ESSENTIAL PSYCHOPHARMACOLOGY, 2011:
TREATMENT OF BIPOLAR DISORDER

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LITHIUM

• Most data available for acute treatment
• Best data for maintenance treatment
• Blood levels correlate with response and side effects
Predictors of good lithium outcome

• Previous good response to lithium
• Pure mania
• Sequence of mania-depression-euthymia
• Positive family history of bipolar disorder
• Lithium level > 0.8 mEq/L
• Relatively few lifetime episodes

Predictors of Lithium non-response

- Rapid-cycling: > 4 episodes/year
- Dysphoric and mixed states
- Episode sequence: D->M->E
- Neurological/EEG abnormality
- Substance abuse
- Adolescence/No family hx
LAMOTRIGINE FOR MAINTENANCE

- Lamotrigine better than lithium for prophylaxis against depression
- Lithium better than lamotrigine for prophylaxis against mania
- Most common lamotrigine side effect was headache
VALPROATE

• Does not induce its own metabolism
• Increases blood levels of phenytoin and carbamazepine
• Increases GABA synthesis and inhibits GABA catabolism
• Decreases glutamate concentrations
VALPROATE DOSING

• Usual dose: 750-3000 mg/d
• Loading dose: 20-30 mg/kg/day for 5 days
• OR, start with 750mg and increase by 250-500 every 2-3 days
CARBAMAZEPINE

- Related to imipramine
- Major metabolite oxcarbazepine has anticonvulsant activity
- Induces its own metabolism
- Induces metabolism of BZs, tricyclics, steroids
Extended Release Carbamazepine

- Similar side effects to carbamazepine including dizziness, nausea, somnolence, and headache.
- Similar decrease in serum concentration of many medications including oral contraceptives and warfarin.
- Starting dose 200 mg bid; may increase by 200 mg daily to 1600 mg daily; do not crush or chew.
- Caution in pregnancy - 1% incidence of neural tube defects, including spina bifida.
Oxcarbazepine (Trileptal)

- Keto analogue of carbamazepine
- Randomized active control comparative trials with haloperidol and lithium for treatment of acute mania
- Mean dosage in trials 2400 mg/qd and 1400 mg/qd
- Comparable efficacy established in treatment of acute mania
- Less hepatic enzyme induction than carbamazepine, fewer drug interactions
- Conversion ratio is 1.2 to 1.5 - 800 mg of carbamazepine equals 1000-1200 mg of oxcarbazepine
- Caution regarding hyponatremia
CLONAZEPAM IN ACUTE MANIA

• Commonly used to control hyperactivity and induce sleep
• No controlled studies of efficacy as solo drug
• Can be used as second drug for management of acute patient
• Common BZ side effects:
  – Sedation
  – Cognitive impairment
  – Unsteadiness
GABAPENTIN

• A synthetic analogue of GABA
• Eliminated through kidneys; does not alter hepatic metabolism
• No drug-drug interactions
• Half-life, 5-7 hours
• Not superior to placebo for acute mania in controlled studies, but effective in open trials
GABAPENTIN - II

- Blood levels do not correlate with response
- Most common side effects:
  - Somnolence
  - Dizziness
  - Ataxia
- Daily dose: 900-3000mg/day
- Side effects are moderate and transient
- Good add-on drug
TOPIRAMATE FOR MOOD STABILIZATION

- Starting dose 25
- 25 mg dose increments daily
- Improvement at 100-200 mg/d
- Main side effects:
  - sedation
  - glaucoma?
  - cognitive impairment at high doses
- Few drug interactions
- Mechanism of action:
  - modulates fast sodium channels and inhibits calcium influx
  - potentiates GABA inhibition
TOPIRAMATE - II

• Common side effects:
  – Somnolence
  – Dizziness
  – Ataxia
  – Cognitive impairment

• Weight loss in some patients (4-15 lbs)
  – Levels off after 3 months
GABATRIL

• Tiagabine (Gabitril)
• Enhances GABA levels by blocking uptake of synaptically released GABA
• Efficacy in partial seizures
• No data for bipolar disorder
NEW ANTICONVULSANTS

• Zonisamide (Zonegran) – blocks sodium channels; modulates GABA and DA neurotransmission. Case series suggest anti manic activity

