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

Relationship	Prior Onset	Treatment Emphasis
I. P → SUD	P	P (SUD)
II. SUD → P	SUD	SUD
III. Independent	?	both
IV. P + SUD → Prognosis	?	both
V. P, SUD related over time	?	both
VI. Common RFs	?	Both and RF

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

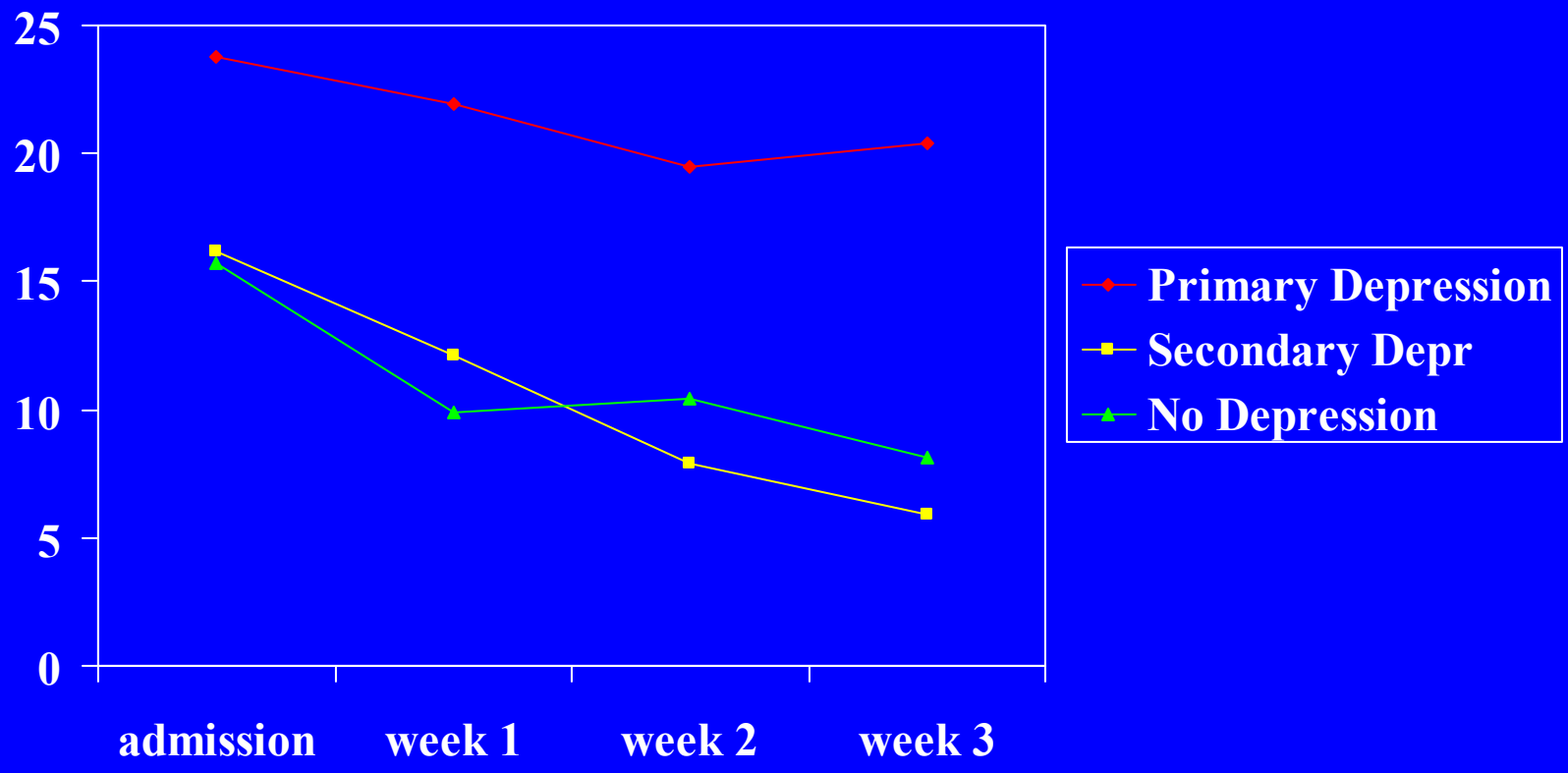
Clinical Implications

- 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



DSM-IV Solution

- 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

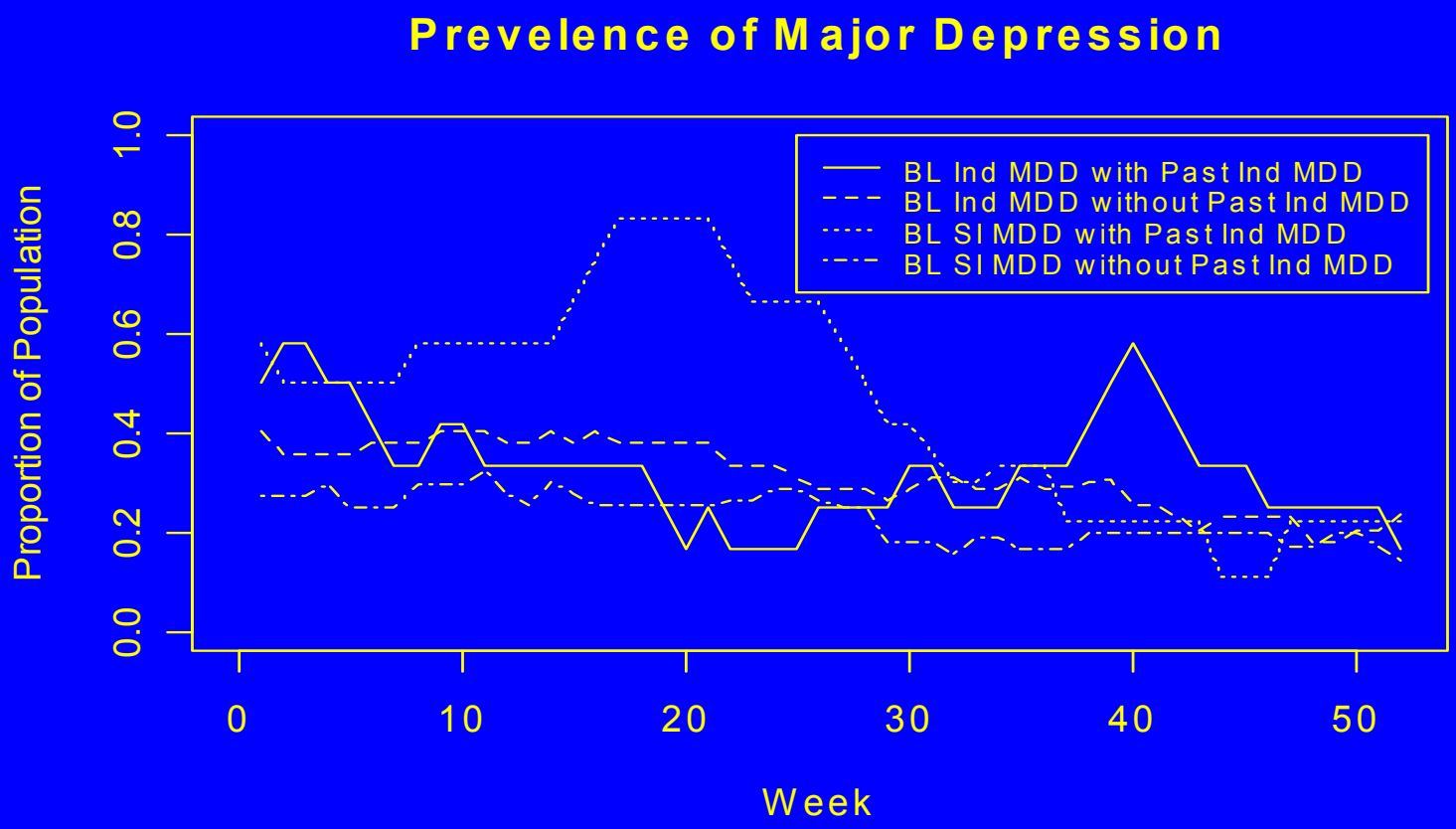
Operationalize DSM-IV?: Modified SCID (Nunes et al)

