




Advances in Diagnosis, Neurobiology, and Treatment of Mood Disorders

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CURSO INTERAMERICANO DE ACTUALIZACIÓN EN PSIQUIATRÍA



Alcohol and Substance Abuse and Their Comorbidity with Mood Disorders

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Disclosures

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 - The National Institute on Alcohol Abuse and Alcoholism (NIAAA)
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 - The Department of Veterans Administration

Learning Objectives



- Describe the relationship between mood disorders and substance use disorders.
- Implement evidence-based, best-practice options for treatment of mood disorders and comorbid alcohol and substance use disorders.

Audience Response

A decorative graphic in the top right corner of the slide. It features a stylized neuron with a glowing green nucleus and several branching dendrites. The neuron is set against a background of a network of blue lines and dots, suggesting a neural network or data connectivity. The overall color scheme is teal and blue.

How confident are you in identifying clinical signs and symptoms of common mood disorders when treating alcohol and substance use disorder patients?

- A. Extremely confident
- B. Confident
- C. Somewhat confident
- D. Not at all confident

Audience Response



What percentage of people with alcohol dependence report having depressive symptoms?

- A. 40%
- B. 50%
- C. 70%
- D. 80%

Audience Response



Which of the following are common measures used in addiction for withdrawal symptoms?

- A. CIWA, COWS
- B. CIWA, OCDS
- C. COWS, CAGE
- D. OCDS, CAGE

Agenda

A decorative graphic in the top right corner of the slide. It features a stylized neuron with a glowing green nucleus and several branching dendrites. The neuron is set against a background of a network of interconnected nodes and lines, suggesting a neural network or a complex system. The overall color scheme is teal and green.

1. Significance of the problem
 - Prevalence & Consequences
2. Challenges
 - Diagnostic & Treatment Issues
3. Pharmacotherapy Trials
4. Summary

Disease Burden

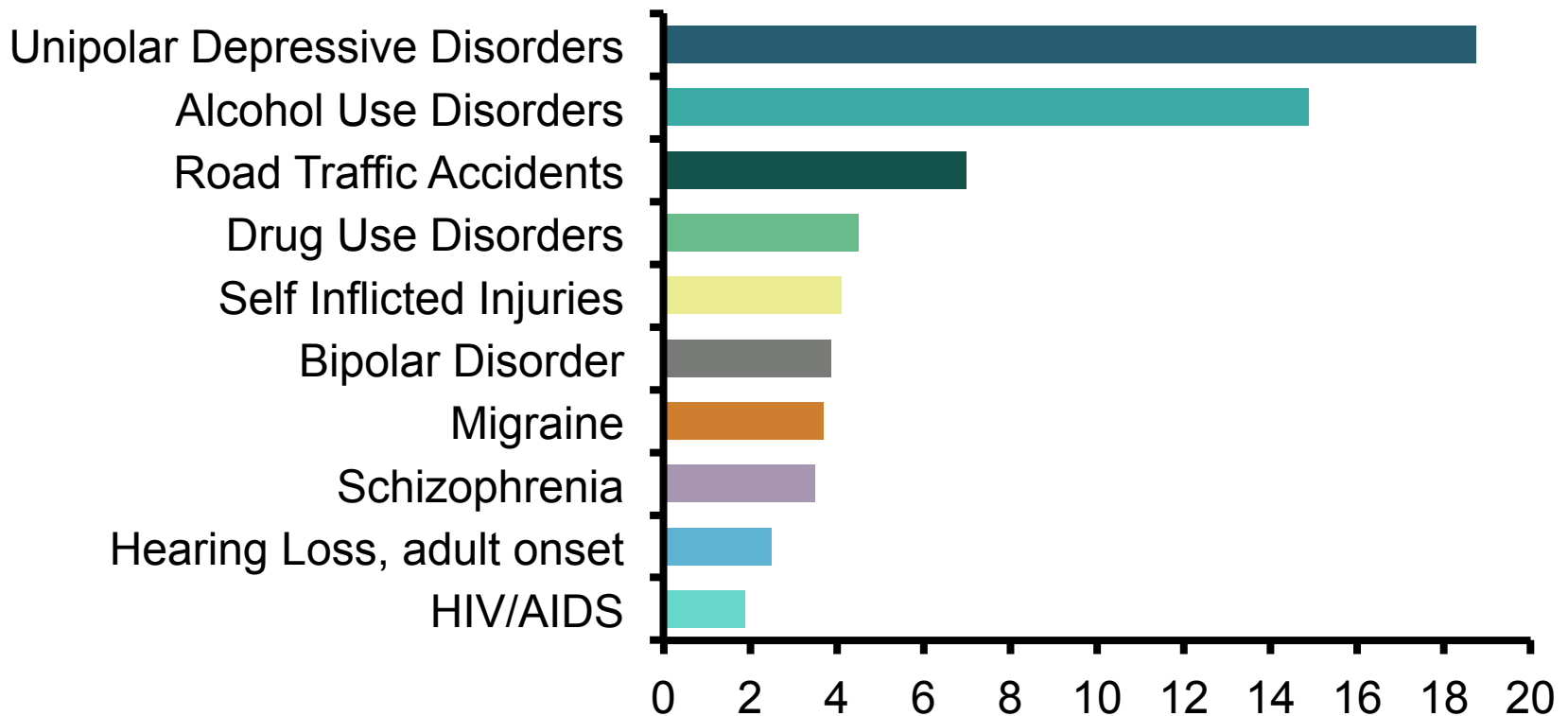


- Mood disorders and substance use disorders are among the most frequent causes of disability worldwide

