Addiction and Bipolar Disorder

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SCHEME

- Epidemiology
- Anxiety, and alcohol and drug abuse
- Polarity of episodes and alcohol and drug abuse
- Using and quitting alcohol and drug abuse, and relation with outcome
- Treating comorbidity
- Conclusions
Comorbid conditions: baseline data from STEP-BD

Pharmacotherapy and comorbidity in bipolar disorder

• The STEP-BD trial examined the association between comorbidity and pharmacotherapy in patients with bipolar disorder.

• A lifetime substance disorder was diagnosed in 48% of the sample; however, only 0.4% were receiving substance abuse-specific medications.

• Use of ‘comorbidity-specific’ pharmacotherapy for anxiety disorders, substance use disorders, and attention deficit disorder was limited, suggesting comorbidity in bipolar disorder may be under-treated.

SUD, substance use disorder; UD, use disorder

Alcohol abuse and gender in bipolar disorder

- Alcohol abuse was more prevalent in bipolar men than women at 49% vs 29%, respectively.

- Relative risk for alcohol abuse compared with the general population was higher in bipolar women than men, with odds ratios of 7.35 vs 2.77, respectively.

Substance abuse in Mania: EMBLEM study data

- **Alcohol (25%)**
  - More compulsory admissions
  - More rapid cycling
  - More abuse of other substances

- **Cannabis (14%)**
  - Greater severity
  - More psychosis
  - More hospitalizations
  - More compulsory admissions
  - More abuse of alcohol and other substances
  - More first episodes

Clinical characteristics of bipolar patients with versus those without substance and/or alcohol abuse

- More mixed episodes and rapid cycling
- Slower recovery
- More hospitalisations
- Earlier age of onset
- More suicide attempts
- Increased aggressivity/criminality
- Poor treatment adherence: 75% of non adherent patients were substance users (González-Pinto et al, 2006)

Keller MB, et al. JAMA 1986;
Vieta E, et al. Bipolar Disord 2001;
González-Pinto et al., Bipolar Disord 2006
Effect of compliance to lithium prophylaxis on bipolar disorder

• Up to 10 years of lithium prophylaxis demonstrated a 5.2-fold greater risk of suicide attempts among patients with poor compliance vs those compliant with treatment.

• Non-adherence was significantly associated with:
  – Being male
  – Being unmarried
  – Having a history of comorbid substance use
  – Having breakthrough episodes
  – Having psychiatric hospitalisation

• At 10 years, poor treatment compliance was significantly associated with risk of suicidal acts (p=0.016)

Gonzalez-Pinto A, et al. Bipolar Disord 2006;8:618-624
### Predictors of suicide in patients with affective psychosis

- The characteristics associated with suicide attempts in first-episode patients with psychosis were assessed over 5 years.

<table>
<thead>
<tr>
<th>Suicide attempts</th>
<th>p-value</th>
<th>OR</th>
<th>95% confidence interval</th>
<th>Inferior</th>
<th>Superior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>ns</td>
<td>0.857</td>
<td>0.129</td>
<td>5.674</td>
<td></td>
</tr>
<tr>
<td>Previous suicide attempts</td>
<td>ns</td>
<td>5.236</td>
<td>0.660</td>
<td>41.527</td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>ns</td>
<td>1.307</td>
<td>0.225</td>
<td>7.606</td>
<td></td>
</tr>
<tr>
<td>Tobacco abuse</td>
<td>ns</td>
<td>0.229</td>
<td>0.032</td>
<td>7.654</td>
<td></td>
</tr>
<tr>
<td>Cannabis abuse</td>
<td>ns</td>
<td>0.532</td>
<td>0.063</td>
<td>4.463</td>
<td></td>
</tr>
<tr>
<td>Stimulant abuse</td>
<td>&lt;0.05</td>
<td>7.239</td>
<td>1.412</td>
<td>37.107</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.05</td>
<td>0.884</td>
<td>0.790</td>
<td>0.989</td>
<td></td>
</tr>
</tbody>
</table>

- A total of 14.5% patients had suicidal behaviour; 2.4% died by suicide.
  - 8-fold higher risk among patients with baseline stimulant abuse.

