  – Changes in DSM-5
• Brief mania and mixed state update
• Prevention of recurrence
  – Overview
  – Recent relevant studies
  – Strategies
Activity is a core feature of mania

- A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy

- Goal: improve specificity of criteria
But DSM5 is less reliable*

* Based on Kappa values in DSM-V field trials

<table>
<thead>
<tr>
<th>Disorder</th>
<th>DSM-5</th>
<th>DSM-IV</th>
<th>ICD-10</th>
<th>DSM-III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized anxiety disorder (GAD)</td>
<td>0.20</td>
<td>0.65</td>
<td>0.30</td>
<td>0.72</td>
</tr>
<tr>
<td>Post-traumatic stress disorder (PTSD)</td>
<td>0.67</td>
<td>0.59</td>
<td>0.76</td>
<td>0.55</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>0.46</td>
<td>0.76</td>
<td>0.79</td>
<td>0.81</td>
</tr>
<tr>
<td>Bipolar disorder type I</td>
<td>0.54</td>
<td></td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>Major depressive disorder (MDD)</td>
<td>0.32</td>
<td>0.59</td>
<td>0.53</td>
<td>0.80</td>
</tr>
<tr>
<td>Major neurocognitive disorder</td>
<td>0.78</td>
<td></td>
<td>0.60</td>
<td>0.91</td>
</tr>
<tr>
<td>Mild neurocognitive disorder</td>
<td>0.50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol use disorder</td>
<td>0.40</td>
<td></td>
<td>0.71</td>
<td>0.80</td>
</tr>
</tbody>
</table>
DSM5 changes mixed definition

• Mixed /state/ -> mixed /features/
• Specifier applies in episodes where subthreshold symptoms from the opposing pole are present during a full mood episode.

• Goal: recognize that depressive and manic symptoms can co-occur, and that subthreshold symptoms are important
• Why worry about subthreshold symptoms?
  – Recurrence risk
  – Suicide risk
Residual manic symptoms are associated with recurrence

<table>
<thead>
<tr>
<th></th>
<th>With residual manic symptoms</th>
<th>Without residual manic symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>156</td>
<td>702</td>
</tr>
<tr>
<td>46</td>
<td>309</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>164</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>N= 858</td>
<td>N= 355</td>
</tr>
<tr>
<td></td>
<td>180</td>
<td>21</td>
</tr>
</tbody>
</table>

Perlis AJP 2006
Diagnosis of bipolar disorder

- Still rests on establishing presence of a manic or hypomanic episode.

- For hypomania (especially among depressed patients), consider using the hypomania checklist (HCL) 16 or 32-item as a waiting-room measure.

- BUT only useful to start the conversation!
• There continues to be no good evidence that bipolar disorder is common among individuals with treatment-resistant depression!

• And some evidence that it is not...
  – “indicators of bipolar diathesis including recent maniclike symptoms and family history of bipolar disorder as well as summary measures of bipolar spectrum features were not associated with treatment resistance”

• Beware diagnosis by family history

Perlis Arch Gen Psych 2011
Treatment of mania
Algorithms?
CANMAT mania algorithm

Step 1
Review general principles & assess medication status
- Not on medication or first-line agent
  - Initiate Li, DVP, AAP, or 2-drug combination
  - Lithium or DVP
  - Add or switch to AAP
  - Replace one or both agents with other first-line agents

Step 2
Initiate/optimize, check compliance
- On first-line agent
  - AAP
  - 2-drug combination (Li or DVP + AAP)
  - Add or switch to Li or DVP
  - Consider adding or switching to second or third-line agent or ECT

Step 3
Add-on or switch therapy
- No response

Step 4
Add-on or switch therapy
- No response

Step 5
Add-on novel or experimental agents
- Consider adding novel or experimental agent
### Treatment options

