Sleep Issues in the Bipolar Patient

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Overview

1. Rationale
2. Bipolar Disorder (BD) Background
3. Case Presentation
4. Circadian View of BD
5. Interaction between BD and Sleep
6. Implications for Management
7. Case Concludes
Why are we talking about this?

1. Sleep disturbance is a feature of all phases of BD.
2. On-going sleep disturbance indicates vulnerability to relapse in BD.
3. BD likely has a circadian basis as it has a cyclical course and is influenced by light, dark, and season.
Why are we talking about this?

1. BD is **prevalent**
   a) BD Types I and II: 1.3-2.1%

2. BD is **lifelong**
   a) Average onset = 21 yoa

3. BD is **impairing**
   a. 60% pts- chronic interpersonal & occupational problems & subclinical sx b/t acute episodes

4. BD is **lethal**
   a) Rate of completed suicide 10-15%

Table 2. Diagnostic Criteria for a Manic Episode

Source. Adapted from DSM-IV-TR; manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, ECT, light therapy) should not count toward a diagnosis of bipolar I disorder.

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

1) Inflated self-esteem or grandiosity
2) Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
3) More talkative than usual or pressure to keep talking
4) Flight of ideas or subjective experience that thoughts are racing
5) Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
6) Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
7) Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The symptoms do not meet criteria for a mixed episode.

D. The mood disturbance 1) is sufficiently severe to cause marked impairment in occupational functioning, usual social activities, or relationships with others, 2) necessitates hospitalization to prevent harm to self or others, or 3) has psychotic features.

E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).
Course of Bipolar Disorder

• 3-years of follow-up of 138 pts with BD I & II
• Pts spent approximately **half** this time in varying mood states
  o Majority of this time occupied by minor and subsyndromal symptoms

Joffe RT et al, A prospective, longitudinal study of percentage of time spent ill in patients with bipolar I or II disorder, Bipolar Disorders, 2004.
The number of American children and adolescents treated for bipolar disorder increased 40-fold from 1994 to 2003, researchers report today in the most comprehensive study of the controversial diagnosis.

Experts say the number has almost certainly risen further since 2003.

Many experts theorize that the jump reflects that doctors are more aggressively applying the diagnosis to children, and not that the incidence of the disorder has increased.
Misperceptions about Bipolar Disorder

• Good movie
• **Not** an accurate depiction of BD
• BD is not ‘mood swings’
• BD is not angry or violent outbursts
Portrayals of Bipolar Disorder

• Good book
• *Better* depiction of BD

• Formerly underdiagnosed
• Currently overdiagnosed?
• Possible role of FDA-drug approvals
Case

48 yo female admitted to inpt psych unit

• Severe depression, marital problems
• **Insomnia** precipitated inpt admission
• Numerous past suicide attempts
• PMH: obesity, GERD, HTN, migraines, Etoh in remission
• PSH: s/p appy, CCY, T&A, partial hysterectomy
• Stabilized while inpt
• Carbamazepine, Haldol, **Amitriptyline** (50 mg), Lamotrigine
• Insomnia= trigger for relapse in pt
• Referred to Sleep Clinic
Case- Sleep Evaluation

48 yo female Bipolar I

• Chief complaint: Insomnia
  o In bed 9:30-10p, difficulty initiating sleep
  o Takes Benadryl, 25 mg, 1 hr prior to bed
  o “Mind races”; feels more awake once in bed
  o Feels only sleeps 3 hrs, daytime fatigue
  o Naps 2x/week for 45 min
  o Hit parked car in early a.m.

• Sleep ROS
  o Loud snoring- sometimes awoken by own snoring
  o Morning headaches, no witnessed apneas
  o Denies RLS (concern with antipsychotic)
Case- Sleep Evaluation

48 yo female Bipolar I

• Physical Exam
  • BMI 35.5, Mallampati IV

• Assessment
  • Insomnia- residual anxiety and depression, negative conditioning, napping/nighttime computer use
  • Risk factors for OSA
  • Some element of Delayed Sleep Phase Syndrome?

