Long-term Treatment in Bipolar Disorder: Fall 2017 Update

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

Roy H. Perlis, MD, MSc

- Commercial Interest What was received For what role?
- Example: Company X Speaker Fee Promotional Speaker
- Psy Therapeutics (equity) - Founder/SAB member
- Genomind (consultant fee) - SAB member
- RID Ventures (consultant fee) - advisor
- H5 Health (equity) - Founder
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*

<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>

* Based on Kappa values in DSM-V field trials
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>Total</td>
<td>858</td>
<td>355 180 21</td>
</tr>
<tr>
<td>N=</td>
<td>156 46 16 2</td>
<td>702 309 164 19</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
+ 
Step 2
Initiate/optimize, check compliance

No response 
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

Assess safety/functioning
Establish treatment setting
D/C antidepressants
Rule out medical causes
D/C caffeine, alcohol, and illicit substances
Behavioural strategies/rhythms, psychoeducation

Not on medication or first-line agent

Lithium or DVP

Add or switch to AAP

Replace one or both agents with other first-line agents

Consider adding or switching to second or third-line agent or ECT

Consider adding novel or experimental agent

On first-line agent

Initiate Li, DVP, AAP, or 2-drug combination

AAP

2-drug combination (Li or DVP + AAP)

Add or switch to Li or DVP

Replace one or both agents with other first-line agents

CANMAT Bipolar Disorders 2013
## Treatment options

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

<table>
<thead>
<tr>
<th>Line</th>
<th>Therapy Options</th>
</tr>
</thead>
</table>
| **First line** | Monotherapy: lithium, divalproex, **divalproex ER**\(^a\), olanzapine\(^b\), risperidone, quetiapine, quetiapine XR, aripiprazole, ziprasidone, **asenapine**\(^a\), **paliperidone ER**\(^a\)  
Adjunctive therapy with lithium or divalproex: risperidone, quetiapine, olanzapine, aripiprazole, **asenapine**\(^a\) |
| **Second line** | Monotherapy: carbamazepine, carbamazepine ER, ECT, **haloperidol**\(^a\)  
Combination therapy: lithium + divalproex |
| **Third line** | Monotherapy: chlorpromazine, clozapine, oxcarbazepine, tamoxifen, **cariprazine**\(^a\)  
(not yet commercially available)  
Combination therapy: lithium or divalproex + haloperidol, lithium + carbamazepine, adjunctive tamoxifen |
| **Not recommended** | Monotherapy: gabapentin, topiramate, lamotrigine, verapamil, tiagabine  
Combination therapy: risperidone + carbamazepine, olanzapine + carbamazepine |

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

\(^a\) *New or change to recommendation.*  
\(^b\) Given the metabolic side effects, use should be carefully monitored.
Among antipsychotics, efficacy/tolerability data favors haloperidol, risperidone, olanzapine, quetiapine.
Decreased risk of postmanic depression with second generation antipsychotic vs haloperidol

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)

• Brexpiprazole: *no published/pending mania trials*

• Cariprazine: *2 positive phase III mania trials*
  – FDA approval fall 2015
  – No clear benefit vs existing options
Longer-term treatment

• A marathon, not a sprint
About Half of Patients RecurWithin 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

<table>
<thead>
<tr>
<th>Line</th>
<th>First Line</th>
<th>Second Line</th>
<th>Third Line</th>
<th>Not Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td>lithium, lamotrigine (limited efficacy in preventing mania), divalproex, olanzapine&lt;sup&gt;a&lt;/sup&gt;, quetiapine, risperidone LAI&lt;sup&gt;b&lt;/sup&gt;, aripiprazole&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Monotherapy, carbamazepine, paliperidone ER&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Monotherapy: asenapine&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Monotherapy: gabapentin, topiramate, or antidepressants</td>
</tr>
<tr>
<td><strong>Adjunctive therapy with lithium or divalproex</strong></td>
<td>quetiapine, risperidone LAI&lt;sup&gt;b&lt;/sup&gt;, aripiprazole&lt;sup&gt;b&lt;/sup&gt;, ziprasidone&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Combination therapy: lithium + divalproex, lithium + carbamazepine, lithium or divalproex + olanzapine, lithium + risperidone, lithium + lamotrigine, olanzapine + fluoxetine</td>
<td>Adjunctive therapy: phenytoin, clozapine, ECT, topiramate, omega-3-fatty acids, oxcarbazepe, gabapentin, asenapine&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Adjunctive therapy: flupenthixol</td>
</tr>
</tbody>
</table>

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

<sup>a</sup>Given the metabolic side effects, use should be carefully monitored.