- 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

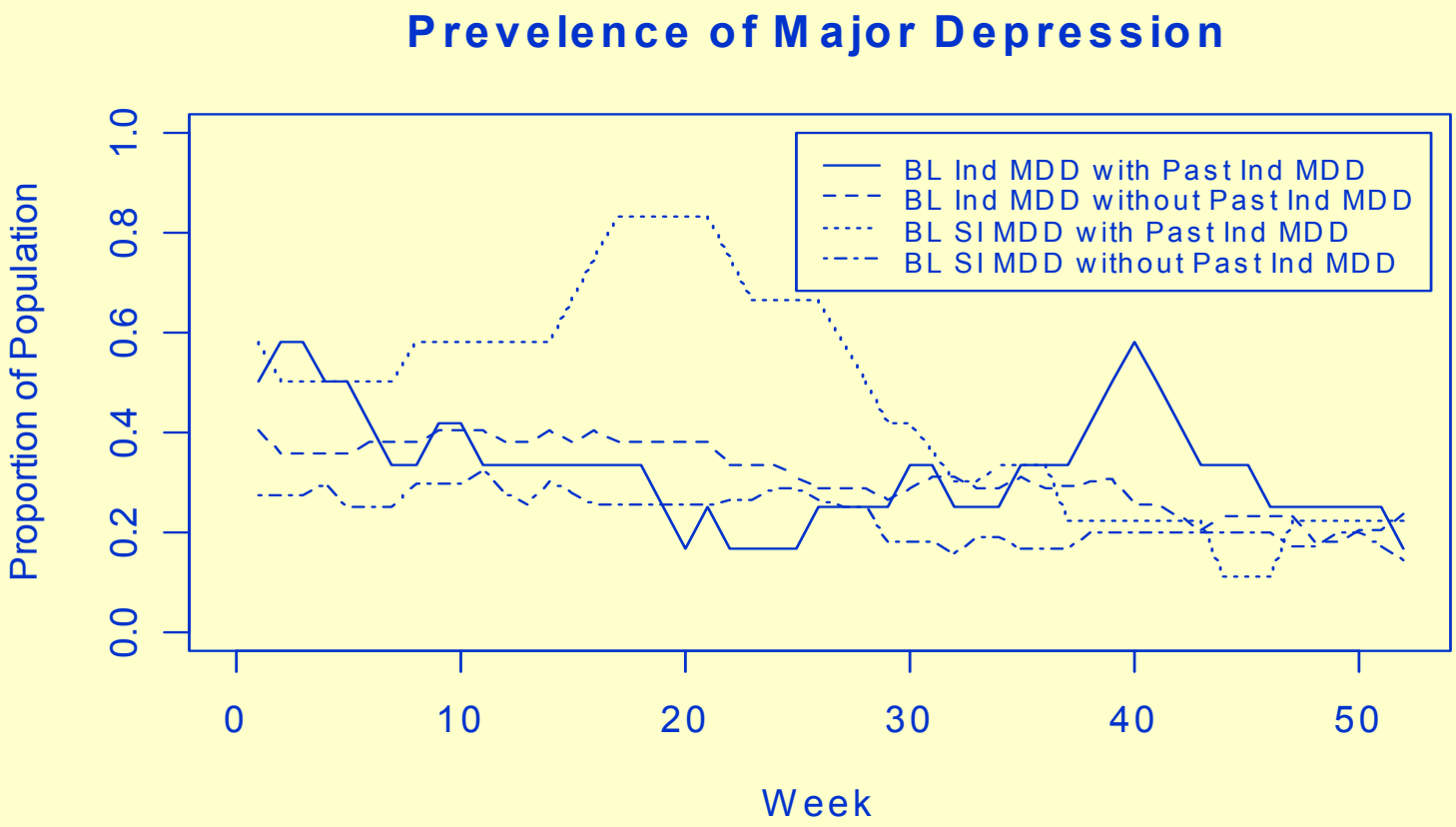
Operationalize DSM-IV?: PRISM interview

(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**)
    - (Nunes, Liu, Samet, Matseone and Hasin, J Clin Psych 2006)



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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