• What would you do?
Circadian Rhythm

• "Any biological process that displays an endogenous, entrainable oscillation of about 24 hours." (Wikipedia)
  o Physical, mental, and behavioral components
  o Linked to light and dark in environment
Circadian View of Mood Disorders

Lines of Evidence:
1. Sensitivity to Effects of Light
2. Alterations in Melatonin
3. Response to Lithium
4. Effects of Social ‘Zeitgebers'
Sensitivity to Light

- Case series: 9 women with bipolar depression
- Bright Light Therapy in a.m.
  - 3/4 mixed states (depression + mania)
  - 1/4 improved mood
- Bright Light Therapy (BLT) at midday
  - 4/5 improved mood
- BLT: antidepressant effects
  - May also induce mania

Alterations in Melatonin

• Phase delay in Bipolar subjects
• Bipolar subjects $\Rightarrow$ evening types
  – Lower score on Composite Scale of Morningness
  – Stable trait- subset followed for 2 yrs
  – Current depression severity correlated with increased ‘eveningness’ as well

Alterations in Melatonin: Seasonality

• **Seasonal Affective Disorder**
  – 15-25% in general population (Axelsson et al, 2002)
  – 4:1 female:male ratio (Rosenthal, 1993)

• **MDD**
  – 12-22% pts have marked seasonality

• **Bipolar Disorder**
  – 78-88% pts have marked seasonality
Response to Lithium

• Lithium lengthens circadian period
  – Slows down circadian cycling (Abe M et al, Neuroreport 2000)
  – Mechanism unknown- Glycogen Synthetase Kinase 3β (GSK3) dysregulation possible

• Case series: 7 rapid-cycling BD pts
  – 5 with ‘fast’ circadian rhythm
  – Lithium slowed rhythm in these subjects (Kripke DF et al, Biol Psychiatry 1978)
Effects of Social ‘Zeitgebers’

• Core Concept of ‘Interpersonal and Social Rhythm Therapy’ (IPSRT)
  – Life event- negative or positive- disrupts customary routines that queue daily timing of energy, activity, and sleep patterns
  • Change in mealtimes, socialization, bedtimes

Frank E et al, Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. Arch Gen Psychiatry, 2005.
Social Zeitgeber Hypothesis

Interaction between BD and Sleep

1. ↓ Sleep = Feature of Bipolar Disorder
2. ↓ Sleep = Precipitant to Mania
3. Total Sleep Time (TST)
   a. Marker of Treatment Response
1. Decreased Sleep in Mania

- Review by Harvey (American Journal of Psychiatry, 2008)
  - Reduced need for sleep: 69-99%
  - 6/6 studies reported this
  - 4/6 studies: ≥90% subjects had decreased sleep
Decreased Sleep in Mania

- Decreased *Need for Sleep* = Hallmark of Mania
  - Patients maintain sufficient (often excessive) energy with reduced sleep
    - In contrast to insomnia
  - In present age, patients do not die from prolonged sleeplessness during manic episodes
2. Decreased Sleep = Precipitant to Mania

• Review of 73 reports of prodromal symptoms of BD and unipolar depression/mania
  – In BD, sleep disturbance = *most common* prodrome of mania

## Development of Mania in Depression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to either hypomania or mania</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated or expansive mood</td>
<td>1.35</td>
<td>0.78—2.33</td>
<td>0.28</td>
</tr>
<tr>
<td>Decreased need for sleep</td>
<td>3.07</td>
<td>1.78—5.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unusually energetic</td>
<td>2.71</td>
<td>1.72—4.26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Increase in goal-directed activity</td>
<td>2.29</td>
<td>1.43—3.66</td>
<td>0.0005</td>
</tr>
<tr>
<td>Grandiosity</td>
<td>1.73</td>
<td>0.92—3.22</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Time to mania</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated or expansive mood</td>
<td>1.64</td>
<td>0.73—3.71</td>
<td>0.23</td>
</tr>
<tr>
<td>Decreased need for sleep</td>
<td>3.37</td>
<td>1.49—7.61</td>
<td>0.003</td>
</tr>
<tr>
<td>Unusually energetic</td>
<td>3.49</td>
<td>1.78—6.83</td>
<td>0.003</td>
</tr>
<tr>
<td>Increase in goal-directed activity</td>
<td>2.91</td>
<td>1.46—5.80</td>
<td>0.003</td>
</tr>
<tr>
<td>Grandiosity</td>
<td>3.68</td>
<td>1.70—7.97</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Fiedorowicz J et al, Subthreshold Hypomanic Symptoms in Progression from Unipolar Major Depression to Bipolar Disorder, American J Psych, 2011.
Sleep Reduction → Mania

