Management of Bipolar Depression

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Bipolar Disorders (Manic-Depressive illness)
Objectives:

- Diagnostic challenges in Bipolar Depression
- Bipolar depression: Co-occurring disorders
- Acute and maintenance treatment of bipolar depression
- Psycho-education/Psycho-therapeutic interventions
Goals of Treatment in Bipolar Disorder

- Identify acute symptoms
- Prevent relapses/recurrences
- Result in fewest and mildest episodes
- Monitor/Manage/Minimize side effects
- Improve patient compliance
- Prevent/Manage Suicide

No single agent is likely to be completely effective for all therapeutic objectives
DSM: Today & Tomorrow
BIPOLAR DISORDERS

_Bipolar I disorder:_

- Recent episode mania
- Recent episode hypomania
- Recent episode depression
- Recent episode Mixed
- Rapid cycling

_Bipolar II Disorder:_

- Depression
- Hypomania

_Bipolar Disorder NOS:_

_Cyclothymia:_
Bipolar Disorder: Epidemiology

Lifetime prevalence: 3.9% (range 1.5-6%)

12 Month prevalence: 6.6% -- 14-15 M adults in US

Male : Female (Female > Bipolar II)

Commonly confused with ADHD/Anxiety d/o

Gap between onset and diagnosis is about 10 years
Why people get manic/depressed?

A maladaptive response:

Psychosocial: Stressors/trauma/injury

Neurobiology: Chemicals/receptors

Genetic predisposition:
BAD: Genetics

- No single gene identified
- Chromosomes 5, 11, 18 & X
- Monozygotic twins 33-90%
- Dizygotic twins 5-25%
- One parent with BAD: 25%
- Both parents with BAD: 50%
Screening

Over the past 1 week, have you felt high, or on top of the world?

Over the past 1 weeks, have you felt angry, irritable and out of control?

### Mood Disorder Questionnaire

Please answer each question to the best of your ability.

<table>
<thead>
<tr>
<th>1. Has there ever been a period of time when you were not your usual self and...</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were so irritable that you shouted at people or started fights or arguments?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you felt much more self-confident than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you got much less sleep than usual and found that you didn’t really miss it?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were more talkative or spoke much faster than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...thoughts raced through your head or you couldn’t slow your mind down?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were so easily distracted by things around you that you had trouble concentrating or staying on track?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you had more energy than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were much more active or did many more things than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were much more interested in sex than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...spending money got you or your family in trouble?</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time? ☐ ☐

3. How much of a problem did any of these cause you - like being unable to work; having family, money or legal troubles; getting into arguments or fights?

- ☐ No problems
- ☐ Minor problem
- ☐ Moderate problem
- ☐ Serious problem
Bipolar Disorder: Depressive Symptoms Experienced Longer Than Manic Symptoms

BP I, $n = 146$, $m = 12.8$ years

BP II, $n = 86$, $m = 13.4$ years

BP I, $n = 405$, $m = 1$ year

BP II, $n = 102$, $m = 1$ year
Comorbidities…the Rule, Not the Exception: The Multidimensionality of Bipolar Disorder

# Metabolic Syndrome and Bipolar Disorder

<table>
<thead>
<tr>
<th>Article</th>
<th>Definition of Metabolic Syndrome</th>
<th>Prevalence of Metabolic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yumru 2007</td>
<td>NCEP ATP III</td>
<td>32.0%</td>
</tr>
<tr>
<td>Cardenas 2008</td>
<td>NCEP ATP III</td>
<td>49.0%</td>
</tr>
<tr>
<td>Correll 2008</td>
<td>NCEP ATP III</td>
<td>43.2%</td>
</tr>
<tr>
<td>Fagiolini 2008</td>
<td>Modified NCEP ATP III</td>
<td>40.0%</td>
</tr>
<tr>
<td>Fiedorowicz 2008</td>
<td>NCEP ATP III</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Garcia-Portilla 2008</td>
<td>Modified NCEP ATP III (NHANES 1999-2000)</td>
<td>22.4%</td>
</tr>
<tr>
<td>Salvi 2008</td>
<td>NCEP ATP III, IDF</td>
<td>25.3%</td>
</tr>
<tr>
<td>Sicras 2008</td>
<td>NCEP ATP III</td>
<td>24.7%</td>
</tr>
<tr>
<td>van Winkel 2008</td>
<td>NCEP ATP III, Modified NCEP ATP III, IDF</td>
<td>16.7%, 18.3%, 30.0%</td>
</tr>
<tr>
<td>Vuksan-Cusa 2009</td>
<td>NCEP ATP III</td>
<td>27.5%</td>
</tr>
<tr>
<td>Elmslie 2009</td>
<td>NCEP ATP III</td>
<td>50.0%</td>
</tr>
<tr>
<td>Chang 2009</td>
<td>IDF 2005</td>
<td>33.9%</td>
</tr>
<tr>
<td>John 2009</td>
<td>IDF</td>
<td>67.0%</td>
</tr>
</tbody>
</table>
Pharmacotherapy: Acute Episode