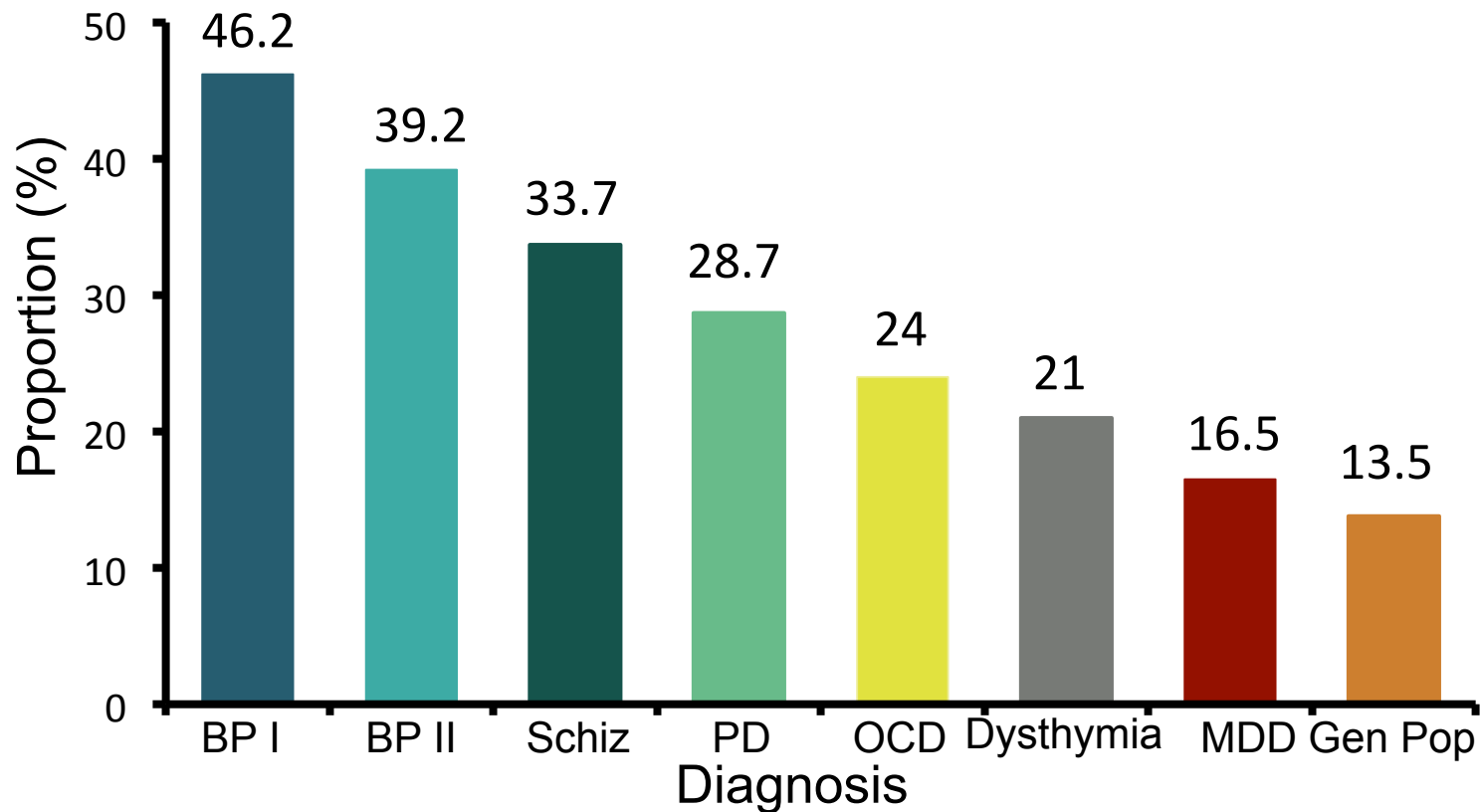
Disease Burden DALY

USA, Canada, and West Europe, 2000

Disability Adjusted Life Year (DALY), 15 – 44 yr olds



Lifetime Rates of Alcoholism in Major Psychiatric Disorders

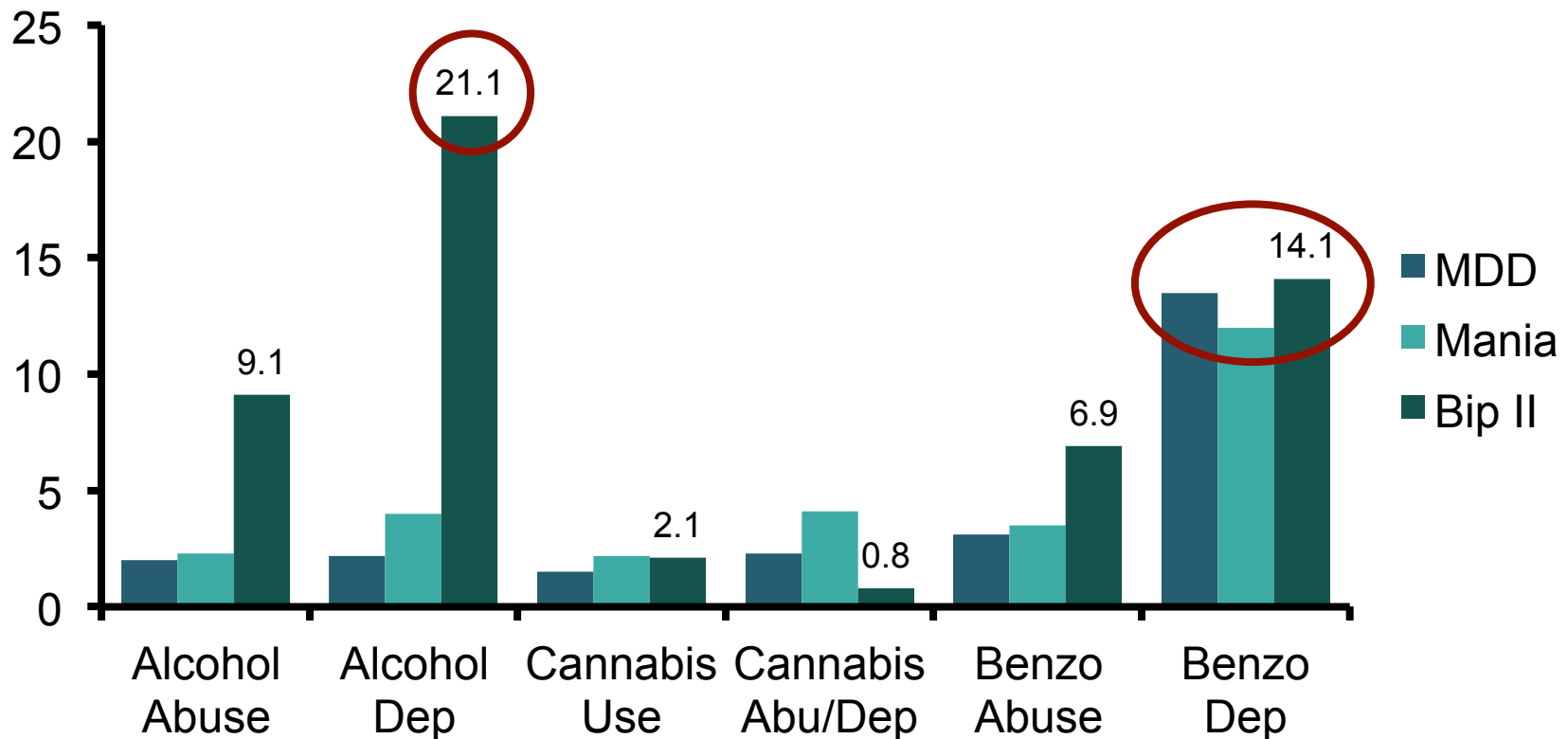


BP = bipolar disorder; Schiz = schizophrenia; PD = Panic disorder, OCD = obsessive compulsive disorder; MDD = major depression

Regier DA, et al. *JAMA* 1990;264(19):2511–2518.

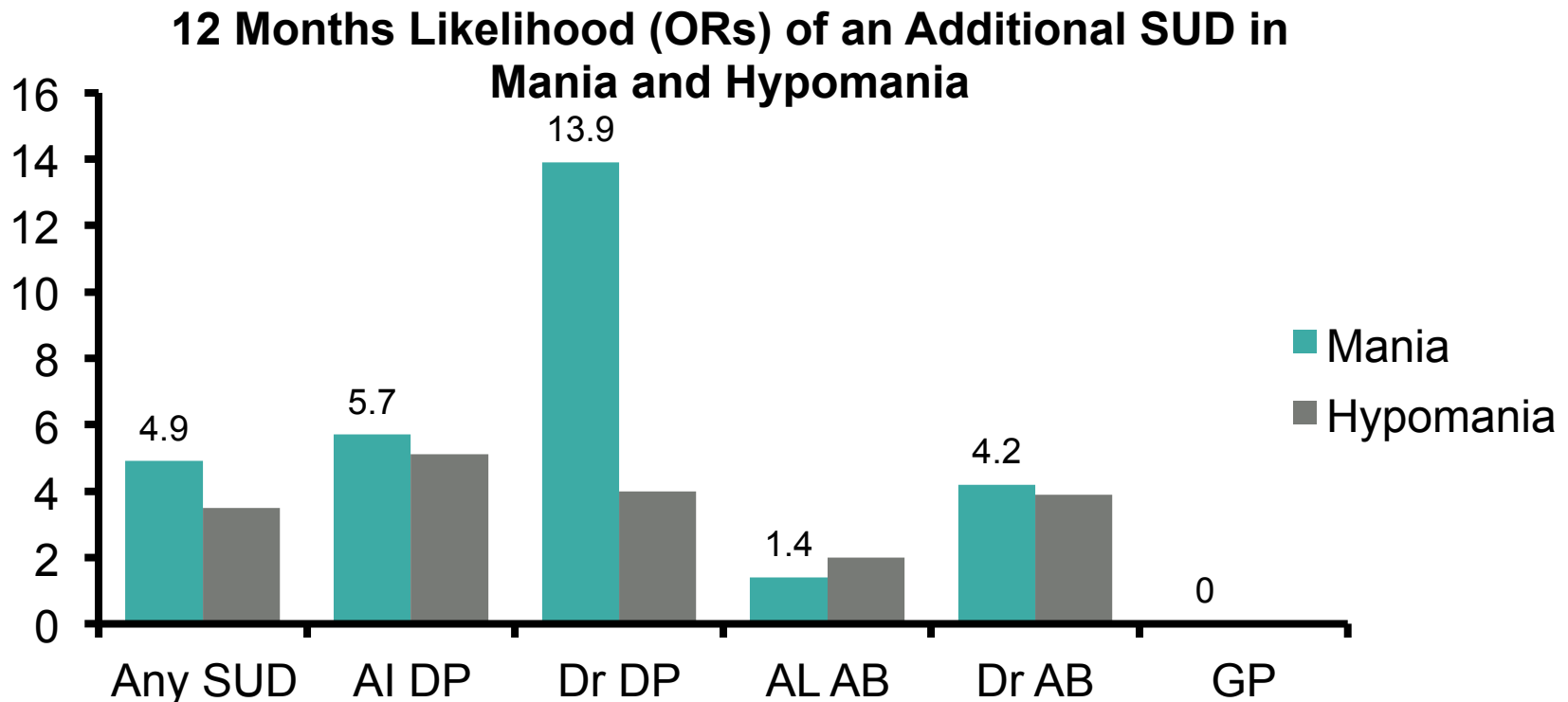
Mood Disorders and Substance Abuse

20 Yrs Follow-Up: The Zurich Cohort Study



Merikangas, KR, et al. *Arch Gen Psychiatry* 2008;65(1):47-52.

Substance Use and Mood Disorders



AL = Alcohol; Dr = Drugs; DP = Dependence, AB = Abuse; GP = General Population
N = 42,000 (NESARC) Odds Ratio

Grant BF, et al. *Arch Gen Psychiatry*. 2004;61(8):807-816.

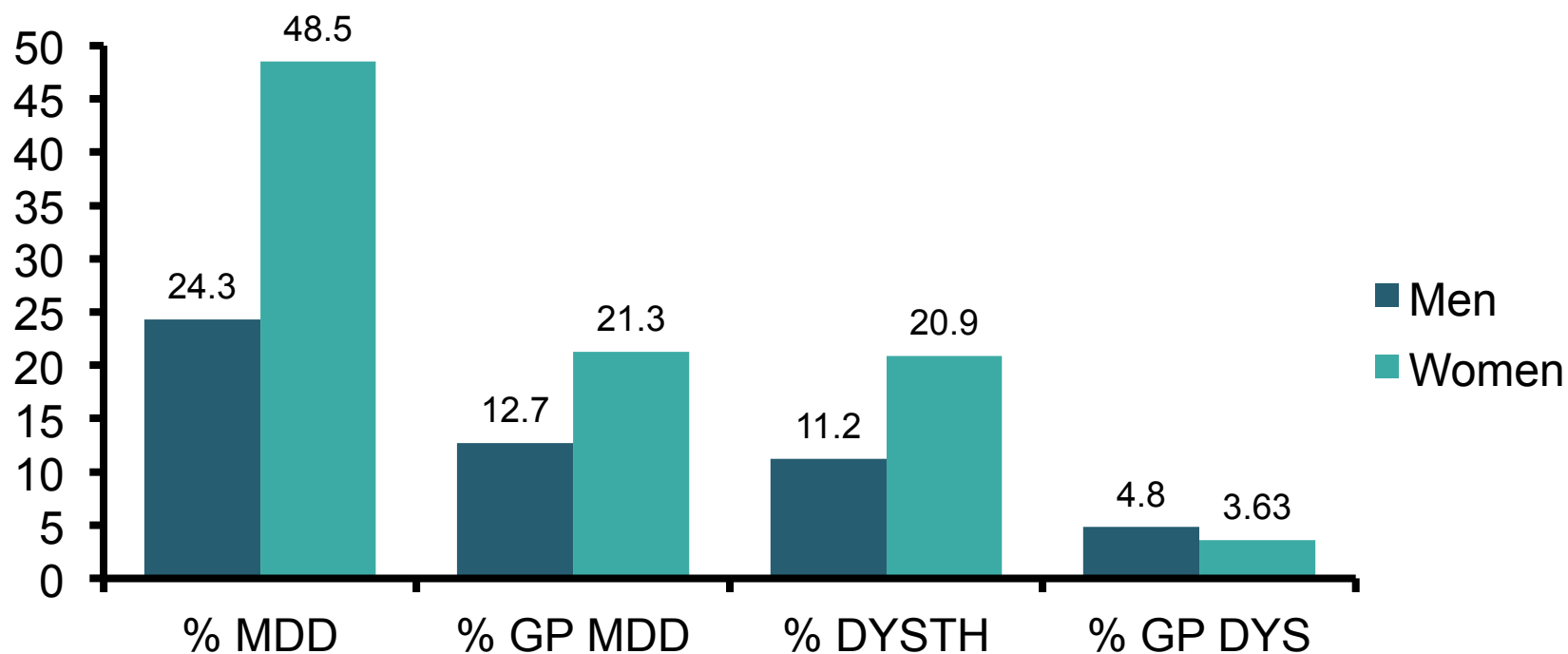
Depression is Very Common in Alcohol Dependence



Those with alcohol dependence:

- 80% report depressive symptoms
- 33% have MDD diagnosis
- Women > men

Alcohol Dependence with Comorbid Major Depression or Dysthymia

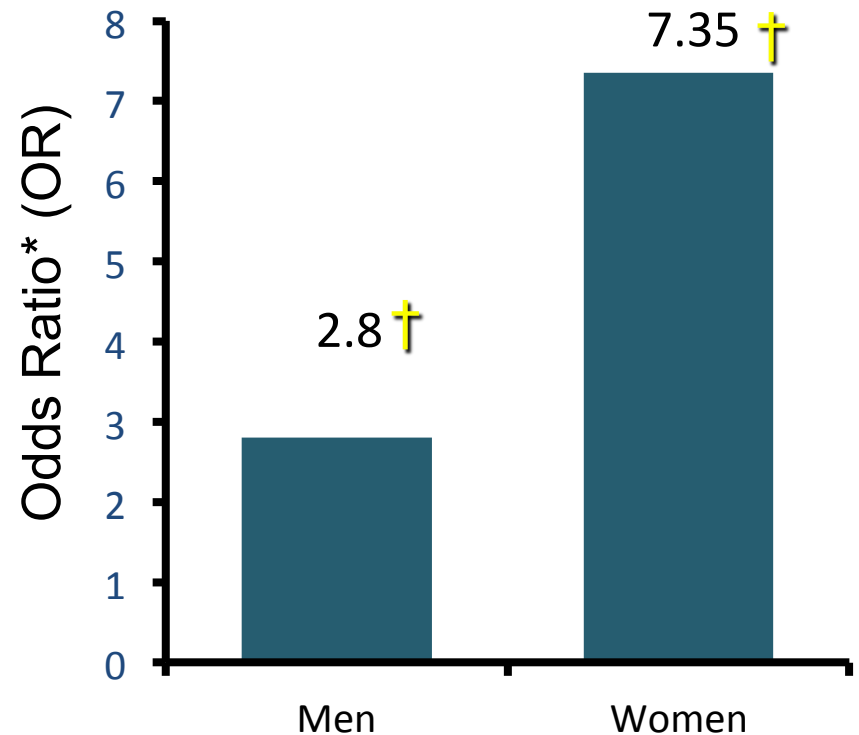


OR MDD = Men: 2.95; Women: 4 – OR DYS = Men: 3.8; Women: 8

Kessler R, et al. *Arch Gen Psychiatry*. 1997;54(4):313-321.

