The Challenge of Treating Bipolar Disorder and Substance Abuse

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Management and Treatment of Substance Abuse in Bipolar Disorder

- Comorbidity vs co-occurrence
- Epidemiology and gender risk
- Impact of alcohol on:
  - Symptom presentation
  - Service utilization
- Mood stabilizers in the treatment of:
  - Acute alcohol withdrawal
  - Alcohol abuse relapse prevention
  - Mood stabilization and relapse prevention
Comorbidity vs Co-Occurrence

- 2 discrete disease processes
  - Different etiologies
  - Independent courses
- Bipolar patients exhibit both patterns
- Simultaneous symptoms
  - Dipsomania
  - Pathological drinking
- Different phenotypic presentation of same illness??
- Courses of illness parallel each other

Mood-State–Dependent Alcohol Intake?

Treat insomnia
Impulsivity
Maintain euphoria
Disinhibition

Self-medicating
Induce numbness
Anxiolytic
Blunt trauma

Alcohol Bipolar Internet Survey.
### Prevalence Rate/Odds Ratio* of Bipolar Disorder and Substance Use

<table>
<thead>
<tr>
<th>Drug Use</th>
<th>BD I</th>
<th></th>
<th>BD II</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>OR</td>
<td>%</td>
<td>OR</td>
</tr>
<tr>
<td>Any substance</td>
<td>60.7</td>
<td>7.9</td>
<td>48</td>
<td>4.7</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>46</td>
<td>5.6</td>
<td>39</td>
<td>4.2</td>
</tr>
<tr>
<td>Drug dependence/abuse</td>
<td>40.7</td>
<td>11.1</td>
<td>21</td>
<td>4.1</td>
</tr>
</tbody>
</table>

*OR, compared to general population.

BD=bipolar disorder.

Lifetime Prevalence of Alcohol Use*

*Abuse/Dependence. SZ=schizophrenia; PD=panic disorder; OCD=obsessive-compulsive disorder; DYS=dysthymia; MD=major depression; GP=general population.

“Alcoholism occurs among male patients in about a quarter of the cases, but it is to be regarded as the consequence of debaucheries committed in excitement, not as a cause.”

Kraepelin 1921
Alcoholism in Bipolar Men and Women

- Rate of alcoholism
- BD % (n=116)
  - 49%
- BD Š (n=151)
  - 29%

*Odds ratio compared to the Epidemiologic Catchment Area (ECA) sample weighted by age, race, gender;
BD % OR=2.8 (95% CI: 1.59-4.81); BD Š OR=7.35 (95% CI: 3.32-16.26); †P<.0001.
Gender Differences in BD/EtOH Clinical Correlates*

**BD/EtOH women**
- Polysubstance use
- Family history
  - Alcoholism
- Verbal abuse
- Depressive episodes
- Social phobia

**BD/EtOH men**
- Family history
  - Alcoholism
  - Drug abuse
  - Bipolar disorder
- Physical abuse
- Suicide attempts

* vs BD women and men without substance use.
EtOH=ethanol.
Increased Depressive Burden in Female Bipolar Alcoholics*

*Symptom inventory from semistructured assessment, Initial Evaluation Form (IEF).
Clinical Presentation and Treatment Response: Bipolar Disorder and Substance Abuse

- Earlier age of bipolar illness onset
- Higher rates
  - Mixed states
  - Rapid cycling
  - Polysubstance abuse
  - Impulsivity
  - Aggressivity
  - Suicidality
  - Novelty seeking
- Increased healthcare utilization
  - ER visits
  - Hospitalization (particularly 1st several episodes)
- Treatment response
  - Slower time to recovery
  - Decreased lithium response
  - Increased treatment nonadherence (particularly lithium)
Lithium in the Treatment of Alcoholism

- Significant reduction in EtOH consumption in lithium-treated rats
- Not clinically useful for EtOH withdrawal
- Detoxified alcoholics in a 14-day lithium challenge, regardless of concurrent mood disorder, endorsed:
  - Less intoxication
  - Less desire to continue drinking
  - Less cognitive dysfunction


The following information concerns a use that has not been approved by the US Food and Drug Administration.
Lithium in the Treatment of Alcoholism: Mood- or Alcohol-Specific?

- **Nagel 1991**
  - Li vs PLC x 2 weeks
  - Li ↓ hypomania (noted anxiolytic)

- **Merry 1976**
  - Li vs PLC x 40 weeks
  - ↓ Drink days EtOH/Depressed (n=9) vs EtOH (n=11)

- **Kline 1974**
  - Li vs PLC x 48 weeks in EtOH/Depressed
  - ↓ binges with Li (n=16) vs PLC (n=14)

- **Fawcett 1987**
  - Li vs PLC x 12 months (n=122)
  - Higher abstinence rate in subjects with Li >/= 0.4 mmol/L vs placebo or Li noncompliant
  - Depressive symptoms did not affect outcome

- **Dorus 1989**
  - Li vs PLC X 52 weeks (n=457)
  - No difference in abstinence rates, drinking days, or depression in alcoholics males regardless of mood or comorbid diagnosis

- **Fawcett 2000**
  - Li vs buspirone vs PLC X 6 mos (n=156)
  - No difference in abstinence/ compliance

Li=lithium; PLC=placebo.