• *FDA-Approved treatments*
  
  Quietipine Fumarate
  Olanzapine/fluoxetine combination
  Lurasidone

• *Non-FDA Approved treatments*
  
  Anti-depressants
  Lamotrigine
  Lithium carbonate
Initial Treatment of Bipolar Disorders in the United States (N = 7760)

Antidepressant monotherapy twice as common as mood stabilisers

Mood stabilisers: lithium, valproate, carbamazepine, gabapentin, lamotrigine, oxcarbazepine, topiramate, levetiracetam, and zonisamide.

Quetiapine IR and XR Trials

- Double Blind Placebo controlled 8-weeks
- MADRS used as primary outcome measure
- 58% improvement in mean MADRS scores.
- Well-tolerated
Olanazepine/Fluoxetine combination

- 3 Double blind placebo controlled (8-Weeks)
- All three studies were positive
- It is combination drug therapy
- Weight gain was observed more than placebo
Do Antidepressants Work in Bipolar Depression?

- **STEP-BD 26-week study**
  - Mood stabilizer (MS) + AD vs MS + placebo (PBO)
  - Bupropion or paroxetine
- **16-week outcome**
  - DR = 8 weeks euthymia
  - Transient remission (1-7 weeks euthymic)
  - Treatment effective response = 50% improvement in depression without switch

**Graph:**
- **Participants (%):** Durable Recovery, Remit, Response
- **Legend:**
  - MS + AD (n = 179)
  - MS + PBO (n = 187)

**References:**
Bipolar Patients Receiving TCA or MAO-I Alone

- Switch rate 31%-70%
  - Prien 1973, 1984
  - Akiskal 1977, 1979
  - Wehr & Goodwin, 1979
  - Quitkin, 1981
  - Pickar, 1984
Switch Risk: BP I Greater Than BP II

<table>
<thead>
<tr>
<th></th>
<th>All BP I</th>
<th>All BP II</th>
<th>All BP I</th>
<th>All BP II</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With Mood Elevation</td>
<td>19.4*</td>
<td>12.5</td>
<td>12†</td>
<td>2</td>
</tr>
<tr>
<td>With AD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


*P<0.05; †P<0.04.
### Guidelines for Short-Term Treatment of Bipolar Depression

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy vs Combination Therapy</th>
<th>First-Line Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AD</td>
</tr>
<tr>
<td>APA 2002 (Hirschfeld)</td>
<td>M</td>
<td>✓</td>
</tr>
<tr>
<td>Expert Guidelines 2004 (Keck)</td>
<td>M or C</td>
<td>✓</td>
</tr>
<tr>
<td>Australian &amp; New Zealand 2004 (Mitchell)</td>
<td>M</td>
<td>✓</td>
</tr>
<tr>
<td>NICE 2006</td>
<td>C</td>
<td>✓</td>
</tr>
<tr>
<td>Texas MAP 2007 (Suppes)</td>
<td>M</td>
<td>✓</td>
</tr>
<tr>
<td>International Consensus 2008 (Kasper)</td>
<td>M</td>
<td>✓</td>
</tr>
<tr>
<td>CANMAT 2009 (Yatham)</td>
<td>M or C</td>
<td>✓†</td>
</tr>
<tr>
<td>BAP 2009 (Goodwin)</td>
<td>M or C</td>
<td>✓†</td>
</tr>
</tbody>
</table>

AA, atypical antipsychotic; AD, antidepressant; QTP, quetiapine; Li, lithium; LTG, lamotrigine; DVP, divalproex.