Alcoholism in Bipolar Men and Women

- N = 267
 - 116 men, 151 women
- Rates of alcoholism:
 - BP men = 49%
 - BP women = 29%



*Odds ratio compared to ECA sample weighted by age, race, gender;
BP men OR=2.8 (95% CI: 1.59-4.81); BP women OR= 7.35 (95% CI: 3.32-16.26)
† $P < .0001$

Frye MA, et al. *Am J Psychiatry* 2003;160:883-889.

The Challenge of Mood Disorders–SUD comorbidity



- Complicated course (Rec/Relap/polysympt.)
- Suicidality and increased mortality
- Dysfunctions (family, social, emp/edu)
- Multiple morbidities (Medical & psychiatric)
- Unstable housing and homelessness
- Violence, legal problems, incarceration
- More service use (days in hospital, ER visits, use of SUD and MH services)

SUD = substance use disorder, MH = mental health

Salloum IM, Thase M. *Bipolar Disorders* 2000;2(32):269-280.

Reciprocal Negative Impact

MD ↔ SUD


- Diagnostic confusion
- Treatment compliance
- Treatment response
- Course and outcome of illness

Diagnostic Issues



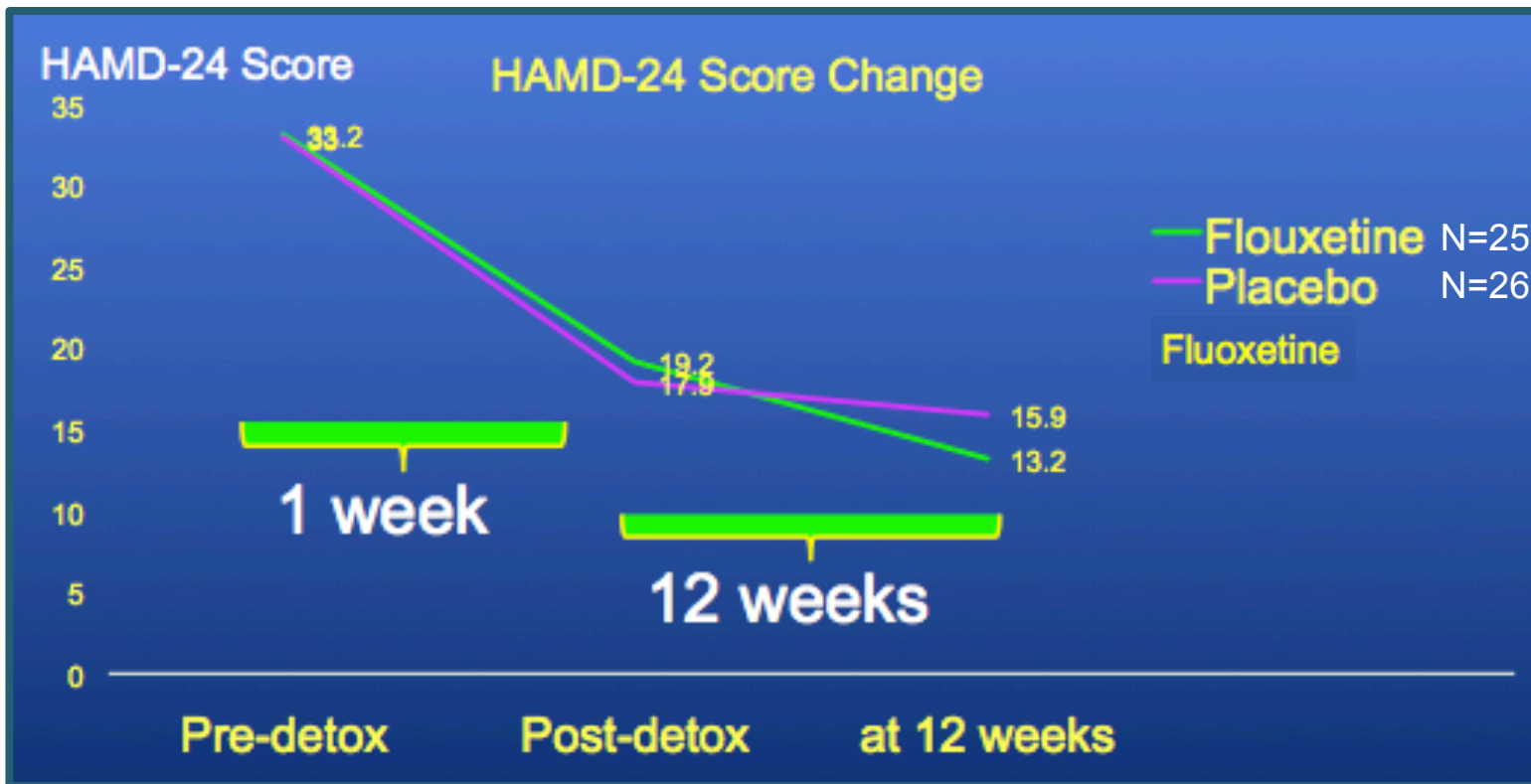
- Drinking vs. alcoholism; sadness vs. depression; alcohol induced vs. primary
- Rating scales & structured interviews
- *DSM-5* guidelines
 - Prior or during abstinence from alcohol
 - Better accounted for by depression
 - Does not occur only during intoxication/withdrawal
- Prior episodes & family history

Diagnostic Accuracy & Medications in the Context of Alcoholism & SUD



- Diagnostic Accuracy
 - Duration of drug free observational period: 4 vs..... 1 week?
 - Advantage & disadvantage of initiating medication
 - Studies of depressed alcoholics

Limited Change in Depressive Symptoms on Placebo (HAMD-24)



Cornelius JR, Salhoum, IM, et al. *Arch Gen Psychiatry*. 1997;54(8):700-705.

Alcohol & SUDs Impact on the Course of Mood Disorders



Mood Disorders Course	Alcohol & SUD Impact
Response	Worsens respond to medication
Remission	Prolong sick state
Recovery	Maintain persistent symptom & impair coping skills
Relapse	Increase risk for depression relapse
Recurrence	Maintain sub-syndromal state; Psychosocial stress

Mood Disorders as a Risk for Alcohol & SUDs Relapse



- Alcohol & substance use as “self-medicating” the symptoms of mood disorders?
- Mood disorders increases vulnerability to alcohol relapse by decreasing stress coping abilities

Depression as a Risk for Alcohol & SUDs Relapse



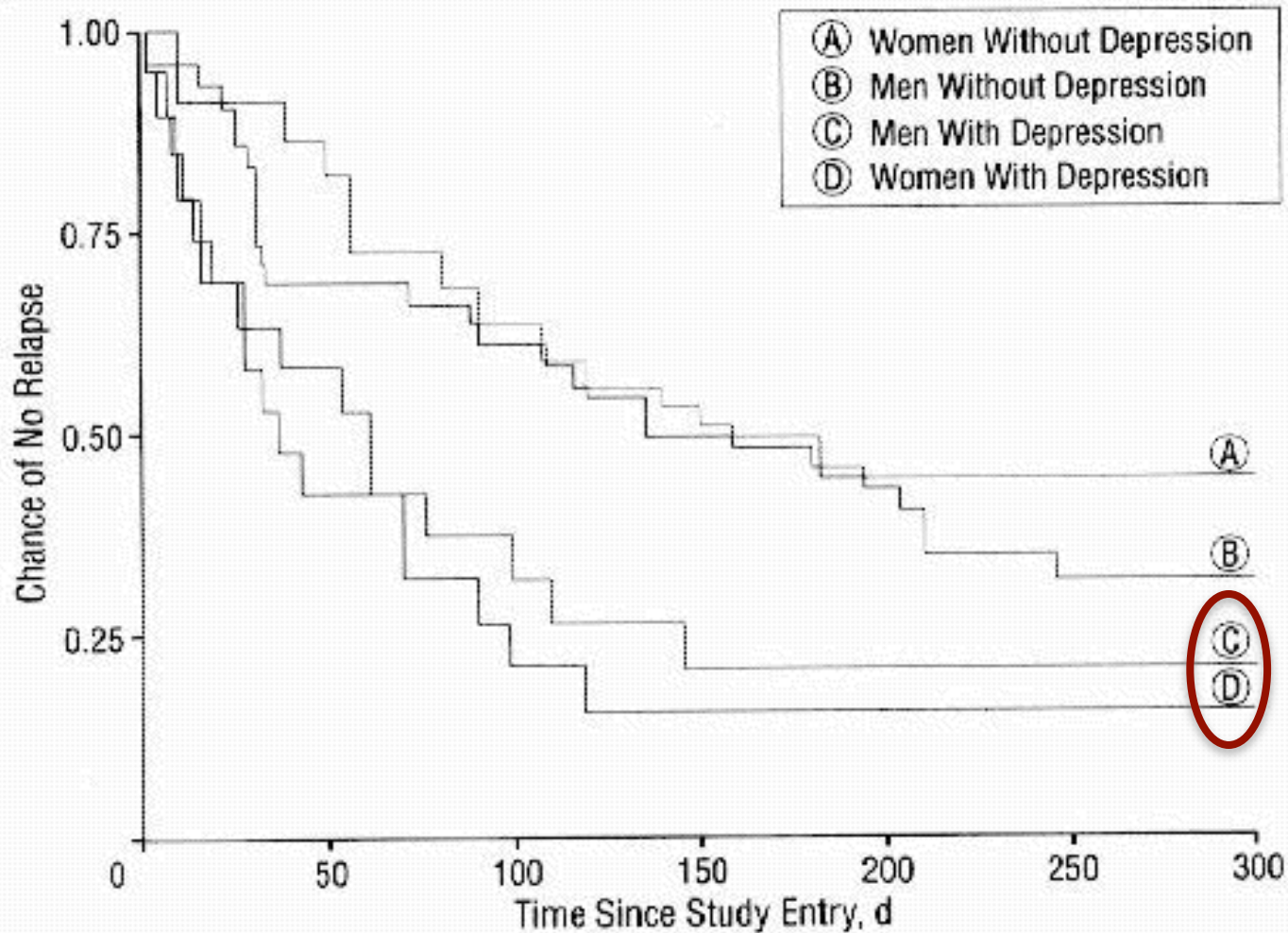
- Stressors that exceed the adaptation capacity of the individual lead to relapse
- Depression impacts multiple areas of adaptation abilities predictive of relapse
- Effect of stress on alcohol problem was found to be mediated by depression

