Manic episodes and drug abuse – diagnosis and treatment

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Bi-polar spectrum disorders and addiction often co-occur
They are reciprocal risk factors
Subjects falling in the bipolar spectrum have increased risk for substance abuse and move towards addiction
Frequently misdiagnosed especially in milder forms
The use of opioid agonists in heroin addicts with bipolar disorder has proved to be mood stabilizing and with combined mood stabilizing drugs it reaches best therapeutic effects
Cocaine Abuse and Bipolar Spectrum

- Specific relationship between bi-polar disorder and stimulant abuse
- It has been assumed that cocaine use is intended to optimize hyperthymia, hypomania, cyclothymia.
- It is frequently co-morbid with heroin addiction
- A study on 1090 heroin addicts in treatment between 1994-2005, aged 29+-6, 76% males showed a link between current cocaine abuse and double pathology, with special relevance to the bipolar spectrum, and psychotic disorders
- Possible model linking bipolarity and cocaine
- Sub-threshold bi-polarity seems to predispose to heroin addiction
Cocaine Abuse and Bipolar Spectrum

- Craving for the suppressed hypomania could lead to cocaine abuse
- Unmasking of frank bipolar disorder- mixed states, severe mania, and psychotic states
- Further research needed

SUD AND YOUTH ONSET BIPOLAR DISORDER

- Co-morbid bipolar disorder and cannabis use is well known among adults
- Youth-onset bi-polar disorder confers higher risk of SUD compared with adults
- Bipolar disorder precede SUD in 55-83% of cases
- Opportunity for prevention: screening for SUD in bipolar youth since the age of 10
- Education and family intervention
- Preventive intervention has been found successful
Study conducted on 211 offspring aged 12> with one BD parent
Lifetime SUD in 24% offspring
Cannabis use the most common
Peak hazard of SUD 14-20 years of age
Male sex, previous mood disorder, parental history of SUD contributed to the risk of SUD in the offspring
SUD predicted increased risk of psychosis
The estimated hazard of a major psychosis in SUD youth was 3 fold
Clinical outcomes in BD patients with cannabis use

- The study compared clinical outcomes and neuro-cognitive functions of BD I patients with and without cannabis use
- RETROSPECTIVE STUDY OF A LARGE COHORT-200 PATIENTS
- The Cannabis group had more males, and a higher proportion of psychosis
- Interestingly they showed better neuro-cognitive performance but poorer prognosis

Alcohol and Cannabis use and age of onset of BD

- Cannabis use coincided with previous manic or hypo-manic episodes while alcohol with previous depressive episodes
- Cannabis use is also associated with the development of manic symptoms and lifetime cannabis use is associated with 5 fold increase in BD.
- Patients with alcohol use had a significant later onset of BD and were similar to non-users.
- Family history of affective or psychotic disorders was higher in cannabis users
Alcohol and Cannabis use and age of onset of BD

- Alcohol users had lower rates of other substances abuse than cannabis users.
- In cannabis users the use of cannabis generally preceded the onset of BD while in alcohol users the opposite was true.
- Early onset of BD is associated with higher risk for cannabis use.
- There seems to exist a common genetic pathway for cannabis use and BD.

Bipolar disorders are frequently associated with SUDs.

Therapeutic efficacy may differ due to the presence of SUD.

THE NEED TO PROVIDE GUIDANCE TO CLINICIANS

First choice recommendations were possible only for alcohol, cannabis, and cocaine with bipolar disorder.

Psychotherapies were considered an essential component of the overall treatment of comorbid SUD and Bipolar Disorder.

Michael’s Case: Introduction

- 22-year-old man, in good general physical health
- Presents with a 7-10 day history of decreased need for sleep (5 hours), restlessness, and difficulty concentrating
- In office, found to be somewhat agitated, impatient, rude (unusual for him)
- No current medications
- Drinks alcohol socially; occasional THC use
- Usually gets along well with others, has no history of impulsivity and has a steady circle of friends.
- 2 years ago had an episode of depression that lasted for 3 months, with no apparent precipitating event
- Family history: alcoholic father with history of depression, impulsivity, grandiosity, and aggression
What supplemental information would you ask for at this stage?

- How bad is your sleep?
- How low has your mood become?
- Any suicidal ideations?
- How bad is your concentration/attention?
- Is your mood variable throughout the day?