• Levetiracetam (Keppra) – no data available
ALTERNATIVE MOOD STABILIZERS

• Calcium channel blockers
  – Verapamil
  – Diltiazam
  – Nimodipine

• Omega-3

• Allopurinol

• tamoxifen
RECENT INFORMATION ON MOOD STABILIZERS

• Valproate increases risk of polycystic ovary disease in reproductive age women
• High doses of Omega-3 does not augment mood stabilizers for bipolar disorder
• Tiagabine (Gabitril) may increase seizures
POLYPHARMACY IN BIPOLAR DISORDER

- Almost 10% of patients (in STEP-BD) study take more than one second-generation antipsychotic drug;
- Not clearly more effective
- More side effects:
  - Dry mouth, tremor, sedation, sexual dysfunction, constipation
- 3x more psychiatric incidents requiring attention; 2x more medical incidents
ATYPICAL NEUROLEPTIC AUGMENTATION

- Olanzapine equally potent to valproate
- Risperidone added to paroxetine helpful for bipolar depression
- Weight gain for risperidone 5.9 kg
- Weight gain for olanzapine 11.3 kg
- Quetiapine improves rapid-cycling symptoms over a 2-month period
OLANZAPINE ADDED TO A MOOD STABILIZER FOR BIPOLAR DISORDER

• Olanzapine 5-20 mg/d added to lithium or valproate
• Olanzapine + lithium or valproate effectively prolongs time in remission compared with lithium or valproate alone

(Tohen, 2001)
Aripiprazole Is Effective in Acute Mania

Response defined as ≥50% reduction in YMRS.


Data on file, Otsuka America Pharmaceutical, Inc.

*P*<0.01; †*P*<0.001.
TREATMENT OF RAPID CYCLING

• Anticonvulsants superior to lithium
• Clozapine and other atypical neuroleptics
• Nimodipine
• T3
• Commonly requires two mood stabilizers
LAMOTRIGINE FOR RAPID-CYCLING BIPOLAR DISORDER

- Rapid cycling is greater in bipolar II patients (5 times higher than bipolar I)
- Effective as a maintenance treatment in rapid-cycling bipolar disorder
- May be effective as monotherapy for bipolar depression
- Therapeutic dose 100-300 mg/d
- Common side effects: rash (8%)
- Possible additional side effects: motor and/or vocal tics
- Low incidence of CNS toxicity and cognitive dysfunction
- Antidepressant response begins at 50 mg, increased at 200 mg
- May be prophylactic for rapid cycling

Calabrisi, 1999; Baldessarini, 2000)
BIPOLAR DEPRESSION

• Very difficult to treat; all antidepressants can precipitate switch into mania (tricyclics are the worst)
• Must use mood stabilizer or neuroleptic with antidepressant
• Retrospective data suggesting that long-term antidepressant use induces rapid cycling
Guides to treating bipolar depression

- Lithium: 9 controlled trials with 79% response, complete response in 35%
- Depakote: 6 open trials - response rate 32%
- Lamotrigine: controlled trial at 50 mg and 200 mg qd dosage - positive response by week 4 in 16 of 22 patients
Divalproex in Bipolar Depression

Responder Analysis

<table>
<thead>
<tr>
<th>Percentage of Subjects Meeting Recovery Criteria</th>
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<tbody>
<tr>
<td>45</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
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<td>10</td>
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<td>5</td>
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</table>

- Divalproex (n=21)  
- Placebo (n=22)

$p=0.347$

Treatment of Acute Bipolar Depression: Efficacy of Divalproex vs Placebo

- Placebo (n=22)
- Divalproex (n=21)

Mean HAM-D Change From Baseline (LOCF)

Week

P<0.01

Baseline HAM-D scores: placebo=20.5; divalproex=22.6.

LAMOTRIGINE FOR BIPOLAR DEPRESSION

- 962 patients
- Open-label treatment
- Mean dose 200 mg/d effective in stabilizing mood in bipolar depressed patients

(Sachs, 2001)
LAMOTRIGINE IN BIPOLAR DEPRESSION: RESPONDER ANALYSIS
(≥50% IMPROVEMENT FROM BASELINE)

% Improvement

HAMD-17  MEDRS  CGI

Placebo
Lamotrigine 50 mg/day
Lamotrigine 200 mg/day

* p<.05 LTG vs. placebo
** p<.01 LTG vs. placebo

TREATMENT OF BIPOLAR DEPRESSION WITH 2 MOOD STABILIZERS VS. MOOD STABILIZER + SSRI

![Graph showing HAM-D score over treatment duration](image)