Depression Impacts on Adaptation Capacity Which Predicts Relapse



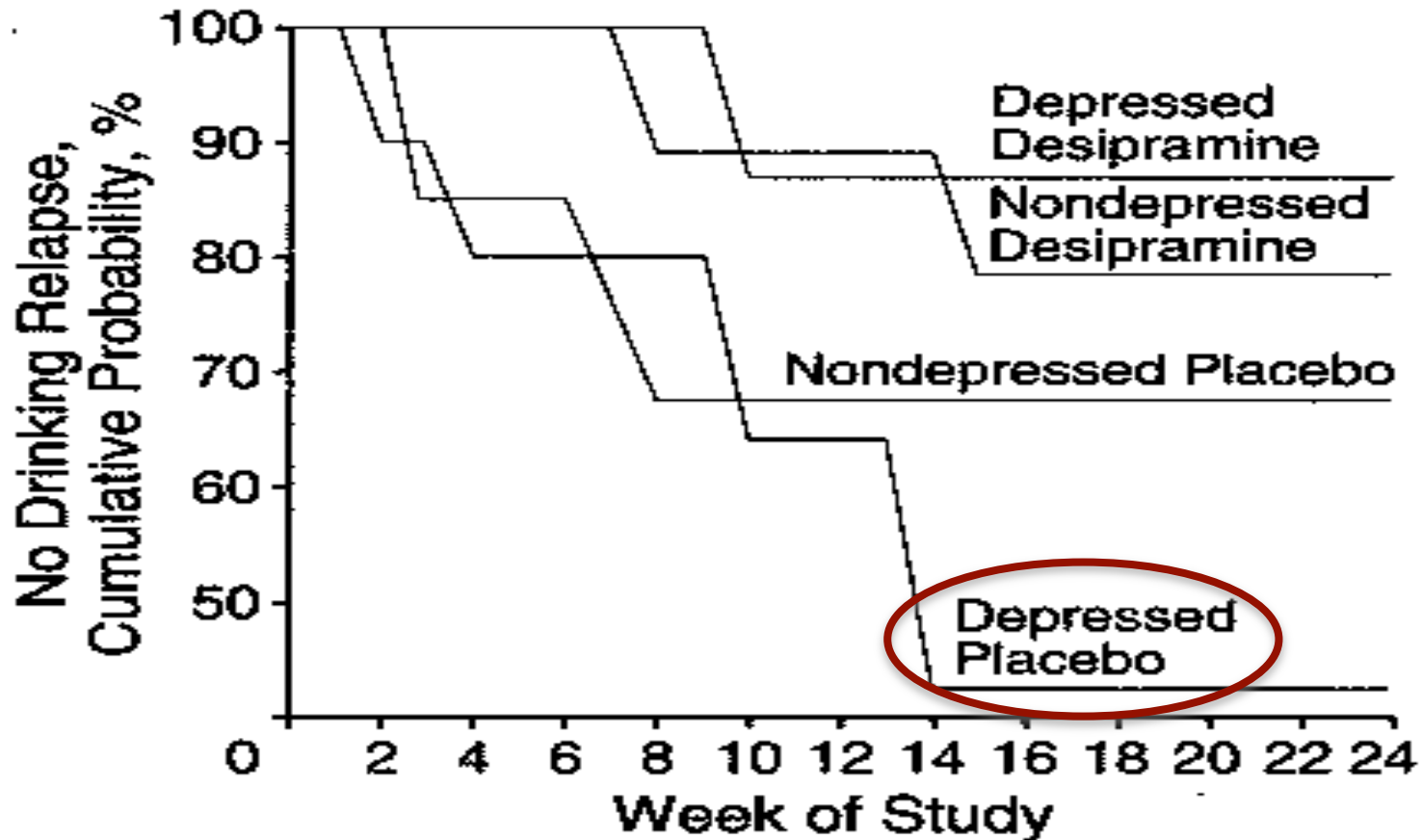
- Impairment in coping skills
- Impairment in self-efficacy
- Influence availability of social support
- Cognitive distortion
- Irrational beliefs

Major Depression & Gender Predict Relapse



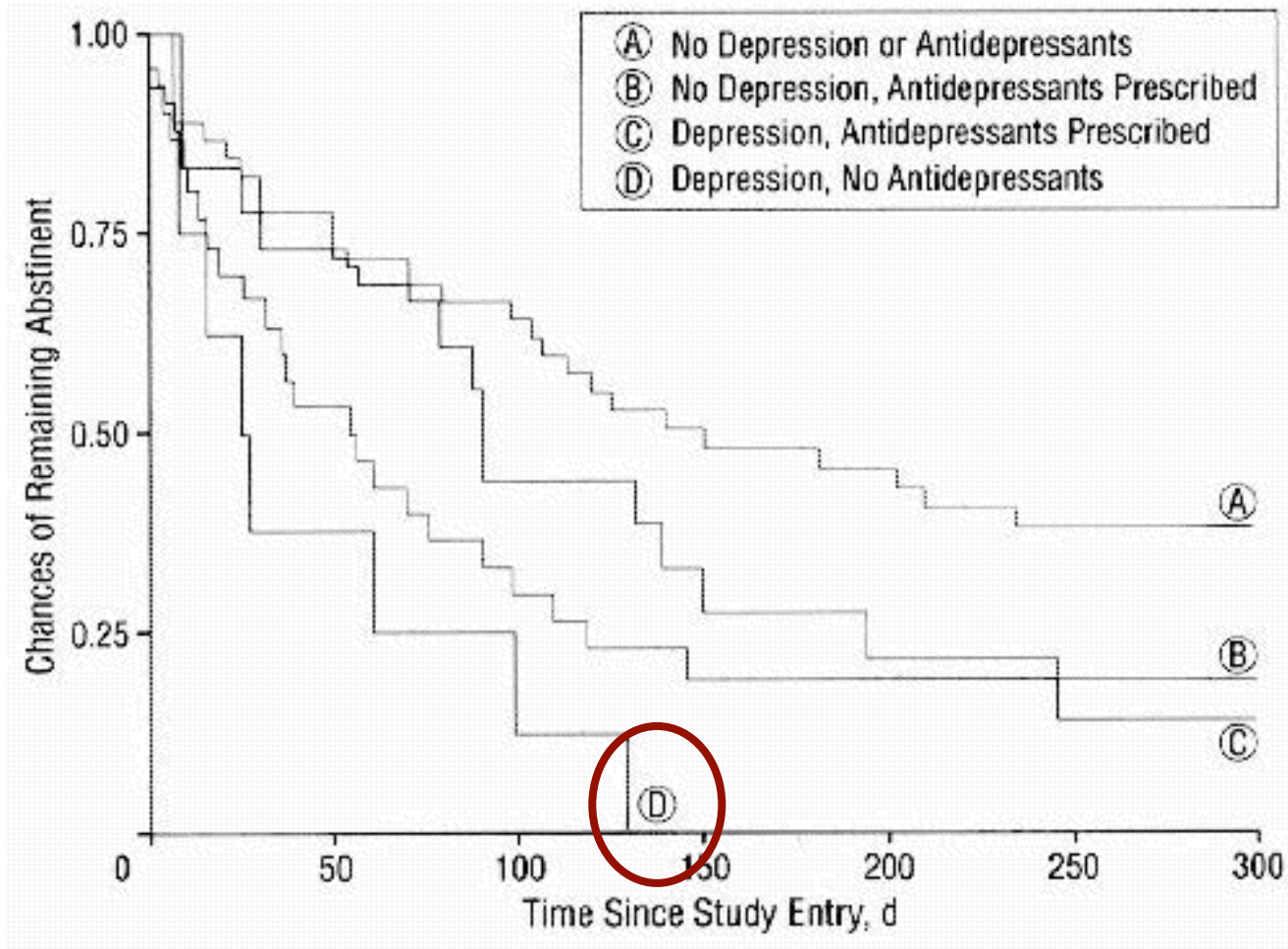
Greenfield SF, et al. *Arch Gen Psychiatry*. 1998;55(3):259-265.

Untreated Depression Leads to Early Relapse



N=71

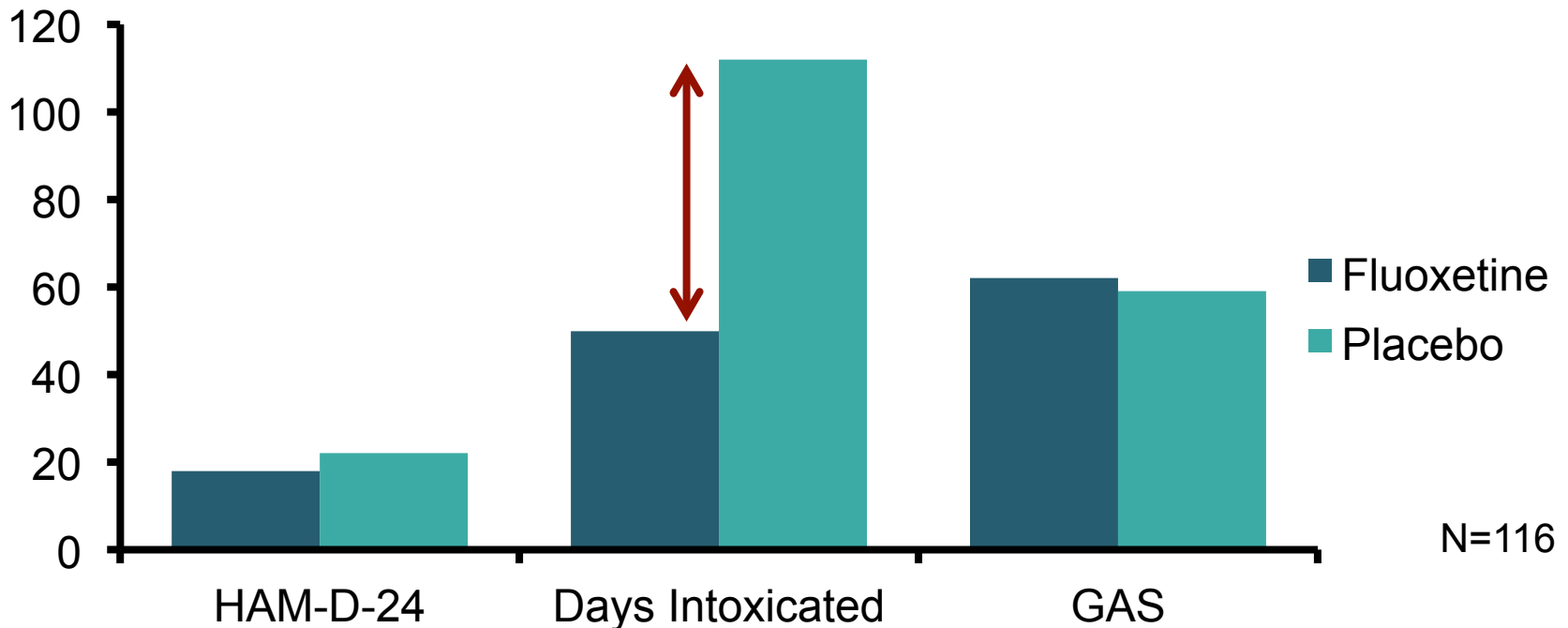
Untreated Depression Leads To Early Relapse



N=40 women
N=61 men

Fluoxetine in Depressed Alcoholics

One Year Follow-up



Bipolar ↔ SUDs Relationship

SUD on Bipolar

- Course Modifier
 - Earlier onset
 - Shorter cycle length
 - Persistent symptom
 - Delayed recovery
 - Rapid cycling?
- Episode Modifier
 - More symptoms
 - Worsens depression
 - Mixed episodes
 - Episode switch?