Reasons for comorbidity between bipolar disorder and substance abuse

- Genetic diathesis
- Genetic diathesis with a common mediator (anxiety)
- Common neurobiological mechanisms (dopamine, etc.)
- Overlap of diagnostic criteria
- Social diathesis
- Self-medication
- Treatment side-effects
- Induction of mania or depression by substances

Vieta E, presented at the IX Symposium on Bipolar Disorders, Barcelona, Spain, January
Comorbid anxiety disorders in bipolar patients with alcohol and substance use

- Anxiety disorders are more common in bipolar disorder patients with alcohol abuse vs patients with cocaine abuse\(^2\)
- Patients with early onset anxiety disorders have an increased lifetime prevalence of bipolar disorder\(^3\)

Prevalence and correlates of bipolar I disorder among adults with primary youth-onset anxiety disorders

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Received 27 December 2006; received in revised form 24 January 2007; accepted 24 January 2007

Comorbid disorders in patients with bipolar disorder and concomitant substance dependence

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Received 26 July 2006; received in revised form 9 December 2006; accepted 4 January 2007

Alcoholism and anxiety in bipolar illness: Differential lifetime anxiety comorbidity in bipolar I women with and without alcoholism

Eric Levander a, Mark A. Frye a,*, Susan McElroy b, Trisha Suppes c, Heinz Grunze d, Willem A. Nolen d, Ralph Kapka e, Paul E. Keck Jr. f, Gabriele S. Leverich g, Lori L. Althuker a, Sun Hwang a, Jim Mintz b, Robert M. Post f

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Received 9 September 2006; received in revised form 14 November 2006; accepted 28 November 2006
Available online 23 January 2007

Objective: Substance dependence is common in bipolar disorder and is associated with an increase in Axis I and II comorbidity. Little research has compared the relative rates of comorbidity among bipolar patients with dependence on different substances.
Table 2
Lifetime prevalence of bipolar I disorder among adult males and females with versus without primary youth-onset anxiety disorders

<table>
<thead>
<tr>
<th></th>
<th>Subjects with lifetime bipolar I disorder, N (%)</th>
<th>χ²</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predictor variable present</td>
<td>Predictor variable absent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>91/572</td>
<td>15.9</td>
<td>488/17,946</td>
</tr>
<tr>
<td>Social phobia</td>
<td>74/513</td>
<td>14.4</td>
<td>505/18,005</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>17/62</td>
<td>27.4</td>
<td>562/18,456</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>18/51</td>
<td>35.3</td>
<td>561/18,467</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>138/9999</td>
<td>13.8</td>
<td>694/23,576</td>
</tr>
<tr>
<td>Social phobia</td>
<td>118/873</td>
<td>13.5</td>
<td>714/23,702</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>20/122</td>
<td>16.4</td>
<td>812/24,453</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>29/127</td>
<td>22.8</td>
<td>803/24,448</td>
</tr>
</tbody>
</table>

⁵ CI = confidence interval.

b p<0.001.
Antidepressant-induced mania in bipolar patients with substance misuse

• Patients with bipolar disorder were interviewed to investigate the relationship between psychoactive substance use and mania