• Total Sleep Deprivation in depressed BD pts
  – Intentional, prospective, 206 patients
  – 4.85% → mania
  – 5.83% → hypomania

Colombo C et al, Rate of switch from depression into mania after therapeutic sleep deprivation in bipolar depression. Psychiatry Res 1999
Decreased Sleep in Mania

Final Common Pathway

• Sleep reduction, regardless of cause, necessary for development of mania
  – Proposed by Wehr
• Plausible, persuasive
• Hard to discern cause and effect
• Medications, substance use?
3. Total Sleep Time ➔ Treatment Response

• Sleep may be a therapeutic target in mania

  – 16 hospitalized manic patients: enforced darkness– dark therapy– for 14 hours/day
  – Faster decrease in manic symptoms
  – Shorter hospital stays and lower doses of anti-manic medications in hospitalized manic patients

Total Sleep Time $\rightarrow$ Treatment Response

- Sleep may be a therapeutic target in mania
  - Melatonin
    - 11 hospitalized patients with medication-resistant mania
    - Decreased sleep NOT improved with benzodiazepines
    - 30 days on MLT $\rightarrow$ substantial improvement in mania and *increase in reported sleep*

Bersani et al, Melatonin add-on in manic patients with treatment resistant insomnia. Prog Neuropsychopharmacol Biol Psychiatry 2000
Implications for Management of Bipolar Disorder

• Rationale for strategies that impact sleep
  – ‘Final Common Pathway’
  – Treat depression and mania and prevent relapse

1. Medications
2. Therapy/behavioral interventions
3. Co-morbid conditions
Implications for Management

• Medications
  – Sedation is effective in treatment of acute mania, though it is unclear if increase in TST is mechanism
    • Benzodiazepines
    • Antipsychotics
    • Melatonin
Therapy for Bipolar Disorder

• Interpersonal Social Rhythm Therapy
  – Based on Social Zeitgeber Hypothesis
  – Aims to minimize mood episodes by maintaining regular sleep-wake schedule and controlling exposure to stimulating activities and situations
# Social Rhythm Metric

## Directions:
- Write the **ideal** target time you would **like** to do these daily activities.
- Record the **time** you actually did the activity each day.
- Record the **people** involved in the activity: 0 = Alone; 1 = Others present; 2 = Others actively involved; 3 = Others very stimulating

<table>
<thead>
<tr>
<th>Activity</th>
<th>Target Time</th>
<th>Sunday</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time</td>
<td>People</td>
<td>Time</td>
<td>People</td>
<td>Time</td>
<td>People</td>
<td>Time</td>
<td>People</td>
</tr>
<tr>
<td>Out of bed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First contact with other person</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Start work/school/volunteer/family care</td>
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<td></td>
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<td></td>
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<tr>
<td>Dinner</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>To bed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate MOOD each day from −5 to +5</td>
<td>−5 = very depressed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Efficacy of IPSRT

Table 2. Time to First Affective Episode in the Maintenance Phase as a Function of Acute Treatment Assignment: Survival Model After Stepwise Selection Procedure*