Bipolar on SUD

- Bipolar as risk factor
 - Bipolar predate SUD
 - Mood states (mania)
 - Impulsivity
 - Self-medication
 - Impaired coping skills
 - Neurobiological factors
- Adolescent onset BPD

Bipolar Multi-Symptoms Disorder

MANIA

- Euphoria/ Grandiosity
- Pressured speech
- Impulsivity
- Excessive libido
- Recklessness
- Social intrusiveness
- Decrease need for sleep
- Hyperactivity

PSYCHOSIS

- Delusions
- Hallucinations

DEPRESSION

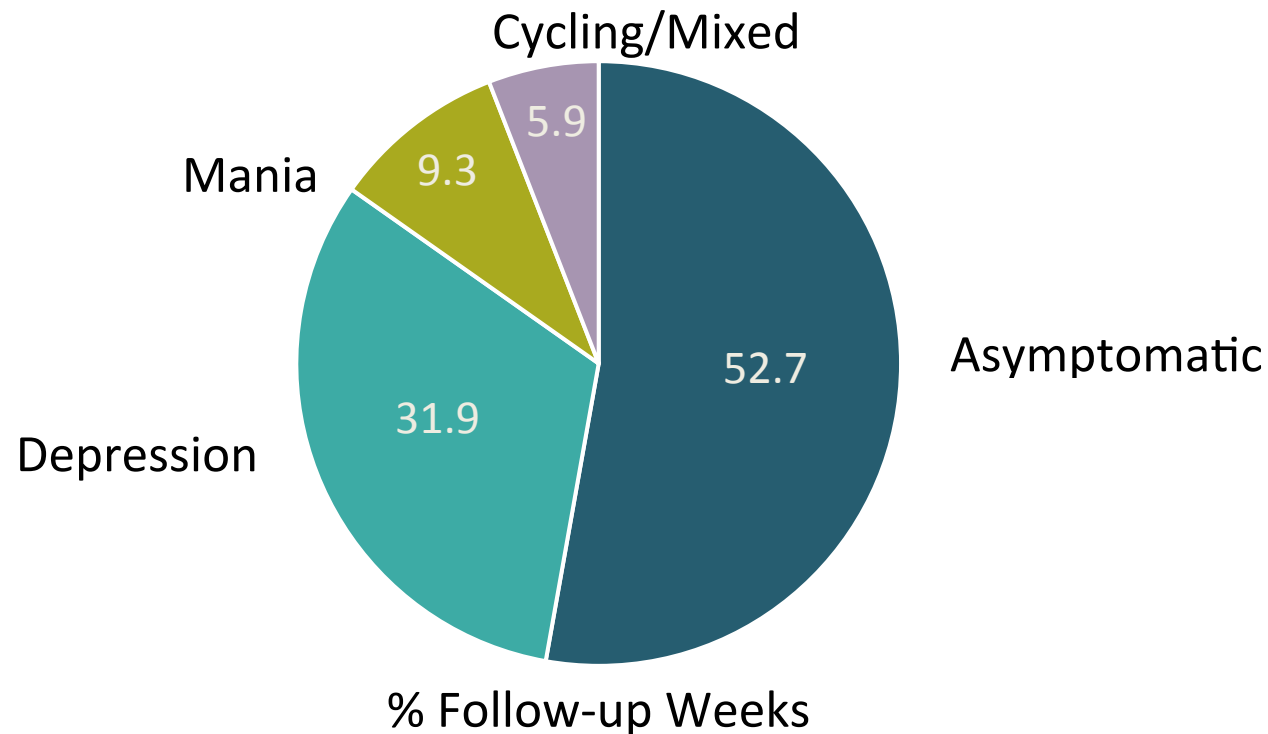
- Depression
- Anxiety
- Irritability
- Hostility
- Violence or suicide

COGNITION

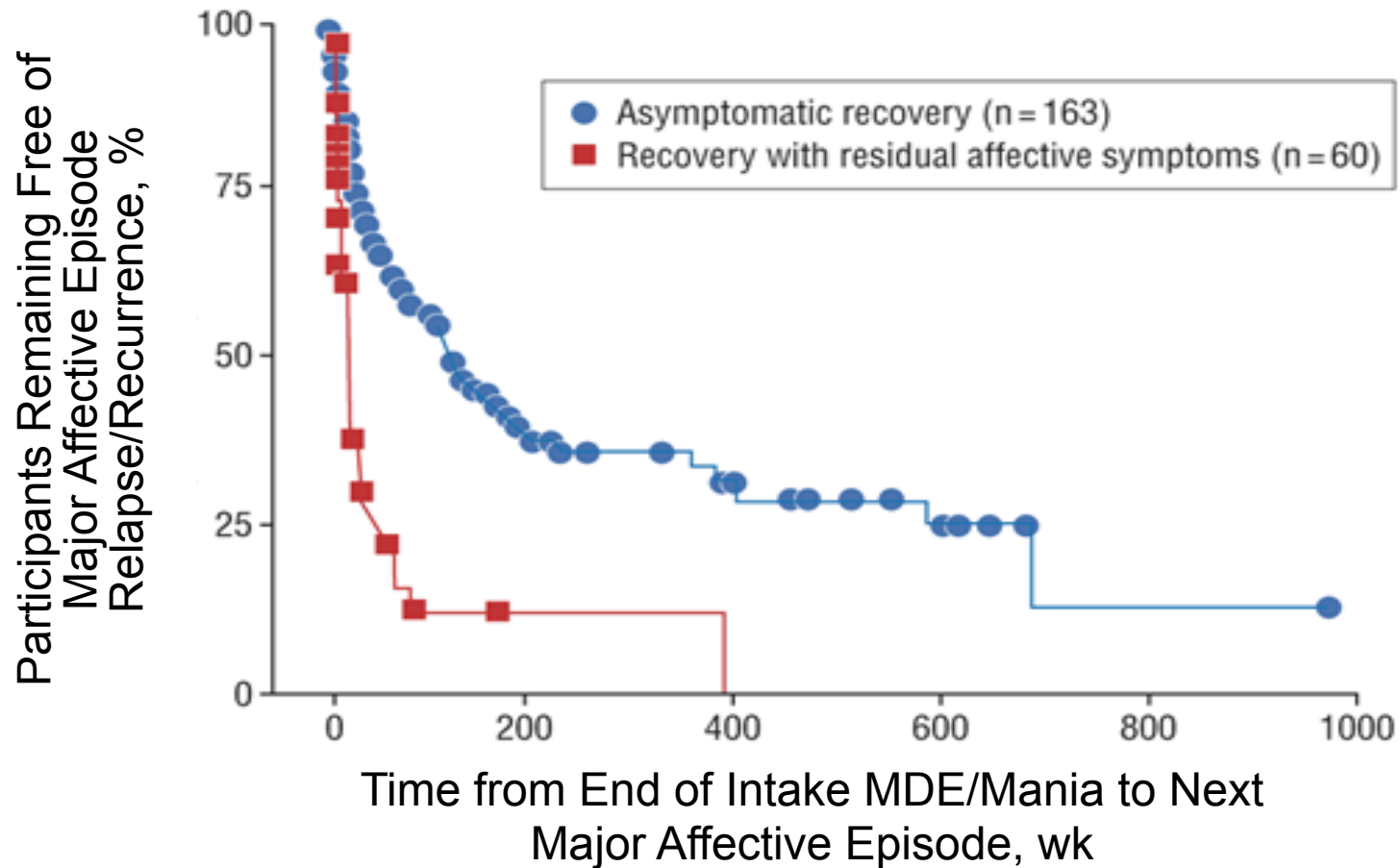
- Racing thoughts
- Distractibility
- Disorganization
- Inattentiveness

Long-term Natural History of the Weekly Symptomatic Status of Bipolar I Disorder

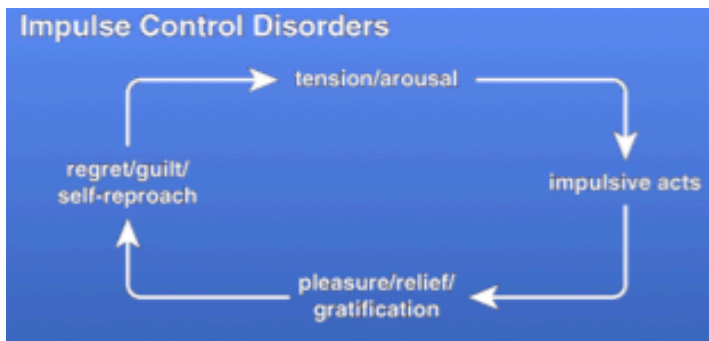
Percentage of Follow-up Weeks Spent at Specific Affective Symptom During Long-term Follow-up of 146 Patients With Bipolar I Disorder



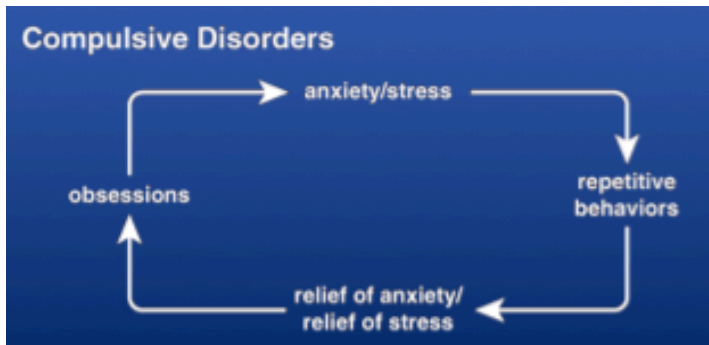
Residual Symptoms Increase Future Episode Relapse Risk



Etiology: Pathophysiology



+Risk Factors: Genetic, Environmental, Stress



Positive Reinforcement

Hypomania
Impulsivity
Sensation-seeking
Mood Instability

Negative Reinforcement

Reward Transmitters Implicated in the Motivational Effects of Drugs of Abuse



Positive Hedonic Effects

- ↑ Dopamine
- ↑ Opioid peptides
- ↑ Serotonin
- ↑ GABA

Mania:
Positive hedonic state

Negative Hedonic Effects of Withdrawal

- ↓ Dopamine ... “dysphoria”
- ↓ Opioid peptides ... pain
- ↓ Serotonin ... “dysphoria”
- ↓ GABA ... anxiety, panic attacks

Depression:
Negative hedonic state

Medical Burden in Patients with Severe Psychopathology

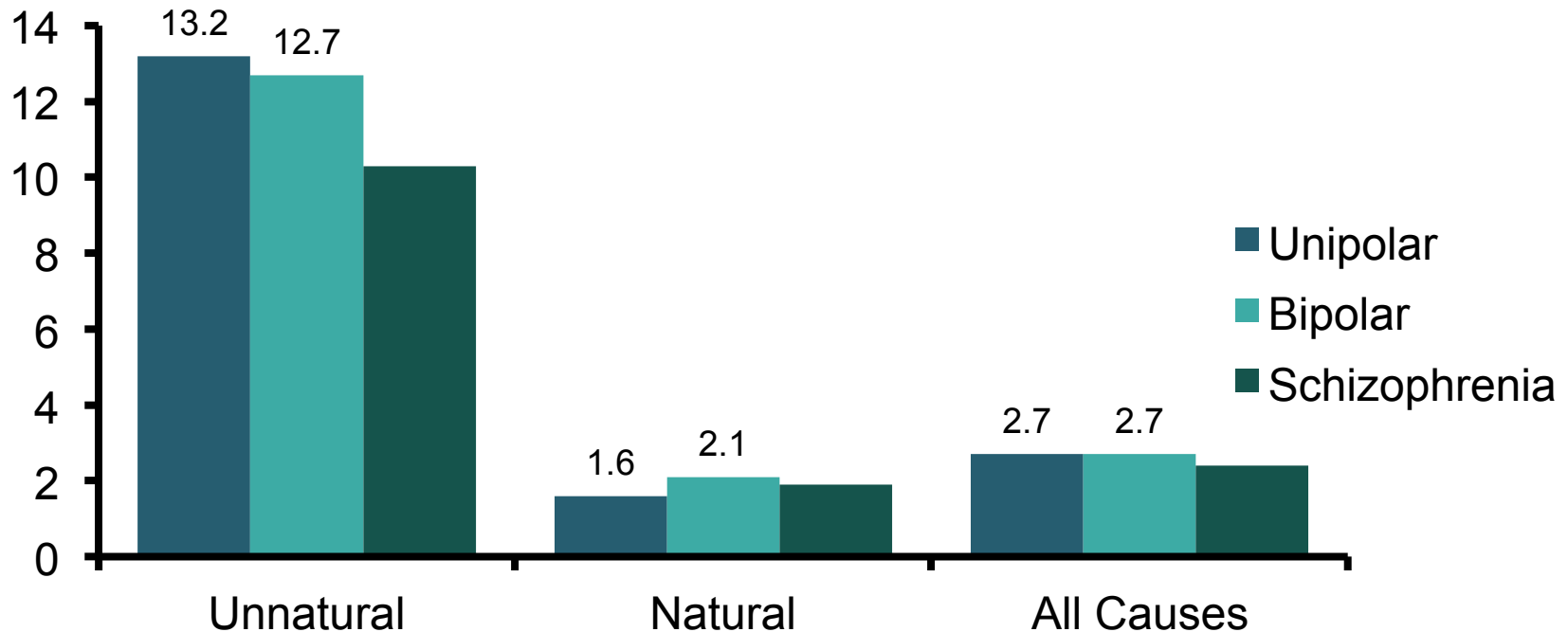
Chronic mental disorders are associated with physical disorders and excess mortality