#### Table 3.3. Recommendations for pharmacological treatment of acute mania

<table>
<thead>
<tr>
<th>Line</th>
<th>Monotherapy</th>
<th>Combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line</td>
<td>Monotherapy: lithium, divalproex, <strong>divalproex ER</strong>&lt;sup&gt;a&lt;/sup&gt;, olanzapine&lt;sup&gt;b&lt;/sup&gt;, risperidone, quetiapine, quetiapine XR, aripiprazole, ziprasidone, <strong>asenapine</strong>&lt;sup&gt;a&lt;/sup&gt;, <strong>paliperidone ER</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Lithium + divalproex</td>
</tr>
<tr>
<td></td>
<td>Adjunctive therapy with lithium or divalproex: risperidone, quetiapine, olanzapine, aripiprazole, <strong>asenapine</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Second line</td>
<td>Monotherapy: carbamazepine, carbamazepine ER, ECT, <strong>haloperidol</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Lithium + divalproex</td>
</tr>
<tr>
<td></td>
<td>Combination therapy: lithium + divalproex</td>
<td></td>
</tr>
<tr>
<td>Third line</td>
<td>Monotherapy: chlorpromazine, clozapine, oxcarbazepine, tamoxifen, <strong>cariprazine</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Lithium + divalproex + haloperidol, lithium + carbamazepine, adjunctive tamoxifen</td>
</tr>
<tr>
<td></td>
<td>(not yet commercially available)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combination therapy: lithium or divalproex + haloperidol, lithium + carbamazepine, adjunctive tamoxifen</td>
<td></td>
</tr>
<tr>
<td>Not recommended</td>
<td>Monotherapy: gabapentin, topiramate, lamotrigine, verapamil, tiagabine</td>
<td>Lithium + divalproex + carbamazepine, olanzapine + carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Combination therapy: risperidone + carbamazepine, olanzapine + carbamazepine</td>
<td></td>
</tr>
</tbody>
</table>

ECT = electroconvulsive therapy; XR or ER = extended release.

<sup>a</sup>*New or change to recommendation.*

<sup>b</sup>*Given the metabolic side effects, use should be carefully monitored.*
Among antipsychotics, efficacy/tolerability data favors haloperidol, risperidone, olanzapine, quetiapine

Figure 6: Ranking of antimanic drugs according to primary outcomes: efficacy (as continuous outcome) and dropout rate
Red colour represents worst treatment and green represents best treatment in a qualitative approach. ARI=aripiprazole. ASE=asenapine. CBZ=carbamazepine. VAL=valproate. GBT=gabapentin. HAL=haloperidol. LAM=lamotrigine. LIT=lithium. OLZ=olanzapine. PBO=placebo. QTP=quetiapine. RIS=risperidone. TOP=topiramate. ZIP=ziprasidone.

Cipriani Lancet 2013;
See also Yildiz Psychol Med 2014
Decreased risk of postmanic depression with second generation antipsychotic vs haloperidol

Aripiprazole
Olanzapine
Quetiapine
Risperidone
Ziprasidone
Overall

N.b. all industry-supported trials; varied haloperidole dosage; only significant when aripiprazole excluded

Goikolea JAD 2013
Anything new for mania?

- **Lurasidone**: *no published/pending mania trials*
  - Secondary analysis of depression trial shows antidepressant benefit in presence of subthreshold hypomanic symptoms (McIntyre JCP 2015)
  - Adjunctive long-term treatment study completed

- **Brexpiprazole**: *no published/pending mania trials*

- **Cariprazine**: *2 positive phase III mania trials*
  - FDA approval fall 2015
  - No clear benefit vs existing options
Efficacy of Antimanic Treatments in Mixed States

**Many authors question this distinction! See, eg, Bowden Int Clin Psychopharm 2010**

### Table 2. Hierarchical summary of agents efficacious in mixed/dysphoric mania

<table>
<thead>
<tr>
<th>Best evidence</th>
<th>Modest evidence</th>
<th>Least/no evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Lithium **</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Asenapine</td>
<td></td>
<td>Paliperidone</td>
</tr>
<tr>
<td>Haloperidol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divalproex **</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