<sup>b</sup>Mainly for the prevention of mania.

<sup>e</sup>New or change to recommendation.
Lithium reduces suicide attempt risk by >60%

Cipriani BMJ 2013
After a 1\textsuperscript{st} manic episode, lithium-treated patients may have greater cognitive improvement.

A single-blind, randomised controlled trial on the effects of lithium and quetiapine monotherapy on the trajectory of cognitive functioning in first episode mania: A 12-month follow-up study.

Daglas 2016; n=16 patients with 1\textsuperscript{st} episode mania
But a big RCT of lithium showed no benefit!? 

**FIGURE 2.** Overall Illness Severity Over Time (Observed Cases) in a Study of Optimized Personalized Treatment With and Without Lithium

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*CGI-BP-S= Clinical Global Impression Scale for Bipolar Disorder-Severity; OPT= optimized personalized treatment (guideline-informed, evidence-based, and personalized based on current symptoms, prior treatment history, and course of disorder). No significant differences were observed between groups.*
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+

- Post hoc analysis of SPaRCle trial – time to recur

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

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

<table>
<thead>
<tr>
<th>Feature</th>
<th>Univariate, odds ratio</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Sex, male</td>
<td>0.68</td>
<td>0.57</td>
</tr>
<tr>
<td>Race/ethnicity, white</td>
<td>1.63</td>
<td>1.53</td>
</tr>
<tr>
<td>Age (per decade)</td>
<td>1.80</td>
<td>1.55</td>
</tr>
<tr>
<td>Charlson index (Log 10)</td>
<td>2.68</td>
<td>1.46</td>
</tr>
<tr>
<td>Insurance, private</td>
<td>1.01</td>
<td>1.29</td>
</tr>
<tr>
<td>Lifetime hypertension</td>
<td>4.74</td>
<td>2.62</td>
</tr>
<tr>
<td>Lifetime smoking</td>
<td>1.79</td>
<td>1.27</td>
</tr>
<tr>
<td>Lifetime diabetes mellitus</td>
<td>3.16</td>
<td>1.17</td>
</tr>
<tr>
<td>Any schizophrenia/schizoaffective</td>
<td>1.72</td>
<td>1.63</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

#### Figure 1a: Relative risk of any mood episode – monotherapies.

<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: Aripiprazole</td>
<td>0.63 (0.43–0.92)</td>
<td>5.93</td>
<td>(p = 0.017)</td>
</tr>
<tr>
<td>ARP 15-30: Keck et al. 2007</td>
<td>0.63 (0.43–0.92)</td>
<td>5.93</td>
<td>(p = 0.017)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.63 (0.43–0.92)</td>
<td>5.93</td>
<td>(p = 0.017)</td>
</tr>
<tr>
<td>2: Divalproex/volatile</td>
<td>0.63 (0.44–0.90)</td>
<td>6.36</td>
<td>(p = 0.012)</td>
</tr>
<tr>
<td>DVP 71-125: Bowden et al. 2000b</td>
<td>0.63 (0.44–0.90)</td>
<td>6.36</td>
<td>(p = 0.012)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.63 (0.44–0.90)</td>
<td>6.36</td>
<td>(p = 0.012)</td>
</tr>
<tr>
<td>3: Lamotrigine</td>
<td>0.80 (0.65–0.99)</td>
<td>10.20</td>
<td>(p = 0.047)</td>
</tr>
<tr>
<td>LTG 100-300: Calabrese et al. 2000</td>
<td>0.80 (0.65–0.99)</td>
<td>10.20</td>
<td>(p = 0.047)</td>
</tr>
<tr>
<td>LTG 50-400: Calabrese et al. 2003</td>
<td>0.96 (0.79–1.18)</td>
<td>10.52</td>
<td>(p = 0.047)</td>
</tr>
<tr>
<td>LTG 100-400: Bowden et al. 2003</td>
<td>0.68 (0.50–0.92)</td>
<td>7.81</td>
<td>(p = 0.047)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.83 (0.68–1.00)</td>
<td>26.32</td>
<td>(p = 0.047)</td>
</tr>
<tr>
<td>4: Lithium</td>
<td>0.80 (0.54–1.20)</td>
<td>5.61</td>
<td>(p = 0.047)</td>
</tr>
<tr>
<td>Li 0.8-1.2: Bowden et al. 2000b</td>
<td>0.80 (0.54–1.20)</td>
<td>5.61</td>
<td>(p = 0.047)</td>
</tr>
<tr>
<td>Li 0.8-1.1: Bowden et al. 2003</td>
<td>0.58 (0.39–0.85)</td>
<td>5.89</td>
<td>(p = 0.047)</td>
</tr>
<tr>
<td>Li 0.8-1.1: Calabrese et al. 2003</td>
<td>0.84 (0.66–1.08)</td>
<td>9.11</td>
<td>(p = 0.047)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.75 (0.60–0.94)</td>
<td>20.60</td>
<td>(p = 0.047)</td>
</tr>
<tr>
<td>5: Olanzapine</td>
<td>0.58 (0.49–0.69)</td>
<td>11.81</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>OLZ 5-20: Tohen et al. 2008</td>
<td>0.58 (0.49–0.69)</td>
<td>11.81</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.58 (0.49–0.69)</td>
<td>11.81</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>6: Quetiapine 300</td>
<td>0.73 (0.50–1.07)</td>
<td>5.97</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>QTP 300: Young et al. 2008</td>
<td>0.73 (0.50–1.07)</td>
<td>5.97</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>QTP 300: McIntyre et al. 2009</td>
<td>0.57 (0.34–0.94)</td>
<td>4.09</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.67 (0.49–0.90)</td>
<td>10.07</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>7: Quetiapine 600</td>
<td>0.41 (0.23–0.74)</td>
<td>3.34</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>QTP 600: McIntyre et al. 2009</td>
<td>0.41 (0.23–0.74)</td>
<td>3.34</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>QTP 600: Young et al. 2008</td>
<td>0.64 (0.42–0.95)</td>
<td>5.58</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.54 (0.36–0.81)</td>
<td>8.92</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>8: Risperidone LAI</td>
<td>0.54 (0.41–0.73)</td>
<td>7.99</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>RLAI 12.5-50: Queroz et al. 2010</td>
<td>0.54 (0.41–0.73)</td>
<td>7.99</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.54 (0.41–0.73)</td>
<td>7.99</td>
<td>(p &lt; 0.001)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.68 (0.60–0.77)</td>
<td>100.00</td>
<td>(p &lt; 0.001)</td>
</tr>
</tbody>
</table>