- Major depression
- Bipolar disorder
- Schizophrenia
- Alcoholism and other substance use disorders



Obesity
Diabetes
Cardiovascular
Chronic resp.
HIV / V.Hep /
STD/ TB
Trauma, Suicide

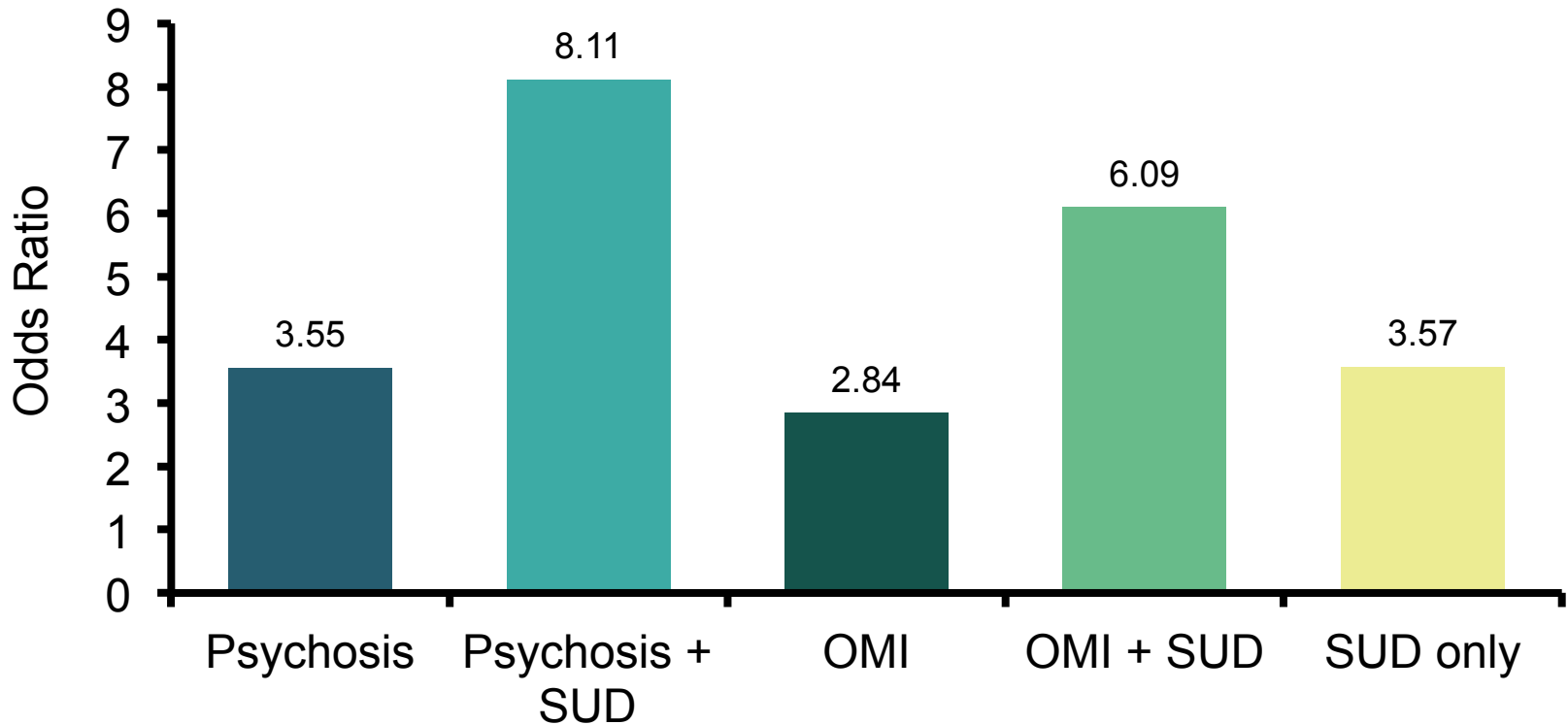
Mortality in Unipolar, Bipolar, and Schizophrenia for Females (SMR)




SMR = standardized mortality ratio (# of observed cases / # of expected)
Osby U, et al. *Arch Gen Psychiatry*. 2001;58(9):844-50.
Osby U, et al. *Schizophr Res*. 2000;29;45(1-2):21-8.

Death by Injury

Adjusted Odds of Death by Injury in Medicaid Beneficiaries



OMI = other mental illness; SUD = substance use disorders
Dickey B, et al. *J Behav Health Serv Res.* 2004;31(1):75-85.



Management of Mood Disorders with Comorbid SUD

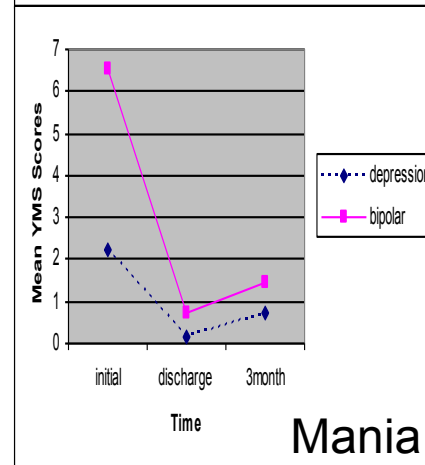
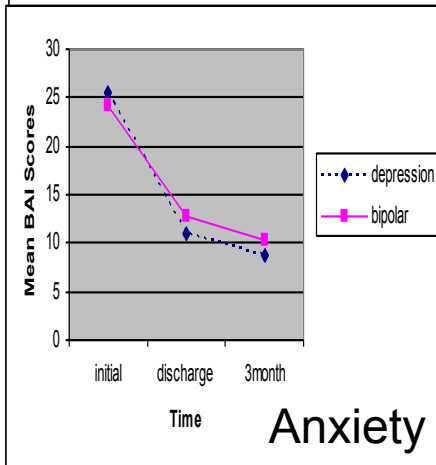
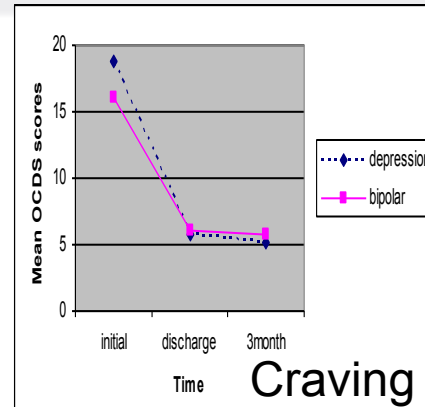
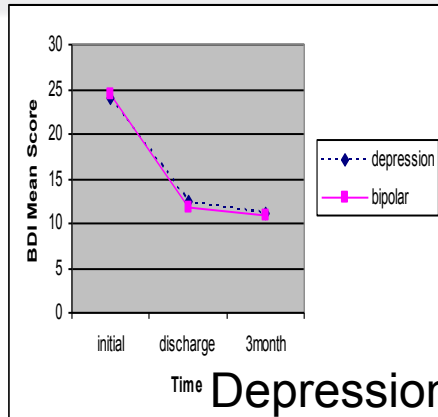
Treatment Integration for Comorbid Bipolar & Addictive Disorders



- System Integration
 - From financing to access
- Provider Factors
 - Training and commitment
- Interventions
 - Medications and psychosocial interventions
- Consumer Factors
 - Recognition of interrelationship of the two diseases


Integrated RX at the Programmatic Level

Outcome of “FIRESIDE” program, Alcoholism + Mood
(N = 228 adults) Abstinence rates: 60% @ 3m; 50% @ 6m



Slide Courtesy of Dr. Conor Farren
Farren C, McElroy S. *J Affect Disorder*. 2008;106(3):265-272.

Common Measures Used in Addiction



- Short screening & syndrome measures:
 - CAGE, AUDIT, AUDIT-C, DUDIT, TLFB, DSM-5 checklist
- Measures of craving:
 - Penn Alcohol Craving Scale, OCDS
- Measures of consequences/severity:
 - SIP, ASI (alcohol, drug, social, family, medical, employment and legal)
- Measures of withdrawal syndromes:
 - CIWA, COWS

Alcohol Use Disorder Identification Test-C (Score 0-12)

- How often did you have a drink containing alcohol in the past year?
 - 0: never, 1: 1 or less month, 2: 2-4 month, 3: 3x week, 4: 4-5/week, 4: 6 x week
- How many drinks did you have on typical day when you were drinking in the past year?
 - 0: 0 or 1-2 drinks, 1: 3-4, 2: 5-6, 3: 7-9 , 4: 10 or more
- How often did you have 6 or more drinks on one occasion in the past year?
 - 0: never, 1: <1/month, 2: monthly, 3: weekly, 4: daily

Score of 3: Sensitivity: 90% active abuse/dep; 98% heavy drinkers;
Specificity 60%;

Score of 4: 86% specificity heavy drinking; 72% for abuse/dependene

Stabilization of Bipolar Disorder and Substance Abuse

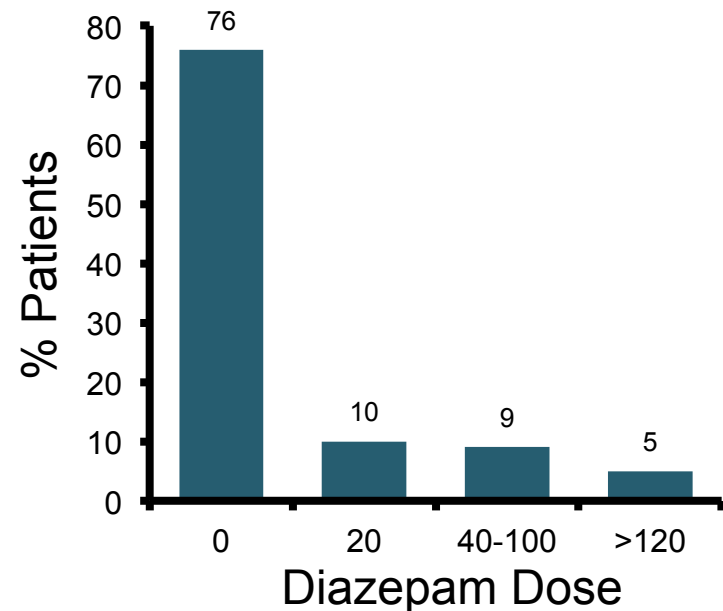


- Aggressive acute stabilization
 - Mania
 - Depression
 - Rapid cycling
 - Alcohol/SUD withdrawal
- Relapse Prevention
 - Maintenance mood stabilization
 - DBS Support Alliance
 - Alcohol relapse prevention
 - AA/DD support

Treatment of Alcohol Withdrawal in Psychiatric Patients

- Goals
 - Prevent complications
 - Alleviate withdrawal symptoms
 - Initiate process of recovery “window of opportunity”
- Principles
 - Medication half-life
 - **Symptom-triggered therapy**
 - Effective in preventing complications

WAS Symptom Triggered Diazepam Loading Dose



Diazepam loading dose/ CIWA-Ar (Seller, et al. 1983)
Salloum IM, et al. *Psychopharm Bull.* 1995;31(2):305-310.