McIntyre Bipolar Disord 2012
Longer-term treatment

• A marathon, not a sprint
About Half of Patients Recur Within Two Years of Index Recovery

Perlis et al., *Am J Psychiatry* 2006; 163: 217-224
### Table 5.5. Recommendations for maintenance pharmacotherapy of bipolar disorder

| First line | **Monotherapy**: lithium, lamotrigine (limited efficacy in preventing mania), divalproex, olanzapine, quetiapine, risperidone LAI, aripiprazole.  
| | **Adjunctive therapy with lithium or divalproex**: quetiapine, risperidone LAI, aripiprazole, ziprasidone. |
| Second line | **Monotherapy**: carbamazepine, paliperidone ER.  
| | **Combination therapy**: lithium + divalproex, lithium + carbamazepine, lithium or divalproex + olanzapine, lithium + risperidone, lithium + lamotrigine, olanzapine + fluoxetine. |
| Third line | **Monotherapy**: asenapine.  
| | **Adjunctive therapy**: phenytoin, clozapine, ECT, topiramate, omega-3-fatty acids, oxcarbazepine, gabapentin, asenapine. |
| Not recommended | **Monotherapy**: gabapentin, topiramate, or antidepressants.  
| | **Adjunctive therapy**: flupenthixol. |

LAI = long-acting injection; ER = extended release; ECT = electroconvulsive therapy.

a Given the metabolic side effects, use should be carefully monitored.
b Mainly for the prevention of mania.
c New or change to recommendation.
Lithium reduces suicide attempt risk by >60%

Cipriani BMJ 2013
But a big RCT of lithium showed no benefit!?
Believe it... or not?

- High refusal rate
- 600mg/d x 8wk
- Li levels during study period ~0.43-0.47
- Clinicians unblinded
- No adjustment of lithium for first 8wk
- 6 month trial
Aim for Li level of 0.6+

Nolen Bipolar Disord 2013
New* ideas about an old drug

• Case-control study of 1,445 lithium-treated adults with GFR<60, and 4,306 lithium-treated adults with normal GFR

• Dosing and concomitant treatments may influence lithium risk:
  – Decrease risk:
    • Once-daily dosing (but not extended release...)
    • Concomitant SSRI/SNRI?
  – Increase risk:
    • Lithium levels exceeding 0.6 mEq/L (risk increases as level increases)
    • Concomitant first-generation antipsychotic?

Castro, Neuropsychopharmacology 2016
New ideas about an old drug

Table 2 Multiple Logistic Regression Model of Baseline Clinical and Demographic Features Associated with Renal Failure (N = 3850)

<table>
<thead>
<tr>
<th>Univariate, odds ratio</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Sex, male</td>
<td>0.68</td>
</tr>
<tr>
<td>Race/ethnicity, white</td>
<td>1.63</td>
</tr>
<tr>
<td>Age (per decade)</td>
<td>1.80</td>
</tr>
<tr>
<td>Charlson index (Log 10)</td>
<td>2.68</td>
</tr>
<tr>
<td>Insurance, private</td>
<td>1.01</td>
</tr>
<tr>
<td>Lifetime hypertension</td>
<td>4.74</td>
</tr>
<tr>
<td>Lifetime smoking</td>
<td>1.79</td>
</tr>
<tr>
<td>Lifetime diabetes mellitus</td>
<td>3.16</td>
</tr>
<tr>
<td>Any schizophrenia/schizoaffective</td>
<td>1.72</td>
</tr>
</tbody>
</table>

= Greater risk with older age, schizoaffective, hypertension, smoking...

