Treatment Implications of Determining the Directionality of Comorbid Disorders

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Overview

• Relationships between co-occurring substance use and other mental disorders
  – Implications for directionality and treatment
• DSM-IV and co-occurring disorders
• Evidence from treating depression
• Evidence from treating anxiety, other co-occurring disorders
Potential Relationships between Psychiatric (P) and Substance Use Disorder (SUD)

• I. P causes SUD
  – “Self-medication”
  – P alters brain response to substances
  – SUD may take on a life of its own

• II. SUD causes P
  – Intoxication, withdrawal
  – SUD causes lasting brain changes leading to P
  – P may take on a life of its own
Relationships between Psychiatric (P) and Substance Use Disorder (SUD)

• III. Independent disorders
• IV. P + SUD leads to worse prognosis
  – Interference with treatment, compounding
• V. P, SUD become related over time
  – P symptoms become a conditioned cue triggering S
• VI. Common risk factors underlie P, SUD
  – Stress, trauma, genetic factors
# Implications for Directionality, Treatment

<table>
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<tr>
<th>Relationship</th>
<th>Prior Onset</th>
<th>Treatment Emphasis</th>
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<td>I. P → SUD</td>
<td>P</td>
<td>P (SUD)</td>
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<tr>
<td>II. SUD → P</td>
<td>SUD</td>
<td>SUD</td>
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<tr>
<td>III. Independent</td>
<td>?</td>
<td>both</td>
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<td>IV. P + SUD → Prognosis</td>
<td>?</td>
<td>both</td>
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<td>V. P, SUD related over time</td>
<td>?</td>
<td>both</td>
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<tr>
<td>VI. Common RFs</td>
<td>?</td>
<td>Both and RF</td>
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Comorbidity and Prognosis

• Psychiatric Diagnosis associated with poor alcohol/drug use outcome
  – Greenfield (Arch Gen Psychiatry. 1998 Mar;55(3):259-65)
    • Major Depression in past year, not depression symptoms, predict worse drinking outcome 1 year after index hospitalization
  – Hasin (Arch Gen Psych 2002;59:375-80)
    • DSM-IV Substance Inducted Major Depression, by PRISM interview associated with failure to remit from alcohol or drugs
    • DSM-IV Primary Major Depression associated with drug/alc relapse
  – Depressive Symptoms prognostic effect less clear
Clinical Implications

- Comorbidity is common, worsens prognosis
- Depression + substance use is most visible b/o prevalence of depression
- Other less prevalent disorders (e.g. bipolar, panic, schizoprenia, ASP, are more strongly associated with substance use disorders
- So: If you see depression + substance use, look for other disorders
Early Onset Substance Use Disorders

- Adolescent onset
- Relationship to psychopathology
Typologies of Alcoholism
(Cloninger, Babor)

• Early onset, complicated type
  – Teenage onset regular nicotine, alcohol, drug
  – Externalizing and internalizing psychopathology

• Late Onset type
  – After age 25, less psychopathology

• Depressed/anxious type
  – Emerges in 3 or 4 subtype solutions (e.g. Lesch)
Pathway to Early Onset Alcohol and Drug Dependence

- Premorbid temperament (irritable, hyperactive, impulsive, inattentive, anxious) and neuropsychological deficits
  - School failure and association with deviant peer groups
  - Early experimentation with nicotine, alcohol, drugs
  - Abuse and dependence
Clinical Implications

• Do a careful family history
  – Substance, mood, other psychiatric problems

• Do a careful developmental history
  – ADHD syndrome, school problems, learning problems, antisocial behavior, deviant peer groups, early onset substance use
  – Separation anxiety, school phobia, extreme shyness, social anxiety, early onset depression

• Do a careful trauma history
Diagnosis of Co-Occurring Psychiatric, Substance Use Disorders: Diagnostic Confusion; DSM-IV Solution

- Substance intoxication, withdrawal, chronic use produce depression, anxiety, mania, psychosis
  - Alcohol
  - Other co-occurring drugs (e.g. cocaine)
- Likely to resolve with abstinence
  - Treat substance use disorder
- Outpatients often can’t get abstinent
- How to tell which psychiatric disorders to treat?
Classic Inpatient Studies (Brown and Schuckit 1995):
Order of onset and course during treatment;
Hamilton Depression Scores in inpatient alcoholics

![Graph showing Hamilton Depression Scores over time.](image)
Primary (a.k.a. independent) depression:
- Temporally independent, i.e. preceded drug abuse, or persisted in abstinence
- Ideally abstinence is current, directly observed

Substance-induced depression:
- Not temporally independent
- Exceeds what would be expected from usual toxic or withdrawal effects of substances