Paradigms of Medications Trials for Mood Disorders & SUD



Monotherapy Trials: 1 med.
– 2 outcomes

- Medications Bipolar Dis.
 - Mood Stabilizers (Lithium, Anticonvulsants)
 - Valproic acid, carbamazepine (ER), lamotrigine
 - Antipsychotics (Atypical)
 - Quetiapine, aripiprazole, risperidone, olanzapine, ziprasidone, clozapine
 - Antidepressants SSRIs, SNRIs, TCAs,

Combined meds: 2 meds. – 2 outcomes

- Medications for SUD
 - Alcoholism
 - Disulfiram*, Naltrexone* (PO, IM), Acamprosate*, Topiramate, Gabapentin
 - Tobacco
 - Varenicline, bupropion, NPT
 - Cocaine
 - Cannabis
 - Opioid
 - Methadone, suboxone, naltrexone

* FDA approved for SUD

Placebo-Controlled Trials in Bipolar Disorder and Cocaine Use Disorder



Study	Medication	N	Wks	Design	Cocaine outcome
Brown et al, 2007	Citicoline	44	12	D-blind	Advantage over PBO
Brown et al., 2012	Citicoline	60	12	D-blind	Advantage* Methamphetamine Depression(BP&MDD)
Brown et al., 2012	Lamotrigine	112	110	D-blind	Advantage on money spent on cocaine
Brown et al., 2015	Citicoline	130	12	D-blind	Advantage on + urine early in trial

Brown ES, et al., 2007. *J Clin Psychopharmacol.* 27 (5): 498-502.; Brown ES, et al., 2012. *J Affect Disord.* 143(1-3): 257-260.; Brown ES, et al., 2012. *Neuropsychopharmacology.* 37 (11):2347-2354.; Brown ES, et al. 2015. *Am J Psychiatry.* 172(10):1014-1021.

Placebo-Controlled Trials in Bipolar (I-II) Disorders and Alcoholism



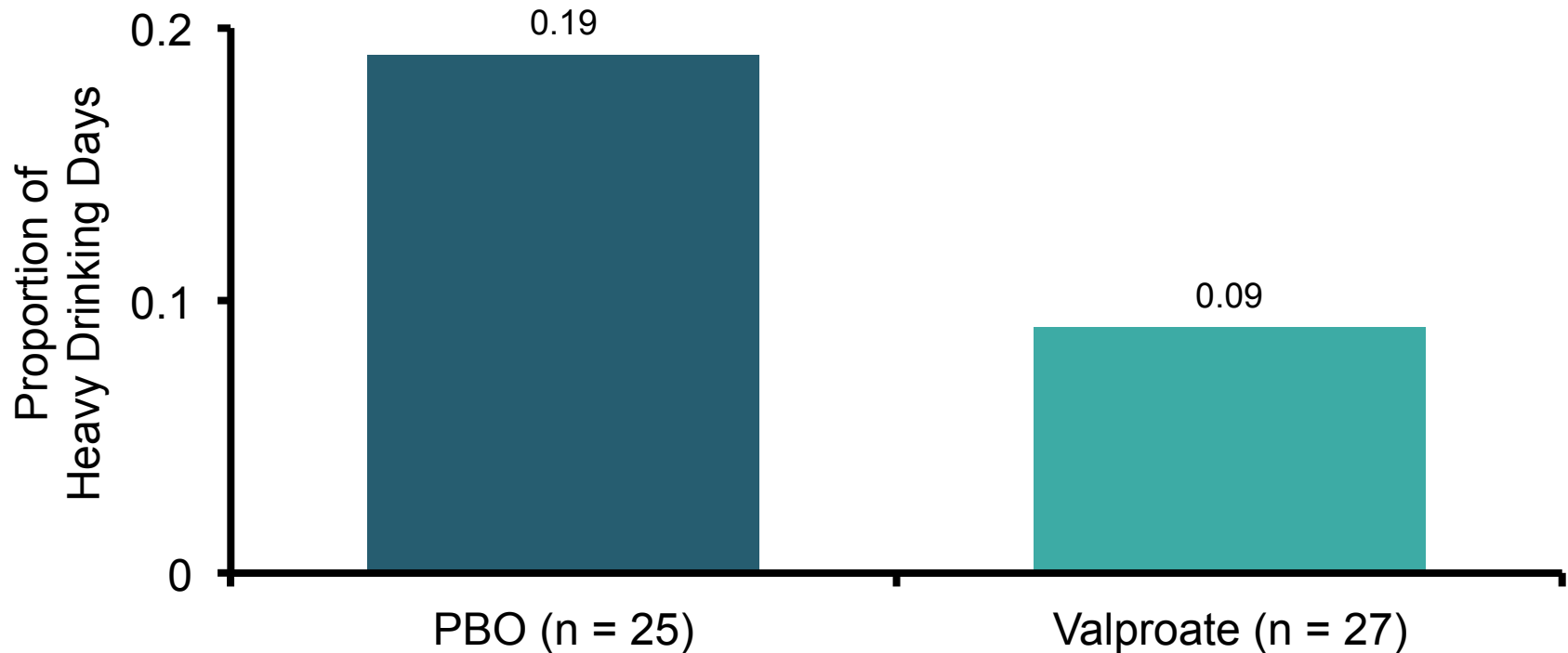
Study	Medication	N	Wks	Design	Alcohol outcome
Salloum et al., 2005	Valproic acid	59	24	D-blind	Advantage over PBO
Brown et al., 2008	Quetiapine	115	12	D-blind	No advantage
Brown et al., 2009	Naltrexone	50	12	D-blind	Trend toward advantage
Stedman et al., 2010	Quetiapine	362	12	D-blind	No advantage
Tolliver et al., 2012	Acamprosate	33	12	D-blind	No advantage
Brown et al., 2014	Quetiapine*	90	12	D-blind	No Advantage

Salloum IM, Olagunju Y. *Current Psychiatry Reviews* 2008, 4: 14-27.

*Brown ES, et al. *Alcoh Clin Exp Res* 2014, 38 (7):2113-2118.

Divalproex Impact on Heavy Drinking Days

Divalproex Significantly Decreases % of Heavy Drinking Days

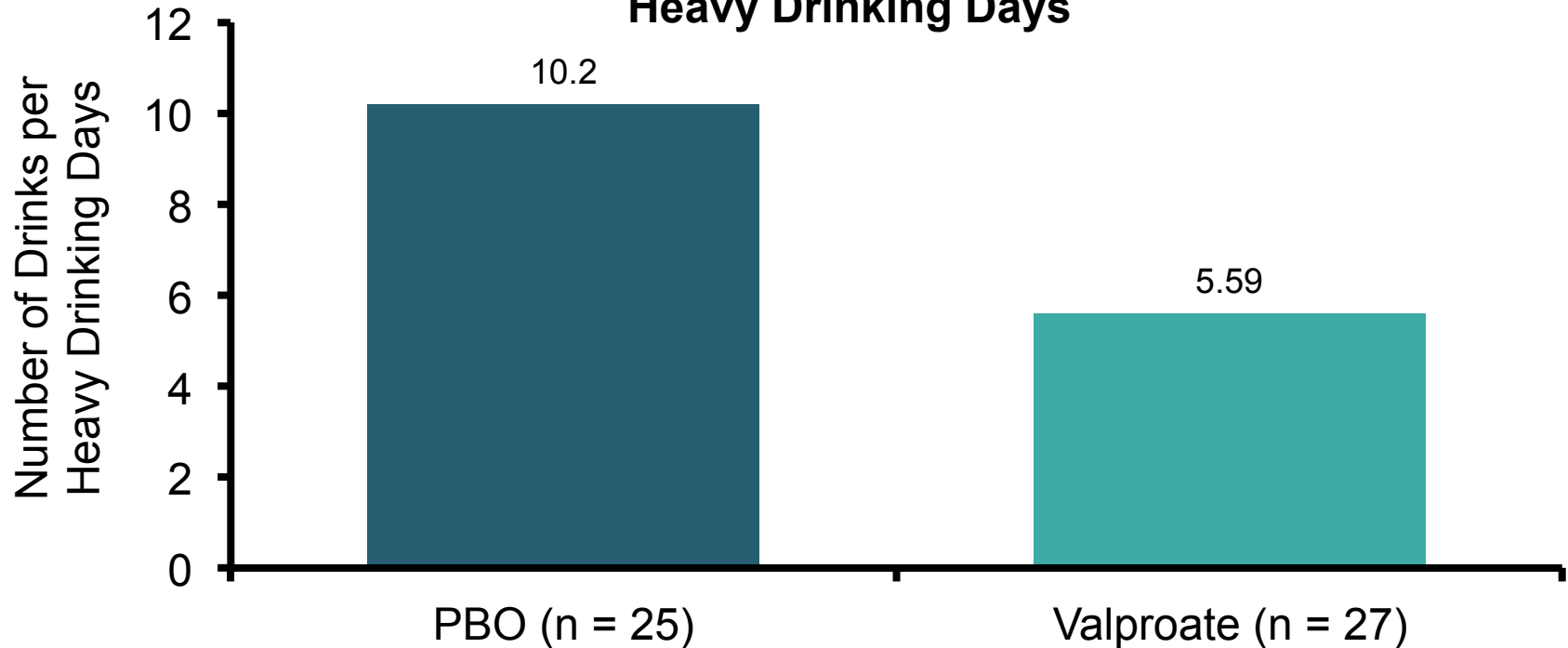


$p = .02$

Salloum IM, et al. *Arch.Gen.Psychiatry*. 2005;62(1):37-45.