The following information concerns a use that has not been approved by the US Food and Drug Administration.
Alcohol Abuse and Bipolar Outcome: Decreased Lithium Response

Lithium nonresponse
Tohen et al, 1990
O’Connell et al, 1991

Compliance?
Subsyndromal symptoms?
Alcohol relapse?
Carbamazepine in the Treatment of Alcoholism

- Alcohol withdrawal
  - 7-day CBZ 800 mg (n=32) = OXP 120 mg (n=34)
    - Greater global improvement with CBZ
  - 5-day CBZ 600-800 mg (n=61) = LOR 6-8 mg (n=75)
    - LOR 3x more likely to have first drink than CBZ in 7 day follow-up
    - Significant benefit in CBZ vs LOR in multiple vs single detox group

- Alcohol dependence
  - 12-month, double-blind, placebo-controlled trial of 29 subjects
  - Decrease in drinking at 2 and 4 months
  - Delay in time to first heavy drinking

- Alcohol abuse in bipolar disorder
  - History of alcohol abuse associated with CBZ antimanic response

CBZ=carbamazepine; OXP=oxazepam; LOR=lorazepam.

The following information concerns a use that has not been approved by the US Food and Drug Administration.
Divalproex for the Treatment of Alcohol Withdrawal and Abstinence

- Open study (n=16) alcohol detoxification
- Standard chlordiazepoxide protocol vs divalproex
  20 mg/kg/d x 5 days vs divalproex 20 mg/kg/d x 6 weeks
- Results
  - CIWA reduction at 12 and 24 hours similar in all 3 groups
  - At 6 weeks, reduction in LFTs in all 3 groups
  - Abstinence rate was highest in divalproex x 6 weeks group

CIWA=Clinical Institute Withdrawal Assessment; LFTs=liver function tests.
The following information concerns a use that has not been approved by the US Food and Drug Administration.
Divalproex Reduces Benzodiazepine Need in Alcohol Withdrawal

- 36 inpatients with DSM-IV alcohol dependence undergoing alcohol withdrawal (CIWA-Ar >10)
- DVPX 500 tid vs placebo X 1 week
  - Day 3 DVPX level 70 mcg/mL
- Oxazepam 30 mg at baseline and in a symptom-triggered manner (CIWA-Ar >10)
- Both groups equally responded
  - CIWA-Ar score reduction
  - LFT reduction
- Decreased total and 1st 24-hour oxazepam dosage with DVPX

DVPX=divalproex.
The following information concerns a use that has not been approved by the US Food and Drug Administration.
Divalproex in the Treatment of Alcohol Dependence

12-week, double-blind, placebo-controlled trial, divalproex 1500 mg/d, cognitive behavioral therapy 1 hour/week. *P<.05.


The following information concerns a use that has not been approved by the US Food and Drug Administration.
Divalproex Reduces Alcohol Use in Mania

<table>
<thead>
<tr>
<th></th>
<th>Baseline (months before study)</th>
<th>Month 1</th>
<th>Per-month (study duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of use (d)</td>
<td>22.2 (± 3.1)</td>
<td>4.4 (± 2.7)</td>
<td>4.2 (± 1.9)</td>
</tr>
<tr>
<td>Longest abstinence (d)</td>
<td>6.3 (± 6.7)</td>
<td>21.4 (±10.3)</td>
<td>74.3* (± 66.8)</td>
</tr>
<tr>
<td>Amount of use (% of baseline)</td>
<td>100%</td>
<td>6.0%</td>
<td>7.7%</td>
</tr>
</tbody>
</table>

*Longest period study duration.


The following information concerns a use that has not been approved by the US Food and Drug Administration.
Topiramate in the Treatment of Alcohol Dependence

- Randomized, controlled clinical trial
  - 2-group design:
    - Escalating topiramate dose (n=75)
    - Escalating placebo dose (n=75)
- Groups balanced on:
  - Chronological age
  - Baseline drinking – 90-day timeline follow-back
  - Age of problem-drinking onset
- All subjects received weekly brief behavioral medication compliance enhancement treatment
- Study duration=12 weeks


The following information concerns a use that has not been approved by the US Food and Drug Administration.
Topiramate in Alcohol Dependence

CI=confidence interval.
Johnson BA et al. Lancet. 2003; 361:1677-1685

At study end, F(1,98)=15.93; P<.0001; effect size (ES)=0.80.
Baseline: 7.78 (topiramate) vs 6.52 (placebo).

The following information concerns a use that has not been approved by the US Food and Drug Administration.
Reinforcing effects of alcohol are mediated by mesolimbic dopamine neurons.

- D$_2$ antagonist (tiapride) increases abstinence.
- 5-HT$_2$ antagonists may reduce alcohol consumption.

In a placebo-controlled study of 26 heavy social drinkers, olanzapine 5 mg:
- Decreased alcohol-cued urge to drink.
- Decreased the subjective “want” for another drink.

To date, no controlled trials of BD/alcohol comorbidity.


The following information concerns a use that has not been approved by the US Food and Drug Administration.
Bipolar Disorder and Alcoholism: Conclusion

- Aggressive acute stabilization
  - Mania, depression, cycling
  - Alcohol withdrawal
    - Data most impressive with carbamazepine and divalproex
- Prevention stabilization
  - Maintenance mood stabilization
  - DBSA support
  - Alcohol relapse prevention (lithium, divalproex, carbamazepine, topiramate, atypical antipsychotics)
  - Alcoholics Anonymous support

DBSA = Depression and Bipolar Support Alliance.