Specificity 68% with sensitivity=80%; AUC=0.81

Castro, Neuropsychopharmacology 2016
New ideas about an old drug

• Every patient deserves a lithium trial
  – Even if rapid cycling or mixed episodes
• Aim for lithium levels as low as feasible:
  – <=0.6 if possible, 0.6-0.8 if not
• Dose once daily at bedtime if possible
• No need for extended release unless gastric discomfort/nausea with standard release
But in the real world, few patients stay on lithium monotherapy

• Danish registry study:
  – After 5 years of follow-up, only 8.9% still on lithium monotherapy

Kessel Int Clin Psychopharm 2011
Maintenance monotherapies

Fig. 1a. Relative risk of any mood episode – monotherapies. Heterogeneity: 3, lamotrigine ($I^2 = 47.4\%$); 4, lithium ($I^2 = 25.7\%$); 6, quetiapine ($I^2 = 0.0\%$); 7, quetiapine ($I^2 = 31.0\%$); overall ($I^2 = 52.3\%$). Dosages are in mg/d. RR, Relative risk; CI, confidence interval; ARP, aripiprazole; DVP, divalproex; Li, lithium; LTG, lamotrigine; OLZ, olanzapine; QTP, quetiapine; RLAI, risperidone long-acting injectable.
Monotherapy bake-off

- Lithium versus valproate
- Lithium versus quetiapine
- Risperidone long-acting injectable versus olanzapine
Primary Outcome – New Treatment/Hospital Admission

**Li or combination > VPA**

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

At risk (events):

<table>
<thead>
<tr>
<th>Combination</th>
<th>110 (14)</th>
<th>96 (17)</th>
<th>77 (10)</th>
<th>67 (7)</th>
<th>59 (4)</th>
<th>53 (2)</th>
<th>47 (4)</th>
<th>36 (1)</th>
<th>20 (0)</th>
<th>2 (0)</th>
<th>1 (0)</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>110 (23)</td>
<td>86 (15)</td>
<td>70 (10)</td>
<td>59 (8)</td>
<td>50 (5)</td>
<td>43 (2)</td>
<td>39 (2)</td>
<td>30 (0)</td>
<td>12 (0)</td>
<td>1 (0)</td>
<td>1 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Valproate</td>
<td>110 (34)</td>
<td>74 (18)</td>
<td>56 (7)</td>
<td>48 (3)</td>
<td>42 (6)</td>
<td>36 (3)</td>
<td>29 (5)</td>
<td>17 (0)</td>
<td>6 (0)</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>0</td>
</tr>
</tbody>
</table>

BALANCE Investigators Lancet 2010
- Adverse events associated with quetiapine: sedation (1.6%) and somnolence (1.1%)
Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness): a pragmatic 6-month trial of lithium versus quetiapine for bipolar disorder

Figure 2. Clinical Improvement Over Study Duration

Abbreviations: APT = adjunctive personalized treatment, CGI-EI = Clinical Global Impressions-Efficacy Index.

Nierenberg, J Clin Psychiatry, 2016: 26845264
Head-to-head: risperidone LAI vs olanzapine

Time to recurrence of an elevated (hypomanic, manic or mixed) mood episode.

Vieta European Neuropsychopharmacology 2012
• When monotherapy fails...
Add lithium to valproate

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

BALANCE Investigators Lancet 2010
Effectiveness of lithium/vpa add-ons in maintenance