- Investigate both the depression and the mania
- Substance abuse – has patient’s THC consumption increased?
- Assess functionality
- Evaluate if they can maintain a relationship
- Look at environmental stressors
- Check thyroid

Scientific Committee. 2010.
• Psychotic symptoms are common in bipolar disorder
  o 58% by clinical evaluation
  o 90% by self-report
  o More common in mania than in depression
Misdiagnosis of Bipolar Disorder

- Patients were incorrectly diagnosed with:
  - Unipolar depression 60%
  - Anxiety disorders 26%
  - Schizophrenia 18%
  - Borderline or antisocial PD 17%
  - Alcohol abuse/dependence 14%

35% were symptomatic for more than 10 years before correct diagnosis

Medical Comorbidities of Bipolar Disorder

- Current alcohol abuse (n = 2154) 11.8%
- Past alcohol abuse (n = 2154) 32.2%
- Smoking (n = 1000) 31.2%
- Past drug abuse (n = 2154) 21.7%
- Current drug abuse (n = 2154) 7.3%
- Anxiety disorders (n = 1000) 31.9%
- ADHD (n = 1000) 9.5%

Medical Comorbidities of Bipolar Disorder

- **Neuroendocrine abnormalities**
  - Affect on corticotropin-releasing hormone (CRH), cortisol levels, and glucocorticoid receptor (GR) function

- **Cardiovascular disease**
  - Patients display an increase in cardiovascular risk factors (smoking, diabetes, hypertension, dyslipidemia, and obesity)

- **Obesity**
  - 31-36% overweight; 26-34% obese

- **Asthma, COPD, emphysema**
  - smoking is prevalent among bipolar patients

- **Compromised immune response**
  - Dendritic cells aberrancies and decrease in lymphocytes

- **Seizure disorders**

- **Migraine headaches**

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References:

Obstacles to Management and Treatment

- Diagnostic confusion
  - Patients more likely to seek treatment for depressive than manic symptoms
- Frequent comorbid substance abuse
- Patient denial, fear of stigma, impaired insight
- Clinician’s reluctance to use stigmatizing diagnosis
- Inconsistent adherence with treatment recommendations
- Previous treatment misadventures

Double pathology including Bipolar Disorder and SUD should be treated with atypical anti-psychotics in the acute manic phase.

It is suggested to add a mood-stabilizing agent which is also effective in preventing craving for substance abuse.
<table>
<thead>
<tr>
<th>Treatment Level</th>
<th>Recommended Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line</strong></td>
<td>Lithium, divalproex, olanzapine, risperidone, quetiapine, quetiapine XR, aripiprazole, ziprasidone, lithium or divalproex + risperidone, lithium or divalproex + quetiapine, lithium or divalproex + olanzapine, lithium or divalproex + aripiprazole</td>
</tr>
<tr>
<td><strong>Second-line</strong></td>
<td>Carbamazepine, electroconvulsive therapy, lithium + divalproex, asenapine*, lithium or divalproex + asenapine, paliperidone mono-therapy</td>
</tr>
<tr>
<td><strong>Third-line</strong></td>
<td>Haloperidol, chlorpromazine, lithium or divalproex + haloperidol, lithium + carbamazepine, clozapine, oxcarbazepine, tamoxifen</td>
</tr>
<tr>
<td><strong>Not Recommended</strong></td>
<td>Mono-therapy with gabapentin, topiramate, lamotrigine, verapamil, tiagabine, risperidone + carbamazepine, olanzapine + carbamazepine</td>
</tr>
</tbody>
</table>

**Treatment Algorithm for Acute Mania**

1. Start a 1st line agent for mania
2. Appropriately dose for 2 weeks as an initial trial period
3. Monitor response
   - Continue therapy
   - Adjust dose
   - Consider switching
   - Add another agent

Alphabetical List of Medications by Generic Name

**Generic name (Trade name)**

**Atypical antipsychotics**

- aripiprazole (Abilify)
- asenapine (Saphris)
- clozapine (Clozaril)
- olanzapine (Zyprexa)
- paliperidone (Invega)
- quetiapine (Seroquel)
- risperidone (Risperdal)
- ziprasidone (Zeldox)
What Additional Issues Should be Considered?