<table>
<thead>
<tr>
<th>Variable</th>
<th>Present</th>
<th>Absent</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>12/21 (57.1)</td>
<td>19/32 (59.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Age at illness onset, mean years (SD)</td>
<td>20.7 (11.9)</td>
<td>18.1 (8.8)</td>
<td>0.532</td>
</tr>
<tr>
<td>Comorbid substance abuse/dependence, n (%)</td>
<td>12/20 (60.0)</td>
<td>5/28 (17.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Depressed polarity at first episode, n (%)</td>
<td>19/20 (95.0)</td>
<td>22/27 (81.4)</td>
<td>0.221</td>
</tr>
<tr>
<td>Bipolar II, n (%)</td>
<td>8/19 (42.1)</td>
<td>10/25 (40.0)</td>
<td>0.887</td>
</tr>
<tr>
<td>Antidepressant trials/year, estimated mean (SD)</td>
<td>0.20 (0.14)</td>
<td>0.12 (0.10)</td>
<td>0.041</td>
</tr>
<tr>
<td>Bipolar family history, n (%)</td>
<td>10/18 (56)</td>
<td>10/22 (46)</td>
<td>0.525</td>
</tr>
</tbody>
</table>

• Patients with a history of substance abuse and/or dependence had a significantly greater risk of mania than those with no such history (OR=6.99, p=0.007)

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A new specifier: Predominant polarity

- **Depressive polarity**
  - 60% bipolar patients
  - More bipolar II
  - More depressive onset
  - More seasonal pattern
  - More suicide attempts
  - Better long-term response to lamotrigine
  - More antidepressant use

- **Manic polarity**
  - 40% bipolar patients
  - More bipolar I
  - More manic onset
  - Younger and earlier onset
  - More substance misuse
  - Better long-term response to atypical antipsychotics

Polarity is also related to treatment
Ten years follow-up of 169 bipolar patients.

Depressive polarity:

- More relapses.
- More hospitalizations.
- More suicide attempts.
- More difficulties in quitting.

González-Pinto y cols., J Affect Dis 2009
Alcohol abuse

González-Pinto y cols., J Affect Dis (2009)
LONG TERM IMPROVEMENT AFTER CANNABIS WITHDRAWAL

Fig. 1. Global Assessment of Functioning (GAF) Outcome by Cannabis Use Group.

Fig. 3. Positive and Negative Symptoms Scale (PANSS) Negative Outcome by Cannabis Use Group.

G Pinto et al. Schizophrenia Bull., 2009
Lithium for adolescent bipolar disorders with secondary substance dependency

- 25 adolescent patients with bipolar disorder and SSD received lithium or placebo
  - Randomised, double-blind, placebo-controlled pilot study
- Addiction to both alcohol and cannabis was the most frequent category of SSD
- The mean scheduled weekly serum lithium level of active responders was 0.9 mEq/L
- Lithium treatment significantly improved:
  - Psychopathology measures
  - Weekly random urine drug assays
- The mean 6-year interval between the onset of BD and onset of SDD strongly suggested that early recognition of BD may enable effective prevention of comorbid substance dependency

BD, bipolar disorder; SDD, substance dependency disorder

Add-on valproate semisodium in bipolar I disorder with alcohol abuse

- n=59, 44 male, mean age 38 years
- Recently detoxed
- BRMS 15.3, HRSD-25 20.8
- All received lithium; valproate semisodium vs placebo added for 24 weeks
- Valproate semisodium improved % heavy drinking days, drinks per heavy drinking day (HD), time to relapse

BRMS, Bech-Rafaelsen Mania Scale; HRSD-25, Hamilton Rating Scale for Depression

Both groups improved equally on mania and depression scores compared with placebo group. Divalproex (valproate) group had fewer heavy-drinking days, fewer drinks per heavy-drinking day, and fewer drinks per drinking day. Outcome was correlated with compliance. Divalproex group had better liver function test scores.