<table>
<thead>
<tr>
<th>Study ID</th>
<th>RR (95% CI)</th>
<th>(%) Weight</th>
<th>Significance test of RR = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Olanzapine+Li/DVP</td>
<td>0.69 (0.29–1.65) 0.69 (0.29–1.65)</td>
<td>7.07</td>
<td>p = 0.406</td>
</tr>
<tr>
<td>OLZ 5-20+Li/DVP: Tohen et al. 2004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2: Oxcarbazepine+Li</td>
<td>0.62 (0.24–1.61) 0.62 (0.24–1.61)</td>
<td>5.87</td>
<td>p = 0.327</td>
</tr>
<tr>
<td>OXC 1200+Li: Vieta et al. 2008a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3: Perphenazine+mood stabiliser</td>
<td>0.47 (0.05–4.78) 0.47 (0.05–4.78)</td>
<td>1.00</td>
<td>p = 0.526</td>
</tr>
<tr>
<td>PPZ 28+Li/DVP: Zarate &amp; Tohen, 2004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4: Quetiapine+Li/DVP</td>
<td>0.36 (0.23–0.58) 0.41 (0.29–0.58) 0.39 (0.30–0.52)</td>
<td>25.23 43.04 68.28</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>QTP 400-800+Li/DVP: Suppes et al. 2009</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTP 400-800+Li/DVP: Vieta et al. 2008b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5: Risperidone LAI+mood stabiliser</td>
<td>0.40 (0.18–0.90) 0.40 (0.18–0.90)</td>
<td>8.08 8.08</td>
<td>p = 0.026</td>
</tr>
<tr>
<td>RLAI 25-50+Li/DVP: Macfadden et al. 2009</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6: Ziprasidone+Li/DVP</td>
<td>0.39 (0.19–0.83) 0.39 (0.19–0.83)</td>
<td>9.70 9.70</td>
<td>p = 0.014</td>
</tr>
<tr>
<td>ZIP 80-160+Li/DVP: Bowden et al. 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.42 (0.33–0.53)</td>
<td>100.00</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

Note: Weights are from random effects analysis.

Fu JCP 2015; nb only ~20% bipolar. Also note:
≥ 7% weight increase in 6.0% for placebo vs 13.0% for paliperidone monthly.
How to choose?

• Select from medications with good efficacy data

• Think about residual symptoms and predominant pole

• What are you trying to treat/prevent?
And about those antidepressants...
Risk associated with antidepressants in long-term treatment

• Acute data *consistently* shows no increase in risk vs placebo (when combined with AAP or mood stabilizer)

• “Among patients treated with a concurrent mood stabilizer, no acute change in risk of mania was observed during the 3 months after the start of antidepressant treatment (hazard ratio=0.79, 95% CI=0.54, 1.15)...

• ... *a decreased risk* was observed during the period 3-9 months after treatment initiation (hazard ratio=0.63, 95% CI=0.42, 0.93).”

• – Viktorin, AJP 2014 (ital. added)

• Debate: risk associated with longer-term use
• BUT: key to recognize that depression->mania transitions are a core part of the illness,
  – *Regardless of treatment!*
Transition from depression to mania is part of the course of illness!

% going directly to manic/mixed

N~2166 bp 1 or 2; Perlis Neuropsychopharm 2010
Risk factors for switch to mania

- 2+ prior depressions
- Rapid cycling, past year
- History of suicide attempt
- Younger age
- Earlier age at onset
- More manic symptoms during depressive episode (subthreshold mixed symptoms)
- Days elevated or irritable, prior year
- Days anxious, prior year

N~2166; Perlis Neuropsychopharm 2010; see also Frye AJP 2009
The number of past manic episodes is the best predictor of antidepressant-emergent manic switch in a cohort of bipolar depressed patients

Total ($n = 1242$)
Switchers ($n = 60$)

Gorwood, Psychiatry Res, 2016: 27138820

Fig. 2. Receiver operating characteristic curve for the lifetime number of manic episodes in depressed patients with bipolar disorder who switched to a manic or hypomanic episode in the first four weeks following prescription of an antidepressant ($N = 1242$).
Even the experts are confused

• “Because of limited data, the task force could not make broad statements endorsing antidepressant use but...

• *Individual bipolar patients may benefit from antidepressants.*

• Serotonin reuptake inhibitors and bupropion may have lower rates of manic switch than tricyclic and tetracyclic antidepressants and norepinephrine-serotonin reuptake inhibitors

• The frequency and severity of antidepressant-associated mood elevations appear to be greater in bipolar I than bipolar II disorder.