<table>
<thead>
<tr>
<th>Effect</th>
<th>Parameter Estimate ± SE</th>
<th>Hazard Ratio</th>
<th>z</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute-phase IPSRT</td>
<td>-1.09 ± 0.42</td>
<td>0.34</td>
<td>-2.58</td>
<td>.01</td>
</tr>
<tr>
<td>Acute-phase IPSRT: anxiety disorder</td>
<td>1.72 ± 0.62</td>
<td>5.61</td>
<td>2.76</td>
<td>.006</td>
</tr>
<tr>
<td>ICM: anxiety disorder</td>
<td>0.06 ± 0.64</td>
<td>1.06</td>
<td>0.09</td>
<td>.93</td>
</tr>
<tr>
<td>Acute-phase IPSRT: inactive medical comorbidities</td>
<td>0.33 ± 0.13</td>
<td>1.39</td>
<td>2.62</td>
<td>.009</td>
</tr>
<tr>
<td>ICM: inactive medical comorbidities</td>
<td>-0.18 ± 0.12</td>
<td>0.84</td>
<td>-1.50</td>
<td>.13</td>
</tr>
<tr>
<td>Active medical comorbidities</td>
<td>0.11 ± 0.07</td>
<td>1.12</td>
<td>1.66</td>
<td>.10</td>
</tr>
<tr>
<td>Married</td>
<td>-1.40 ± 0.39</td>
<td>0.25</td>
<td>-3.58</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Index episode manic</td>
<td>0.34 ± 0.35</td>
<td>1.40</td>
<td>0.95</td>
<td>.34</td>
</tr>
<tr>
<td>Index episode mixed</td>
<td>1.14 ± 0.38</td>
<td>3.11</td>
<td>3.02</td>
<td>.003</td>
</tr>
</tbody>
</table>

Abbreviations: ICM, intensive clinical management; IPSRT, interpersonal and social rhythm therapy.

*Model fit, $R^2 = 0.23$; likelihood ratio test, $\chi^2 = 32.3$; $df = 9$; $P<.001$. 

Frank E et al, Two-Year Outcomes for Interpersonal and Social Rhythm Therapy in Individuals With Bipolar I Disorder. Arch Gen Psychiatry 2005
Implications for Management

• Co-morbid Conditions
  – Any condition that fragments sleep or decreases sleep time may disrupt mood stability
    • OSA
    • RLS
    • Insomnia
OSA in Bipolar Disorder

• Paucity of research
• Phone survey
  – Respondents with moderate or severe daytime sleepiness were more likely to have co-occurrence of OSA and BD
  – No info on prevalence of OSA in BD, or vice-versa

Ohayon MM et al, How sleep and mental disorders are related to complaints of daytime sleepiness. Arch Intern Med 1997
OSA and Bipolar Disorder

• 72 patients with remitted BD I
  – All overweight (BMI ≥ 25)
  – Berlin Questionnaire
  – 54.1% at high-risk of OSA
  – High-risk subjects: higher scores for manic and depressive symptoms

Weight Gain and BD

• Google search for ‘Zyproxa side effects’

• Atypical antipsychotics - notorious for weight gain

• May mediate increased risk of OSA

Metabolic syndrome (Syndrome X)
- Central obesity
- High blood pressure
- High triglycerides
- Low HDL-cholesterol
- Insulin resistance
RLS in Bipolar Disorder

• Again, little data
• Case reports of atypical antipsychotics causing RLS, i.e. Seroquel, Zyprexa
• All antipsychotics that are effective anti-manic agents have some degree of dopamine antagonism
  – May cause/worsen RLS
Insomnia in Bipolar Disorder

• Cognitive Behavioral Therapy for Insomnia
  1. Stimulus Control Therapy
  2. Sleep Restriction Therapy
  3. Relaxation Training
  4. Cognitive Therapy
  5. Sleep Hygiene Education
Insomnia in Bipolar Disorder

• Sleep Restriction Therapy
  • Decreases time spent in bed to time that patient actually sleeps
  • Typically results in some degree of sleep deprivation
  • Could trigger mania
  • Tread lightly, i.e. avoid restriction to less than 6.5 hrs/night
Conclusion to Case

• Findings
  o Moderate OSA: AHI 13.8, O2 nadir 81%
    o REM-dominant
    o Sleep efficiency: 96.8%; no SWS

• Treatment
  o CPAP initiated, chinstrap later
  o Stimulus Control, Sleep Hygiene
  o Consistent wake-up time
  o Trial of Doxepin
Conclusion to Case

• **Outcome**
  - **OSA**
    - Excellent adherence to CPAP
  - **Insomnia**
    - Much improved
    - Transient, stress-related flares
  - **Mood Stability**
    - Fewer inpt admissions
Review

• BD is often misunderstood
• Sleep disturbance = core feature of BD
• Sleep disturbance → bipolar pathology
  – Bidirectional relationship
• Circadian perturbations likely intrinsic to BD
• Stabilizing sleep can decrease symptoms
• Stabilizing sleep can prevent relapse
• IPSRT can prevent recurrences of mood episodes