**Note:** Weights are from random effects analysis.

Vieta Int Neuropsychopharm 2011
Monotherapy bake-off

- Lithium versus valproate
- Lithium versus quetiapine
- Risperidone long-acting injectable versus olanzapine
Li or combination > VPA

**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

**At risk (events):**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total</th>
<th>Event MTH MTH MTH MTH  MTH MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH  MTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination</td>
<td>110 (14)</td>
<td>96 (17)</td>
</tr>
<tr>
<td>Lithium</td>
<td>110 (23)</td>
<td>86 (15)</td>
</tr>
<tr>
<td>Valproate</td>
<td>110 (34)</td>
<td>74 (18)</td>
</tr>
</tbody>
</table>
Head-to-head: quetiapine versus lithium

- 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.

**p = 0.005; ***p < 0.0001 versus placebo (log-rank test stratified by patient type and region)
†p = 0.002 versus placebo (log-rank test stratified by region only [adjusted analysis])

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

How to choose?

• Select from medications with good efficacy data

• Think about residual symptoms and predominant pole

• What are you trying to treat/prevent?
If something is added, how long to continue?
Yatham 2016; n=159 bipolar 1 patients on mood stabilizer plus recent addition of olanzapine or risperidone, randomized to 0, 24, or 52 week discontinuation (n.b.: only olanzapine showed clear benefit beyond 24 weeks!)
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!

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
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
Wacky paper of the year:

Blue-blocking glasses for acutely manic patients!

Henriksen 2017; n=23
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

FIGURE 1. Changes in Functional Impairment Scores Before and After Intervention in Patients With Bipolar Disorder

N=239 euthymic outpatients (bipolar I or II); 21 weekly 90-minute sessions

Torrent AJP 2013; See also Bonnin 2017
Does internet-based therapy work?

- Nope.

Lobban 2016; n=96
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

**FIGURE 1.** Proportion of patients remaining in remission during the maintenance phase in the CORE trial. Reprinted with permission from Kellner et al.\textsuperscript{15} Log-rank test comparing distributions of time to relapse for M-ECT versus M-pharm: $\chi^2 = 0.30; P = 0.59$.