Young et al., Am J Psychiatry 157, 124-128, 2000
Treatment of Acute Bipolar I Depression:
Efficacy of Olanzapine

Mean Change in MADRS Score

Placebo (n=377)
OLZ (n=370)
OLZ + FLU (n=86)

*P<0.05 vs OLZ + FLU; †P<0.05 vs OLZ.
OLZ=olanzapine; FLU=fluoxetine.
# MAOIs in Bipolar Depression: Tranoylcypromine vs. Imipramine

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>n</th>
<th>Response to TCA (%)</th>
<th>Response to Non-TCA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Himmelhoch et al, 1982</td>
<td>Double-blind, tranoylcypromine vs. placebo</td>
<td>29</td>
<td>24/29 (83)</td>
<td>MAOI &gt; placebo</td>
</tr>
<tr>
<td>Himmelhoch et al, 1991</td>
<td>Double-blind, .28 Tranoylcypromine, 28 Imipramine</td>
<td>28</td>
<td>(48)</td>
<td>(81)</td>
</tr>
<tr>
<td>Thase et al, 1992</td>
<td>Crossover</td>
<td>16</td>
<td>1/4 (25)</td>
<td>9/12 (75)</td>
</tr>
</tbody>
</table>

VENLAFAXINE VS. PAROXETINE IN BIPOLAR DEPRESSION

• BP I (n=44) or BP II (n=16) 6-week trial
• N=57 on mood stabilizers, mostly Li
• Mean dosing: paroxetine: 32 mg/day; venlafaxine: 179 mg/day
• Response: 43% paroxetine, 48% venlafaxine

Vieta et al., CINP, Brussels, 2000
DO ANTIDEPRESSANTS WORSEN BIPOLAR DISORDER?

• Bipolar depressed patients taking an antidepressant are 3.8x more likely to develop rapid cycling
  – Rapid cycling is more resistant to effective treatment and leads to chronicity
• No evidence that any antidepressant is less likely to cause increased cycling
• Unclear whether antidepressant dose is a factor

Ghaemi; AJP 2008;165:300
Sachs; NEJM 2007; 356:1711
ANTIDEPRESSANT SWITCH INTO MANIA (self-report)

• Most likely with:
  – Tricyclic antidepressants
  – Fluoxetine & citalopram > other SSRIs

• Moderate risk of switch
  – Bupropion, ECT
  – Paroxetine, sertraline, venlafaxine

• Lowest (but not absent) risk
  – Mirtazepine, fluvoxamine, nefazodone
  – MAOIs

Truman JCPsychiat 2007;68:1473
Adjunctive, standard antidepressants did not increase efficacy of treatment of bipolar depressed patients receiving mood stabilizers (23.5% vs. 27.3%)

No difference in switch rate between the 2 groups

Sachs 2007; NEJM 356:1711
Increased Mania Switch Rates With TCAs

% With Manic Switch

Placebo: 4.2% (2/48)
Sertraline/Paroxetine: 3.7% (9/242)
TCAs: 11.2% (14/125)

*P<.01 vs placebo.
SWITCHING WORSE WITH DUAL ACTING ANTIDEPRESSANTS

FIGURE 3. Ratio of Threshold Switches to Subthreshold Brief Hypomanias in Trials of Bupropion, Sertraline, and Venlafaxine as an Adjunct to Mood Stabilizers in Depressed Patients With Bipolar Disorder

Leverich, 2006
BIPOLAR DEPRESSIONS: NEW DIRECTIONS

• Bipolar depressions should be treated with concurrent mood stabilizers and antidepressants
  – Evidence that atypical antipsychotics may also be effective as adjunct treatment as well as to prevent switch into mania
  – Evidence that lamotrigine has modest antidepressant properties and may serve to prevent recurrence of depression during maintenance treatment
  – Lithium has mild antidepressant properties
• New treatment directions: pramipexole (D3 agonist); riluzole (glutamate antagonist);
Table 4. Outcomes According to Treatment Group.*

<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 because of adverse event</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.
ADJUNCTIVE ANTIDEPRESSANTS NOT USEFUL IN BIPOLAR DEPRESSION (STEP -BD)

Goldberg; 2007; AJP 164:1348