• In bipolar I patients antidepressants should be prescribed only as an adjunct to mood-stabilizing medications.”

ISBD Task Force AJP 2013
Non-pharmacologic interventions
Guidelines: Maintenance

- Pharmacotherapy recommended in all patients with bipolar disorder [I]
- First line:
  - Lithium
  - “Strongly recommended... based on evidence of long-term efficacy, well-understood risks relative to newer alternatives, and evidence that it may reduce suicide risk”.
- Next-step:
  - Lamotrigine [I], quetiapine [III], olanzapine [I], and risperidone LAI [III]
  - Quetiapine and risperidone LAI to be changed to [I] when data published
  - Aripiprazole for use in combination [III]
- Alternatives:
  - Valproate [II], carbamazepine [II]
- Combination medication regimens typically necessary [I]
- Psychosocial interventions recommended for all patients [I]

APA Bipolar Treatment Guidelines Workgroup, presented at WPA 2010
Psychoeducation groups reduce recurrence

Recovery-focused CBT in recent-onset bipolar patients decreases recurrence

Jones BJP 2015; n=67 single-blind RCT, CBT vs TAU; benefit in depression > mania
CBT for insomnia in bipolar disorder

Harvey J. Cons Clin Psychol 2015 (RCT, N=58 bipolar 1)
Functional remediation for bipolar disorder

N=239 euthymic outpatients (bipolar I or II); 21 weekly 90-minute sessions
Role of ECT in mood disorder maintenance remains unclear

- ECT side effects resulting in discontinuation: headache and memory loss. Pharmacologic side effects resulting in discontinuation: dry mouth, tremor, drowsiness, fatigue, constipation.

Kellner, AGP 2006
ECT versus algorithm-based meds in treatment-resistant bp depression

Schoeyen AJP 2015 (n=66 in ITT analysis; blinded raters only) - >50% bipolar II; Minimal difference in cognitive measures between groups (Kessler JCP 2014)
Special considerations

- Rapid cycling
- Smoking
- Anxiety
- Adherence
- Adverse effects
- Personalization
Rapid Cycling

• 6 RCT’S in rapid cycling
• 19 other post-hoc analyses of trials with rapid cycling patients

1. rapid cycling patients perform worse in the follow-up period
2. lithium efficacy comparable to anticonvulsants
3. aripiprazole and olanzapine appear promising for the maintenance of response of rapid cyclers
4. there might be an association between antidepressant use and the presence of rapid cycling.

• “...there is no clear consensus with respect to its optimal pharmacological management.”

Fountoulakis Bipolar Disord 2013
• Bipolar patients have elevated cardiovascular mortality risk (Osby Archives 2001, among many others) – likely exacerbated by atypical antipsychotics and other medications, as well as tobacco use.
• Varenicline appears to be efficacious and safe for smoking cessation (Chengappa JCP 2014)
• And... effective in maintenance of abstinence (at 1 year of treatment, and 6 months after rx discontinuation) (Evins JAMA 2014)
Anxiety comorbidity is common in bipolar disorder...

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Studies (n)</th>
<th>Individuals (n)</th>
<th>Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any anxiety disorder</td>
<td>40</td>
<td>14,914</td>
<td>0.453 (0.400–0.506)</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>40</td>
<td>14,960</td>
<td>0.193 (0.153–0.234)</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>17</td>
<td>9,066</td>
<td>0.117 (0.078–0.156)</td>
</tr>
<tr>
<td>Social phobia</td>
<td>31</td>
<td>13,329</td>
<td>0.199 (0.150–0.248)</td>
</tr>
<tr>
<td>Generalised anxiety disorder</td>
<td>31</td>
<td>11,196</td>
<td>0.204 (0.147–0.262)</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>24</td>
<td>5,093</td>
<td>0.108 (0.080–0.136)</td>
</tr>
<tr>
<td>Obsessive compulsive disorder</td>
<td>35</td>
<td>11,619</td>
<td>0.106 (0.086–0.126)</td>
</tr>
<tr>
<td>Post-traumatic stress disorder</td>
<td>22</td>
<td>8,371</td>
<td>0.173 (0.128–0.217)</td>
</tr>
</tbody>
</table>