Brief Report

NALTREXONE IN PATIENTS WITH BIPOLAR DISORDER AND ALCOHOL DEPENDENCE

E. Sherwood Brown, M.D., Ph.D.,* Laura Beard, M.D., Lauren Dobbs, B.S., and A. John Rush, M.D.

Bipolar disorder is associated with very high rates of substance abuse. However, few clinical trials are reported in this population. Naltrexone is effective for alcohol dependence, but its safety and efficacy are not established in patients with bipolar disorder and alcohol dependence. A 16-week, open-label, add-on pilot study of naltrexone was conducted in 34 outpatients with bipolar disorder and alcohol dependence. Assessments included the 17-item Hamilton Rating Scale for Depression (HRSD-17), Young Mania Rating Scale (YMRS), Brief Psychiatric Rating Scale (BPRS), and an alcohol craving scale. Alcohol use was quantified. Significant improvement was observed in the HRSD-17 and YMRS, and days of alcohol use and craving decreased significantly. Naltrexone was well tolerated. Controlled trials are warranted. Depression and Anxiety 23:492–495, 2006. © 2006 Wiley-Liss, Inc.
Efficacy of naltrexone in patients with bipolar disorder and alcoholism

- A 16-week, open-label pilot study was conducted to assess the effect of naltrexone in patients with bipolar disorder and alcohol dependence
- Assessments included:
  - 17-item Hamilton Rating Scale for Depression (HRSD-17)
  - Young Mania Rating Scale (YMRS)
  - Brief Psychiatric Rating Scale (BPRS)
  - Alcohol craving scale
- Significant improvement observed in HRSD-17, YMRS and days of alcohol use and craving
- Other drugs tried in small, open label studies for bipolar disorder with substance abuse, include gabapentin, lamotrigine, quetiapine and aripiprazole

Brown ES, et al. Depress Anxiety 2006;23:492-495
Group therapy for bipolar disorder and substance dependence

- A RCT assessed integrated group therapy (addresses the two disorders simultaneously) vs group drug counselling (focused on substance use)
  - 62 patients with bipolar disorder and current substance use
- Intention-to-treat analysis showed:
  - Significantly fewer days of substance use for integrated group therapy vs drug counselling during treatment and follow-up
  - Number of weeks ill with bipolar disorder during treatment and follow-up similar in both groups
  - More depressive and manic symptoms in integrated group therapy patients vs drug counselling patients
- Data suggest that integrated group therapy is a promising approach to reduce substance use in patients with bipolar disorder

RCT, randomised controlled trial
Group Therapy for Patients With Bipolar Disorder and Substance Dependence: Results of a Pilot Study

Roger D. Weiss, M.D.; Margaret L. Griffin, Ph.D.; Shelly F. Greenfield, M.D., M.P.H.; Lisa M. Najavits, Ph.D.; Dana Wyner, B.A.; Jose A. Soto, B.A.; and John A. Hennen, Ph.D.

A Randomized Trial of Integrated Group Therapy Versus Group Drug Counseling for Patients With Bipolar Disorder and Substance Dependence

Roger D. Weiss, M.D.
Margaret L. Griffin, Ph.D.
Monika E. Kolodziej, Ph.D.
Shelly F. Greenfield, M.D., M.P.H.
Lisa M. Najavits, Ph.D.
Dennis C. Daley, Ph.D.
Heidi Ray Doreau, B.A.
John A. Hennen, Ph.D.

Group Therapy

Population
- 21 adults received integrated group therapy
- 24 adults received usual care

Integrated group therapy was associated with
- Significantly ($p < 0.02$) greater decrease in Addiction Severity Index drug and alcohol composite scores
- Higher probability of longer (at least 2-month or 3-month) periods of abstinence
Conclusions

- The prevalence of substance use disorders is very high in patients with bipolar disorder.
- Substance use comorbidity carries worse outcome of bipolar disorder.
- Bipolar patients with substance misuse have higher suicide risk and less adherence to treatment.
- Anxiety is frequently a mediator between alcohol and drug abuse and bipolar disorder.
- Treatment of anxiety is crucial, but antidepressants are associated with induced mania in BD with comorbid SUD.
Conclusions

- Evidence-base for treatment is limited, but withdrawal improves dramatically outcome in the long, but not in the short-term.
- Valproate, lithium, and naltrexone can be used to treat bipolar patients with substance use disorders
- Psychoeducation and psychosocial interventions are crucial for patients with comorbidity
CHRISTMAS LUNCH