Usual effects of substances
- See DSM-IV intoxication and withdrawal criteria
Operationalize DSM-IV?: Modified SCID (Nunes et al)

- Establish ages at onset of regular substance use
- Establish periods of abstinence during the history
- Examine whether MDD, or syndromes antedate substance use or persist during abstinence
Operationalize DSM-IV?: PRISM interview

(Hasin et al Arch Gen Psychiatry 2002; Aharonovich et al., AJP 2002)

• Primary ("independent", "abstinence") MDD
  – 1 year follow-up: predicts persistent depression, suicide attempts, relapse

• Substance-induced MDD
  – Rigorous definition: full MDD syndrome, each symptom exceed usual substance effects
  – Clinical sample: 50% of MDDs are substance induced
  – 1 year follow-up: predicts persistent depression; suicide ideation; failure of substance disorder to remit
  – Many/most convert to primary over follow-up
Weekly prevalence of major depression (MDD) over 1 year after hospitalization in 110 substance dependent patients as a function of DSM-IV MDD diagnosis at baseline (BL):

- Whether baseline MDD is independent (BL Ind MDD) or substance induced (BL SI MDD)
- Whether there is a past episode of independent MDD (Past Ind MDD)

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Clinical Implications

• Get history of substance use problems, including age at first onset, and periods of abstinence
• Take parallel history of mood or other psychiatric problems
  – Construct a time-line
• Apply DSM-IV criteria for independent, or substance-induced disorders
  – **Caveat:** DSM-IV substance-induced implies more than “usual effects of substances”
  – Substance-induced depression, rigorously defined like this, often turns out, over time, to be independent of substance abuse
What’s the Evidence on Treatment?

- **Treat the Substance Use Disorder**
  - If substance use decreases, mood likely to improve

- **Treat the Psychiatric Disorder:**
  - **Hypothesis:** Identification and treatment of comorbid psychiatric disorders in substance dependent patients will:
    - 1) improve psychiatric symptoms
    - 2) improve and drug/alcohol outcome
    - 3) improve psychosocial functioning
Early Antidepressant Trials in Alcoholism

- 1960s and 1970s, numerous trials
- Rationale: reduce dysphoria
- Mainly Tricyclic antidepressants, low doses, short trial lengths, no diagnosis
- Two reviews (Ciraulo & Jaffe J Clin Psychopharm 1981; Liskow & Goodwin J Stud Alcohol 1987)
  - No clear evidence of efficacy
SRIs and alcohol

- SRIs found to reduce alcohol intake in animal models
- SRIs reduced alcohol intake in heavy drinkers not seeking treatment
- SRI clinical trials disappointing
  - May reduce drinking in late onset (Type A) alcoholism
  - But may make early onset (Type B) drinking worse
    - Kranzler et al., Alc Clin Exp Res 1996
    - Pettinati et al., Alc Clin Exp Res 2000
Antidepressants and Nicotine

• Hx of depression predicts failure to quit; after quit depression sometimes emerges
• Noradrenergic antidepressants effective in smoking cessation
  – Bupropion, Nortriptyline
  – Does not seem to depend on history of depression
• SRIs ineffective
• Clinical trials have large sample sizes, probably good compliance
Meta-Analysis
(Nunes and Levin JAMA 2004; 291:1887-1896)

• 14 placebo-controlled trials of antidepressant medication
• Patients
  – DSM depression diagnosis, and
  – Alcohol, opiate, or cocaine dependence
Meta-Analysis  
(Nunes and Levin JAMA 2004; 291:1887-1896)

- Hamilton Depression Scale (HamD)
  - $\text{ES} = 0.38$ (95% CI: 0.18 - 0.58)
  - heterogeneity significant ($p < .02$)

- Self-reported substance use outcome
  - HamD $\text{ES} > 0.50$: Substance use $\text{ES} = 0.56$ (0.33 - 0.79)
  - HamD $\text{ES} < 0.50$: Substance use $\text{ES} \sim 0.0$

- Remission or abstinence rates low
14 Placebo-Controlled Trials of Antidepressants
Depressed Substance Patients (Nunes and Levin JAMA 2004)
What Distinguished Studies Where Antidepressant Medication was Effective vs Ineffective?

• Medication Effective
  – Low placebo response
  – Diagnosis during abstinence
  – No structured psychotherapy
  – Tricyclic or other noradrenergic med

• Medication = Placebo
  – High placebo response
  – Diagnosis during active substance use
  – Manual guided psychotherapy
  – Serotonin re-uptake inhibitor?
Clinical Implications

• Treatment of Co-occurring depression works
  – Good diagnosis (DSM-IV, PRISM)
  – Abstinence preferable, not mandatory
  – TCAs, SRIs?, Psychotherapy?
  – Not a panacea (mood effect > substance effect)
What if you can’t get the patient abstinent to make a diagnosis?