*Adjunct to antimanic agent that is not an antipsychotic.
†Adjunct therapy.
‡Adjunct to an antimanic agent in patients with a history of mania.
Long-Term Maintenance: Treatment of Bipolar Disorder
MADRS Response* Rates Across 6 Lamotrigine Multicentre Acute Bipolar Depression Studies

*Response: 50% improvement over baseline. Pooled relative risk of response: 1.22; CI: 1.06-1.41; P = 0.005.

Atypical Antipsychotics in Bipolar Depression: Response Rates

OFC, olanzapine/fluoxetine combination.
*P<0.05; †P<0.001 vs placebo.
Lurasidone Adjunctive Therapy for Bipolar I Depression

Loebel A et al. Poster presented at: 165th Annual APA Meeting; May 5-9, 2012; Philadelphia, PA.

- Mean daily dose of lurasidone: 66.3 mg (90% of subjects were treated with a daily dose ≥60 mg)
Frequency of Side Effects: Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Aripiprazole</th>
<th>Clozapine</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Risperidone</th>
<th>Ziprasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapyramidal symptoms</td>
<td>± to +</td>
<td>±</td>
<td>± to + *</td>
<td>±</td>
<td>± to + *</td>
<td>± to + *</td>
</tr>
<tr>
<td>Decrease in orthostatic blood pressure</td>
<td>±</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>±</td>
</tr>
</tbody>
</table>

* = dose related; ± = no to minimal, + = occasional, ++ = frequent, +++ = substantial occurrence of side effect compared with placebo rates.
**Summary of Currently Available Tolerability and Safety Data for Maintenance Treatment of Bipolar Disorder**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>Tremor, polydypsia, polyuria, hypothyroidism</td>
</tr>
<tr>
<td>Valproate</td>
<td>Weight gain, teratogeny</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Rash, drug interactions</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Rash</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Weight gain, sedation, agranulocytosis, metabolic syndrome</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Extrapyramidal symptoms, hyperprolactinaemia</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Weight gain, sedation, metabolic syndrome</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Sedation, weight gain</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Akathisia</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Akathisia</td>
</tr>
</tbody>
</table>

Modafinil for Bipolar Depression


Change in Score From Baseline

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Modafinil (n = 41)</th>
<th>Placebo (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>-2</td>
<td>-2</td>
</tr>
<tr>
<td>1</td>
<td>-4</td>
<td>-4</td>
</tr>
<tr>
<td>2</td>
<td>-6</td>
<td>-6</td>
</tr>
<tr>
<td>3</td>
<td>-8</td>
<td>-8</td>
</tr>
<tr>
<td>4</td>
<td>-10</td>
<td>-10</td>
</tr>
<tr>
<td>5</td>
<td>-12</td>
<td>-12</td>
</tr>
<tr>
<td>6</td>
<td>-14</td>
<td>-14</td>
</tr>
<tr>
<td>7</td>
<td>-16</td>
<td>-16</td>
</tr>
<tr>
<td>8</td>
<td>-18</td>
<td>-18</td>
</tr>
</tbody>
</table>

*P ≤ 0.05*

*P ≤ 0.01*

*P = 0.07*
Bipolar Disorder: Psychotherapies

Supportive Therapy
Cognitive behavioral therapy
Interpersonal psychotherapy
Family therapy
Psychodynamic psychotherapy
Problem solving therapy
Group therapy
Intensive Psychotherapies for Bipolar Depression vs CC

- N = 293 bipolar depressed outpatients
- Protocol meds + 9 mos:
  - FFT (family-focused therapy)
  - IPSRT (interpersonal and social rhythm therapy)
  - CBT (cognitive behavior therapy)
  - CC (collaborative care)
- Intensive psychotherapies
  - Higher recovery rate
  - Shorter time to recovery
  - 1.6x more likely to be clinically well during any study month

Symptomatic Days Over 5 Years With Psychoeducation

Conclusions

• Long-term maintenance treatment is necessary to achieve optimal response and to prevent further episodes and functional impairment

• Several compounds, including lithium, some anticonvulsants, and most atypical antipsychotics, have proven long-term efficacy

• In the real world, most patients may need a combination of 2 or more drugs and psychoeducation

• The combination of evidence-based pharmacotherapy and psychoeducation for patients and caregivers is efficacious and cost-effective