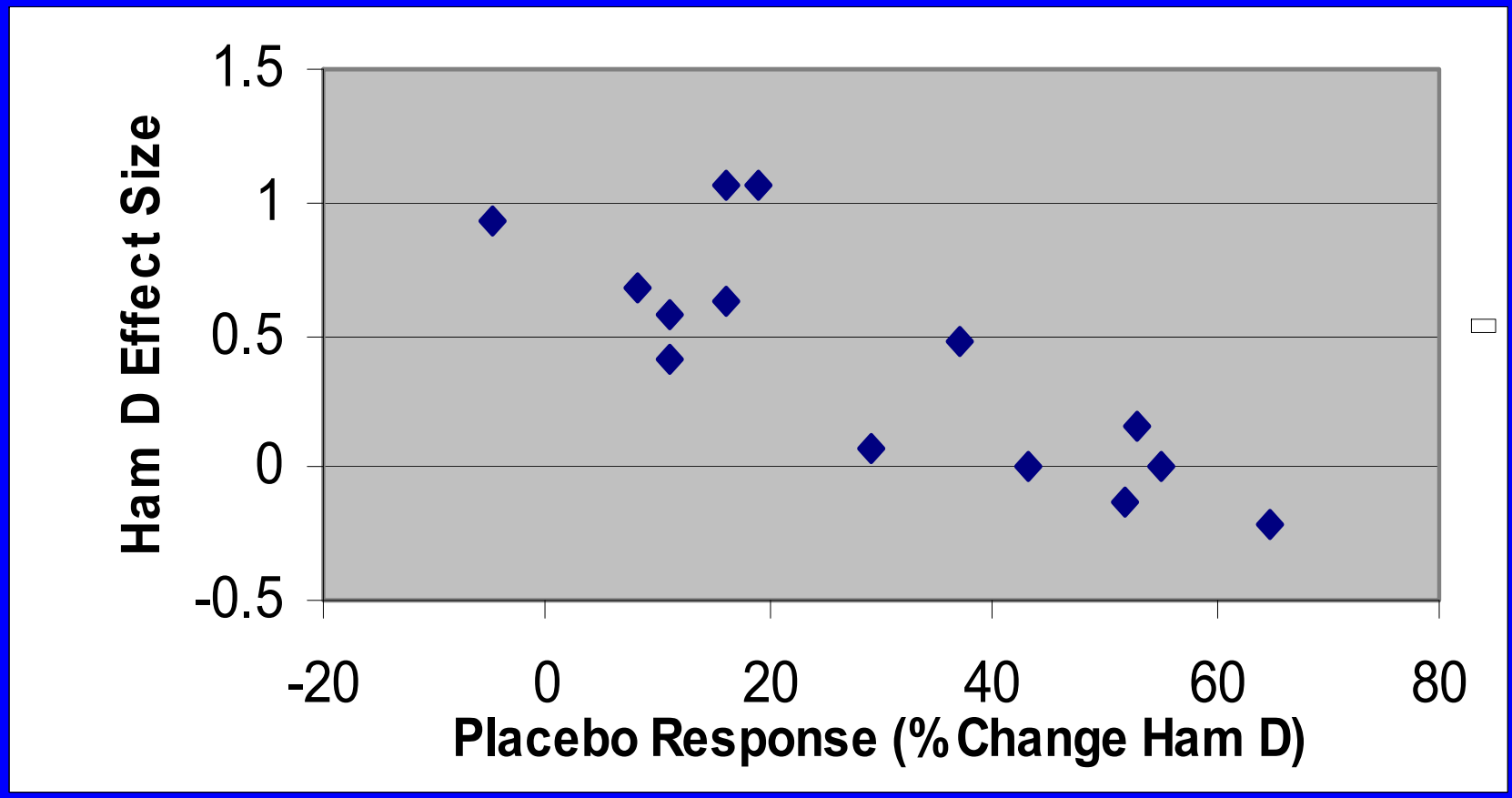
Meta-Analysis

(Nunes and Levin JAMA 2004; 291:1887-1896)

- Hamilton Depression Scale (HamD)
  - ES = 0.38 (95% CI: 0.18 - 0.58)
  - heterogeneity significant ($p < .02$)
- Self-reported substance use outcome
  - HamD ES > 0.50: Substance use ES = 0.56 (0.33 - 0.79)
  - HamD ES < 0.50: Substance use ES ~ 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?