- Evaluate order of onset/offset of psychiatric and substance use disorders by history
  - Modified SCID
  - PRISM
Trials of venlafaxine (Ven; N=128) or desipramine (DMI; N = 111) for patients with cocaine dependence and depression, diagnosed as primary (Prim) or secondary (Sec) by modified SCID: Proportion of patients with depression response (> 50% reduction in Hamilton Depression Scale)

![Bar chart showing comparison between Ven and DMI for Prim and Sec patients, with Placebo and Active Med conditions.](chart.png)
Other Common Treatable Psychiatric Syndromes

• In general, other psychiatric syndromes more strongly associated with substance use disorders than depression, and co-occur with depression
  – Anxiety disorders
  – Attention Deficit Hyperactivity Disorder
  – Explosive temper-aggression
  – Developmental Perspective
  – Bipolar Illness
  – Cognitive impairment
  – Schizophrenia
Anxiety Disorders and Addiction

• Anxiety disorders prevalent, often co-occur with depression in addicted patients
  – Panic disorder, agoraphobia
  – Social Phobia (early onset)
  – Post-Traumatic Stress Disorder

• ? Link to childhood anxious temperament risk factor for addiction?
Anxiety Disorders and Addiction

- Symptoms often distinct from drug toxicity or withdrawal
- Respond to antidepressant medications or cognitive behavioral psychotherapy
- Few studies in addicted patients
Buspirone for Generalized Anxiety in Alcohol Dependent Patients

- Buspirone (Kranzler et al)
  - Inpatient alcoholics
    - Elevated Ham-Anxiety scale score after detoxification
  - Buspirone superior to placebo on drinking outcomes
CBT for Alcohol Dependent Patients with PTSD
(Back, Jackson, Sonne, & Brady, JSAT 2005)

• Examined order of onset (alcohol dependence primary vs PTSD primary) and treatment response

• CBT more effective for those with primary PTSD (early onset PTSD, later onset substance abuse)

• Women with primary alcohol dependence vulnerable to persistent depression
Attention Deficit Hyperactivity Disorder and Addiction

- Childhood onset: inattention, hyperactivity, school and social problems
  - Onset before age of risk for substance abuse

- A risk factor for later substance use disorder

- Prevalence in adults with substance abuse (Levin, Evans, Kleber)
  - ~10% clear childhood + adult syndromes
  - another 10% adult syndrome, unclear early Hx
Clinical Trials for ADHD and Cocaine Dependence

(Levin, Evans, Kleber, et al)

- Methylphenidate, bupropion improve both ADHD and cocaine use in open label trials
- Methylphenidate reduced cocaine euphoria in human laboratory
- Placebo controlled trials
  - Cocaine, methadone patients with cocaine dependence
  - Results are equivocal
Impulsive Aggression and Drug Abuse: Treatment (Donovan et al.)

- Affective subtype of aggression with irritability
- Frequent aggressive outbursts
  - Intermittent explosive disorder vs childhood bipolar
- Childhood onset, before age of risk for drug dependence
- Associated with cannabis dependence
- Both irritability/aggression and cannabis use respond to divalproex in placebo controlled trials
Cognitive Impairment and Treatment (Aharonovich et al)

• Pre-existing learning problems, verbal learning, and executive cognitive deficits in children at risk for substance abuse
• Cognitive deficits may be toxic effects of substance use
• Alcoholics and cocaine dependent patients have deficits
  – Deficits predict poor outcome
• Treatments (e.g. CBT) require intact cognition
Bipolar Disorder

- Strong association with substance abuse and dependence
- Variable age of onset (childhood thru adulthood)
- Two positive medication trials
  - Lithium for adolescents with prior onset bipolar disorder and substance abuse (Geller et al., JACAP 1999)
  - Divalproex for adults with alcohol dependence and bipolar disorder by SCID after detoxification (Salloum et al., Arch Gen Psychiatry 2005)
Kaplan-Meier survival curve for time to relapse to sustained heavy drinking (3 consecutive heavy drinking days [$\geq 5$ drinks per day for men and $\geq 4$ drinks per day for women]), by treatment group (log-rank test, $P = .048$)

Conclusions, Clinical Implications

• Treatment of co-occurring psychiatric disorders is an effective medication strategy for substance use disorders
  – Always treat the substance use disorder, shoot for abstinence to clarify the diagnosis

• Directionality matters
  – Stronger evidence for treatment effect if co-occurring disorder is primary/independent in DSM-IV sense
  – More research is needed, also on DSM-IV substance-induced or secondary disorders

• Where there is one comorbid disorder, look for others
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• National Institute on Alcoholism and Alcohol Abuse

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