Pavlova Lancet Psych 2015

And current symptoms are associated with greater recurrence risk (Perlis AJP 2006)
Caution regarding benzodiazepine use

Perlis JCP 2010; significant differences even after adjustment for anxiety and other comorbidities
Adherence in bipolar disorder

24% poorly adherent on at least 20% of visits

Poorer adherence at 3 months = Poorer function at 12 months

Perlis JCP 2010; pngu.mgh.harvard.edu/~perlis
Keep in mind that injectables may not confer added benefit in schizophrenia...

Rosenheck NEJM 2011; See also Kane AJP 2010
Consider injectables where adherence is poor

- Injectables in the average patient may not be necessary – BUT might show benefit in nonadherent or brittle patients... (Suzuki letter, NEJM 2011)
12-week weight change in treatment-naïve children and adolescents

% weight change

<table>
<thead>
<tr>
<th>Medication</th>
<th>% Weight Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>8</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>16</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>10</td>
</tr>
<tr>
<td>Risperidone</td>
<td>10</td>
</tr>
<tr>
<td>Untreated</td>
<td>0</td>
</tr>
</tbody>
</table>

Correll JAMA 2009
Managing Adverse Effects: weight gain

- Provide education about diet and exercise
- Provide referral to a nutritionist

- Metformin (250tid or 500bid)^
- Topiramate titrated to point of appetite suppression (100-150mg)*
- Zonisamide titrated to point of appetite suppression (100-200mg)*
- Bupropion (SR or XL) 100mg-300mg*
- Sibutramine 10mg PO QD*

- ?Melatonin 5mg (Romo-Nava Bipolar Disord 2014)

http://www.mhmr.state.tx.us/centraloffice/medicaldirector/TMAPtoc.html
Weight loss programs work in serious mental illness

Mean 18-mo weight loss 3.2kg in intervention group (22% bipolar; ~82% on atypical antipsychotic)

Daumit NEJM 2013; see also Kilbourne JCP 2013
Replication of benefits of health coaching

• N=210 patients with serious mental illness, BMI>25
• Randomized to health club membership, or membership plus coaching (SHAPE program)
  – ~5lb wt loss @12 months, vs ~1lb wt gain
  – Increased fitness/exercise tolerance
  – BUT no change in diet, lipids, blood pressure

Bartels AJP 2015
A pilot randomized clinical trial evaluating the impact of genetic counseling for serious mental illnesses
Hippman C, Ringrose A, Inglis A, Cheek J, Albert AY, Remick R, Honer WG, Austin JC

Figure 2. (A) Knowledge Scores by Group and Time and (B) ISMI Alienation Subscale Scores by Group and Time

All error bars represent 95% CI.
Abbreviations: EB = educational booklet, GC = genetic counseling, ISMI = Internalized Stigma of Mental Illness scale.

Hippman, J Clin Psychiatry, 2016: 26930535
Personalized medicine in bipolar disorder?

- Still no *actionable* common genetic variants identified
  - NEJM report of a predictor of lithium response did not replicate in multiple other cohorts (Chen NEJM 2014)

- Family history is not diagnostic, but is useful in two ways
  - Increased suspicion for bipolar disorder
  - *Influences patient attitudes toward medication*

- CYP450 testing not well-studied for bipolar disorder
  - Useful reference: medicine.iupui.edu/clinpharm/ddis/main-table/

- Most useful consideration in treatment selection among drugs with efficacy: adverse effect profile

- “Best drug for 40-y.o. woman with rapid cycling?”
Long-term Treatment in Bipolar Disorder: Fall 2015 Update

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