- **Akathisia**
  - Inner restlessness associated with an urge to move
  - Risk factors: use of typical vs atypical antipsychotic agents, rapid dose escalation, higher doses, switching
  - Made worse by increased dose of antipsychotic

- **Agitation**
  - Unpleasant state of extreme arousal, increased tension, and irritability
  - Made better by increased dose of antipsychotic

- **Activation**
  - Stimulation of neural and symptomatic response

- **Anxiety**
  - Both a psychological and physiological state
  - Characterized by an unpleasant feeling; typically tension, uneasiness, fear, or worry
Significance of Weight Gain

“...Obesity has become an equal, if not greater, contributor to the burden of disease than smoking.”


Weight change in treatment-naive patients with a mood disorder

<table>
<thead>
<tr>
<th></th>
<th>Canadian Population</th>
<th>Patients’ Baseline</th>
<th>Patients 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (BMI 18&lt; 25)</td>
<td>54.30%</td>
<td>42.40%</td>
<td>30.30%</td>
</tr>
<tr>
<td>Overweight (BMI 25 -30)</td>
<td>29.3%</td>
<td>34.90%</td>
<td>41.00%</td>
</tr>
<tr>
<td>Obese (BMI &lt; 30)</td>
<td>16.4%</td>
<td>22.70%</td>
<td>28.80%</td>
</tr>
</tbody>
</table>

# Metabolic Risk of Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Diabetes Risk</th>
<th>Dyslipidemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Low</td>
<td>No effect</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Increased effect</td>
<td>Increased effect</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Low**</td>
<td>Possibly increased</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Ziprasidone*</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

** Data suggest that quetiapine, like other atypical antipsychotics such as olanzapine, can cause clinically meaningful increases in insulin resistance, which may lead to new or exacerbated cases of type 2 diabetes.

Extrapyramidal Side Effects

- Tardive dyskinesia
- Dystonic reactions
- Akathisia
- Pseudoparkinsonism

## Side Effect Profiles

<table>
<thead>
<tr>
<th></th>
<th>EPS</th>
<th>Hyperlipidemia</th>
<th>Weight Gain</th>
<th>QTc Prolongation</th>
<th>Sexual Dysfunction</th>
<th>Sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Risperidone</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ziprasidone*</td>
<td></td>
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</tbody>
</table>

EPS: extrapyramidal side effects

- **Neutral - Low risk**
- **Moderate risk**
- **High risk**

Source:
Prolactin-Related Adverse Effects

Mean Plasma Prolactin Levels After 4 to 8 Weeks of Antipsychotic Treatment

**Frequency of Adverse Event Reports by Antipsychotic**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pituitary Tumor</th>
<th>Hyperprolactinemia</th>
<th>Galactorrhea</th>
<th>Amenorrhea</th>
<th>Gynecomastia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>54</td>
<td>702</td>
<td>530</td>
<td>445</td>
<td>118</td>
<td>1247</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>11</td>
<td>37</td>
<td>17</td>
<td>21</td>
<td>23</td>
<td>93</td>
</tr>
<tr>
<td>Ziprasidone*</td>
<td>6</td>
<td>12</td>
<td>13</td>
<td>2</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1</td>
<td>13</td>
<td>12</td>
<td>3</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>4</td>
<td>16</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>First-Generation Antipsychotics</th>
<th>Second-Generation Antipsychotics</th>
<th>Third-Generation Antipsychotics</th>
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<tbody>
<tr>
<td><strong>Dopamine Antagonists</strong></td>
<td><strong>Dopamine/Serotonin Antagonists</strong></td>
<td><strong>Dopamine Partial Agonists</strong></td>
</tr>
<tr>
<td>(D_2) antagonism ((\text{High receptor affinity}))</td>
<td>(D_2) antagonism ((\text{Variable receptor affinity}))</td>
<td>High affinity for (D_2) receptors</td>
</tr>
<tr>
<td><strong>chlorpromazine</strong></td>
<td><strong>5-HT_{2A}</strong> antagonism ((\text{High receptor affinity relative to } D_2\text{ receptor affinity}))</td>
<td>(5-HT_{1A}) partial agonism ((\text{Low receptor affinity relative to } D_2\text{ receptor affinity}))</td>
</tr>
<tr>
<td><strong>haloperidol</strong></td>
<td></td>
<td>(5-HT_{2A}) antagonism ((\text{Moderate receptor affinity relative to } D_2\text{ receptor affinity}))</td>
</tr>
<tr>
<td><strong>clozapine</strong></td>
<td></td>
<td><strong>aripiprazole</strong></td>
</tr>
<tr>
<td><strong>risperidone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>olanzapine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>paliperidone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>quetiapine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
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