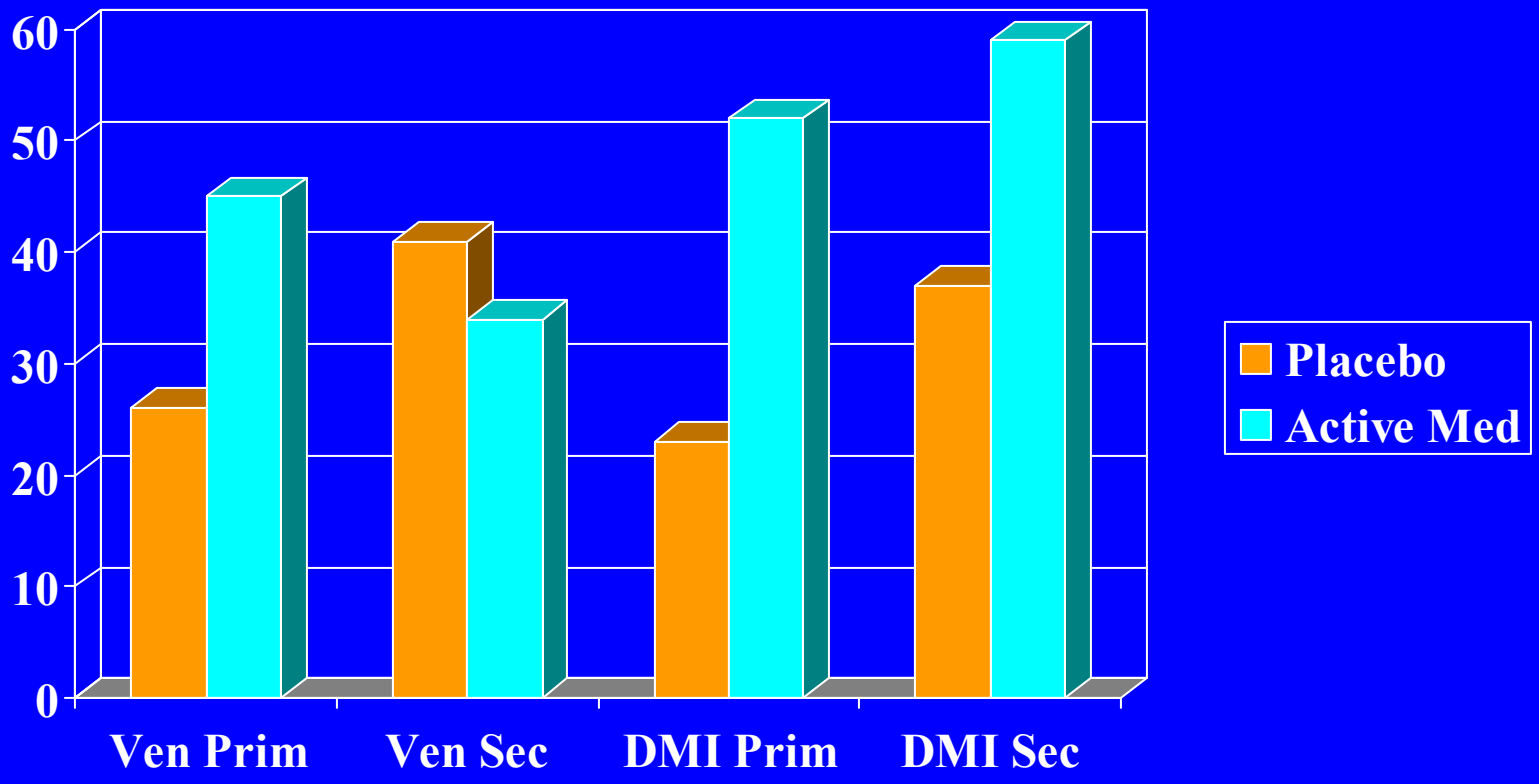
Clinical Implications

- 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



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

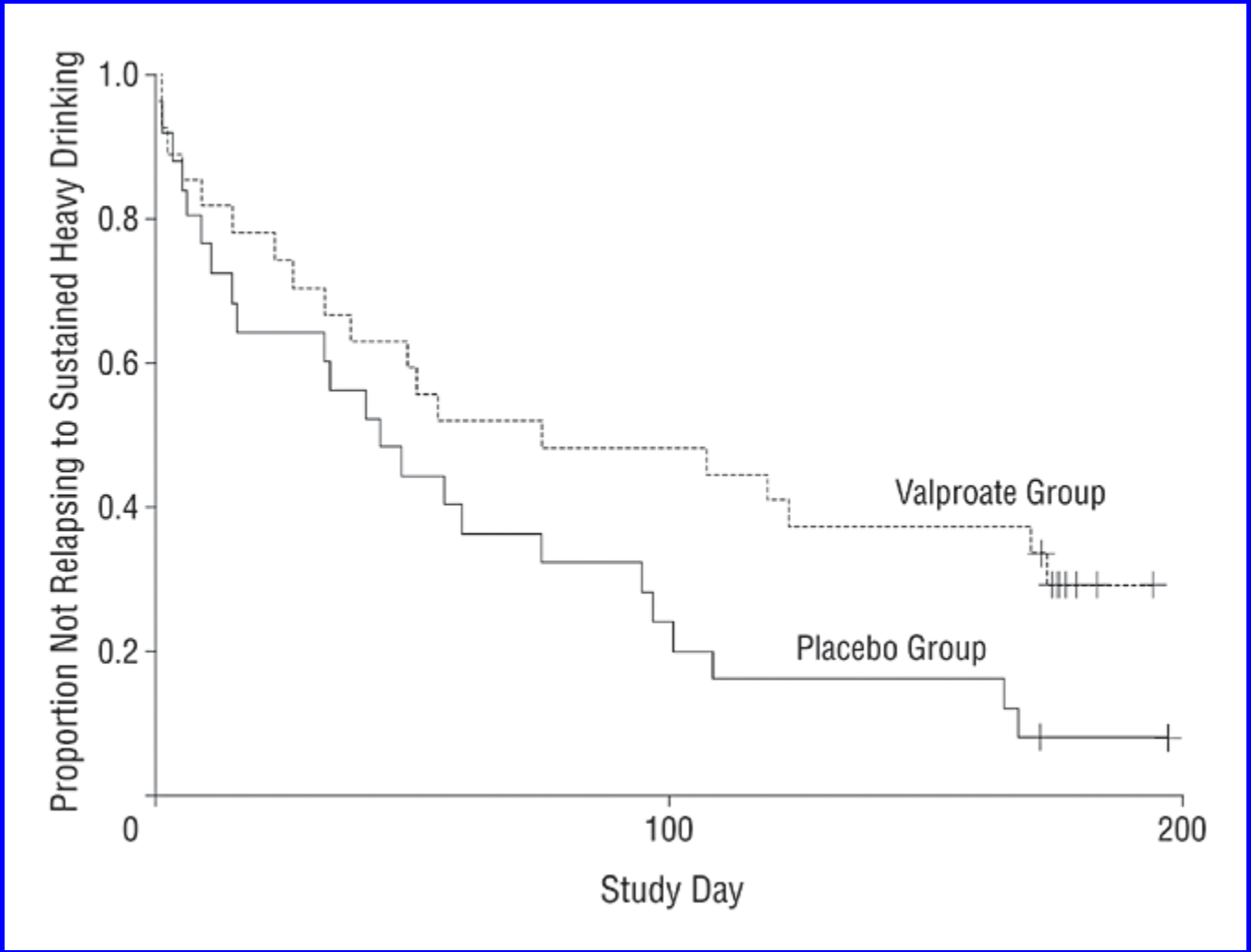
(Aharonovich et al)

- Pre-exisinting 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 [≥5 drinks per day for men and ≥4 drinks per day for women]), by treatment group (log-rank test, P = .048)



Salloum, I. M. et al. Arch Gen Psychiatry 2005;62:37-45.

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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

Acknowledgements

- National Institute on Drug Abuse
- National Institute on Alcoholism and Alcohol Abuse
- New York State