**TABLE 4.** CANMAT Recommendations for ECT in Bipolar Disorders

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Recommendations for ECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute mania</td>
<td>Second line</td>
</tr>
<tr>
<td>Acute bipolar I depression</td>
<td>Third line</td>
</tr>
<tr>
<td>Maintenance therapy of bipolar disorder</td>
<td>Third line (adjunctively)</td>
</tr>
<tr>
<td>Maintenance therapy of bipolar II disorder</td>
<td>Third line</td>
</tr>
</tbody>
</table>

Adapted from Yatham et al.\textsuperscript{26}
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.”
Smoking cessation

• 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

n.b. No benefit for long-acting melatonin in benzo-discontinuation trial (Baandrup 2016)
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
The median proportion of days with missed bipolar medication doses was 53.6%.
Of those taking nonpsychotropic medications, the median proportion of days with missed doses was 33.9%. 

**TABLE 1. Medication adherence among patients with bipolar disorder and poor adherence**

<table>
<thead>
<tr>
<th>Adherence characteristic</th>
<th>N</th>
<th>M</th>
<th>SD</th>
<th>Median</th>
<th>Interquartile range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bipolar disorder medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past week average</td>
<td>88</td>
<td>60.26</td>
<td>25.80</td>
<td>57.14</td>
<td>42.86–76.79</td>
</tr>
<tr>
<td>Past month average</td>
<td>85</td>
<td>54.96</td>
<td>24.71</td>
<td>50.00</td>
<td>33.33–70.00</td>
</tr>
<tr>
<td><strong>Nonpsychotropic medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past week average</td>
<td>62</td>
<td>40.38</td>
<td>30.10</td>
<td>37.86</td>
<td>14.29–57.14</td>
</tr>
<tr>
<td>Past month average</td>
<td>61</td>
<td>33.94</td>
<td>26.30</td>
<td>30.00</td>
<td>13.33–46.67</td>
</tr>
</tbody>
</table>

\(^{a}\) As reported on the Tablets Routine Questionnaire, on which possible scores range from 0 to 100, with higher scores indicating more nonadherence.
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)
Fu JCP 2015; nb only ~20% bipolar. Also note: 
≥ 7% weight increase in 6.0% for placebo vs 13.0% for paliperidone monthly.
Figure 2. Kaplan-Meier Curve of Time From Randomization to Recurrence of Any Mood Episode\textsuperscript{a}

![Graph showing Kaplan-Meier curve with two curves for AOM 400 and Placebo. The Log-Rank Test yields P < .0001.]

Number of Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>AOM 400</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 weeks</td>
<td>132</td>
<td>133</td>
</tr>
<tr>
<td>4 weeks</td>
<td>125</td>
<td>121</td>
</tr>
<tr>
<td>8 weeks</td>
<td>111</td>
<td>104</td>
</tr>
<tr>
<td>12 weeks</td>
<td>101</td>
<td>91</td>
</tr>
<tr>
<td>16 weeks</td>
<td>93</td>
<td>84</td>
</tr>
<tr>
<td>20 weeks</td>
<td>85</td>
<td>75</td>
</tr>
<tr>
<td>24 weeks</td>
<td>84</td>
<td>67</td>
</tr>
<tr>
<td>28 weeks</td>
<td>80</td>
<td>59</td>
</tr>
<tr>
<td>32 weeks</td>
<td>76</td>
<td>55</td>
</tr>
<tr>
<td>36 weeks</td>
<td>72</td>
<td>53</td>
</tr>
<tr>
<td>40 weeks</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td>44 weeks</td>
<td>69</td>
<td>48</td>
</tr>
<tr>
<td>48 weeks</td>
<td>67</td>
<td>43</td>
</tr>
<tr>
<td>52 weeks</td>
<td>62</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Time to recurrence was analyzed using a log-rank test in the efficacy sample of the randomized, double-blind, placebo-controlled phase.

Abbreviation: AOM 400 = aripiprazole once-monthly 400 mg.
Figure 3. Recurrence Rate by Type of Mood Episode

<table>
<thead>
<tr>
<th>Mood Episode</th>
<th>AOM 400 (n = 132)</th>
<th>Placebo (n = 133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Mood Episode</td>
<td>35</td>
<td>68</td>
</tr>
<tr>
<td>Manic</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>Depressive</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Mixed</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

Proportion of Patients, %

P < .0001

P = .864

P = .060

P-values were derived from Fisher exact test.

Abbreviation: AOM 400 = aripiprazole once-monthly 400 mg.
12-week weight change in treatment-naïve children and adolescents

% weight change

- Aripiprazole
- Olanzapine
- Quetiapine
- Risperidone
- Untreated

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

A. Knowledge Score (mean)

B. ISMI Alienation Subscale Score (mean)

EB N = 36 GC N = 36
EB N = 36 GC N = 36
EB N = 31 GC N = 31

a 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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