Divalproex Efficacy in Alcohol Use Disorder

Divalproex Significantly Decreases # of Drinks per Heavy Drinking Days

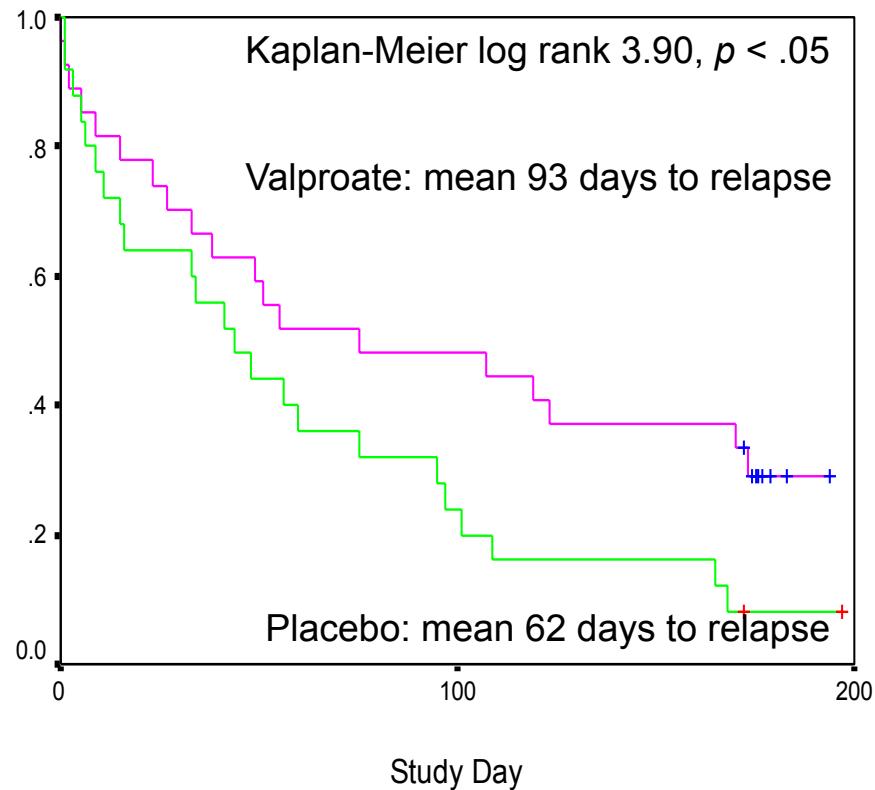


P = .02*; *Medication adherence as covariate in the Mixed Model

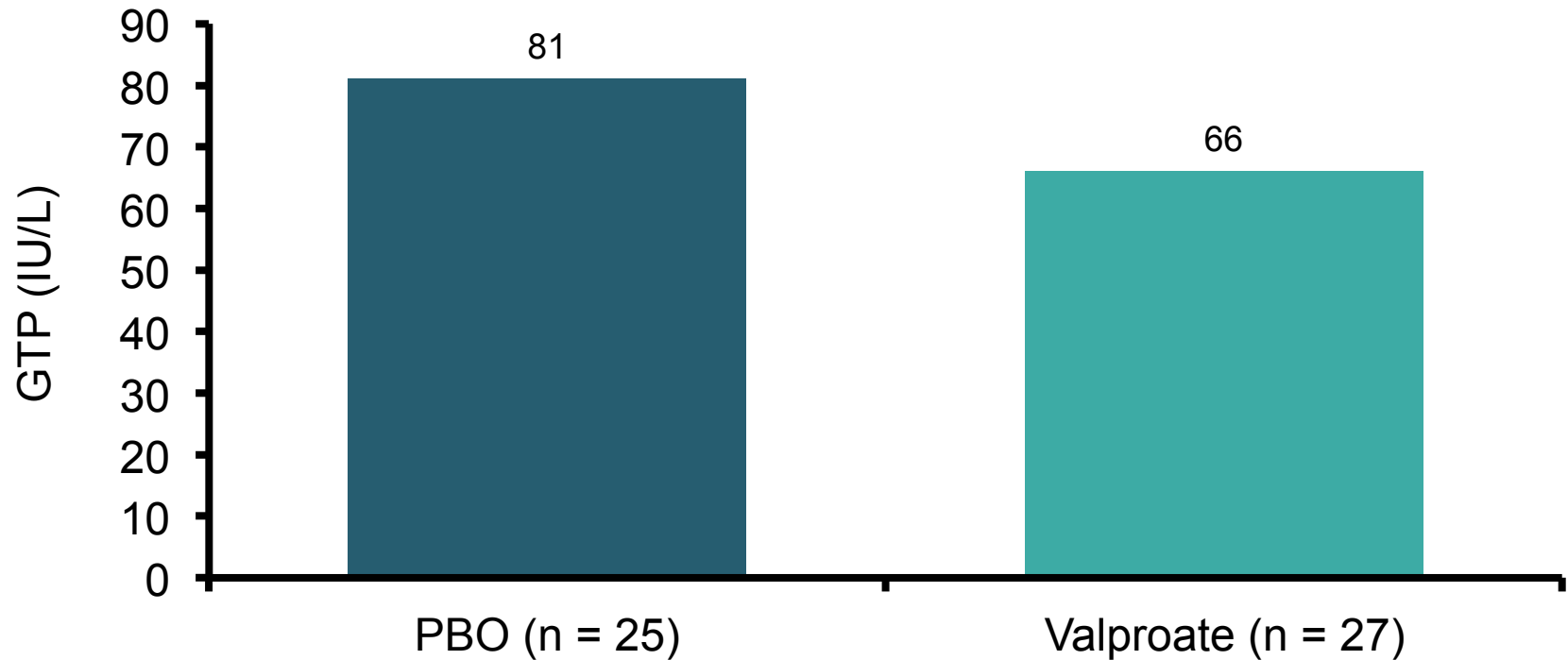
Salloum IM, et al. *Arch.Gen.Psychiatry* 2005;62(1):37-45.

Relapse to Sustained Heavy Drinking

Figure 1



Valproate vs. Placebo Effect on Glutaryl Transpeptidase (GTP)



$p = .045$

Salloum IM, et al. *Arch. Gen. Psychiatry* 2005;62(1):37-45.

SSRIs Studies in Comorbid MDD & Alcoholism

Study	Medication	N	Wks	Design	Conclusion
Kranzler, 2006	Sertraline	328	12	D-blind	No advantage
Gual, 2003	Sertraline	83	24	D-blind	No advantage*
Moak, 2003	Sertraline	82	12	D-blind	No advantage**
Pettinati , 2001	Sertraline	100	14	D-blind	- if MDD hx ***
Roy, 1998	Sertraline	36	6	D-blind	↓ MDD
Cornelius, 1997	Fluoxetine	51	12	D-blind	↓ MDD, ↓ AL
Kranzler, 1995	Fluoxetine	101	12	D-blind	↓ MDD, ↓ AL***
Adamson, 2015	Nalt ± Citalopram	130	12	D-blind	No advantage

*+ on MDD for severe sub.; ** ↓ MDD in females, ↓ # D/DD ; *** Alcohol dep. sample

Salloum IM, Olagunju Y. *Current Psychiatry Reviews* 2008;4:14-27.

Non-SSRI Studies in Comorbid MDD and Alcoholism

Study	Medication	N	Wks	Design	Conclusion
Garcia-Portilla, 2005	Venlafaxine	90	24	Open Label	Improved MDD/AL
Hernandez-Avila, 2005	Nefazadone	40	10	D-blind	Improved AL
Roy-Byrne, 2000	Nefazadone	64	12	D-blind	Improved MD
McGrath, 1996	Imipramine	69	12	D-blind	Improved MD
Mason, 1996	Desipramine	71 (28)	24	D-blind	Improved MDD/AL
Nunes, 1993	Imipramine	60	12	D-blind	Improved MDD/AL
Altamura, 1990	Viloxazine	31	12	D-blind	Improved MDD/AL

Comorbid MDD and Opioid

Study	Medication	N	Wks	Design	Conclusion
Carpenter, Brooks, et al., 2004	Sertraline	95	12	D-blind	No advantage Role of environment
Dean et al. 2002	Fluoxetine	49	12	D-blind	No advantage
Petrakis et al, 1998	Fluoxetine	44	12	D-blind	No advantage
Nunes, 1998	Imipramine	84	12	D-blind	Decreased depression less so drug
Kleber et al, 1998	Imipramine	48	8	D-blind	No advantage

All in methadone maintenance population

Salloum IM, Olagunju Y. *Current Psychiatry Reviews* 2008, 4: 14-27.

Comorbid MDD and Cocaine

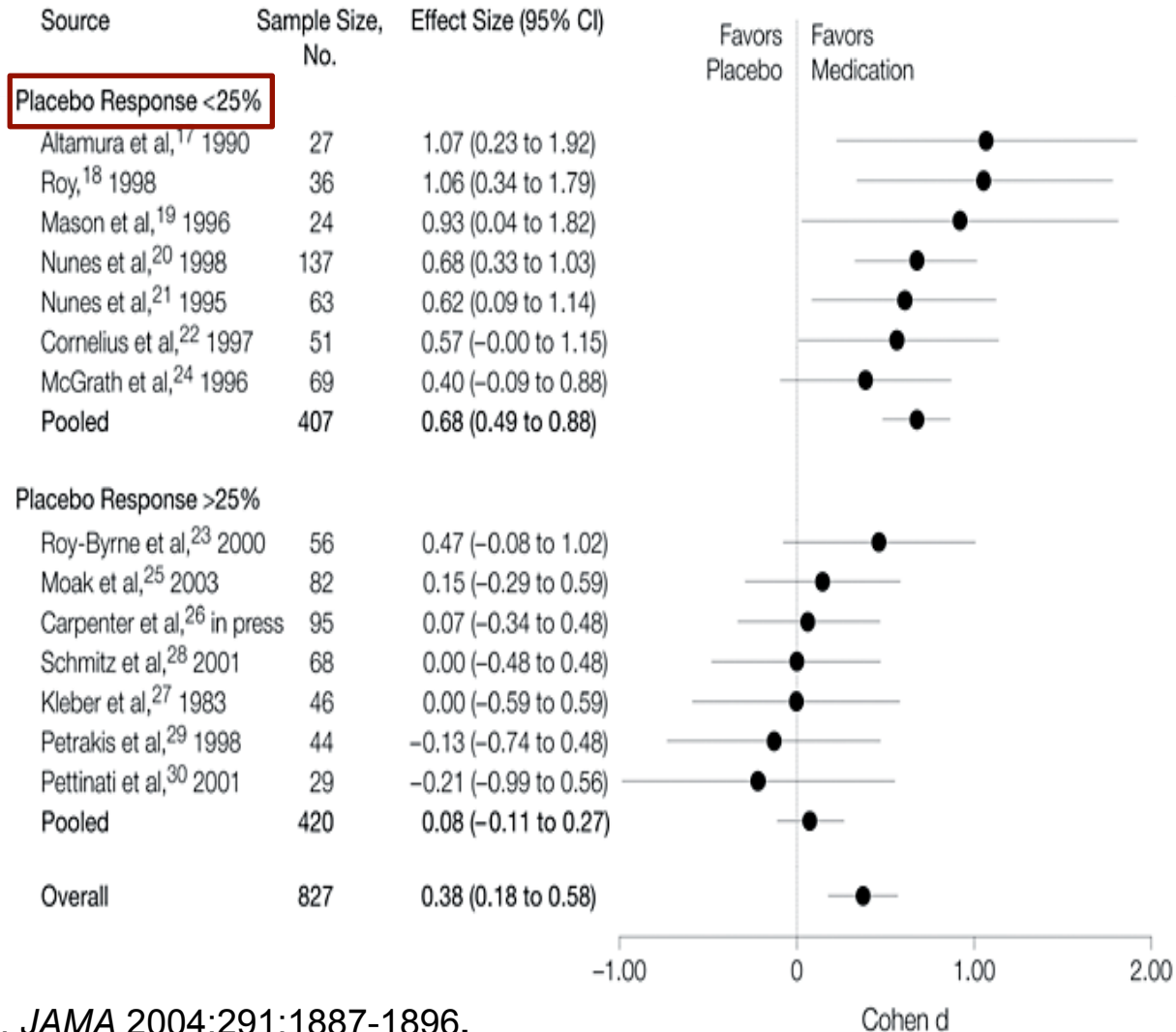


Study	Medication	N	Wks	Design	Conclusion
Schmitz et al., 2001	Fluoxetine	68	12	D-blind	No advantage
Ciraulo et al. 2005	Nefazadone	69	8	D-blind	Dec cocaine*
McDowell et al, 2005	Desipramine	111	12	D-blind	Dec depression but not cocaine
Nunes, 1995	Imipramine	113	12	D-blind	Dec depression but not cocaine

*Groups not balanced at baseline

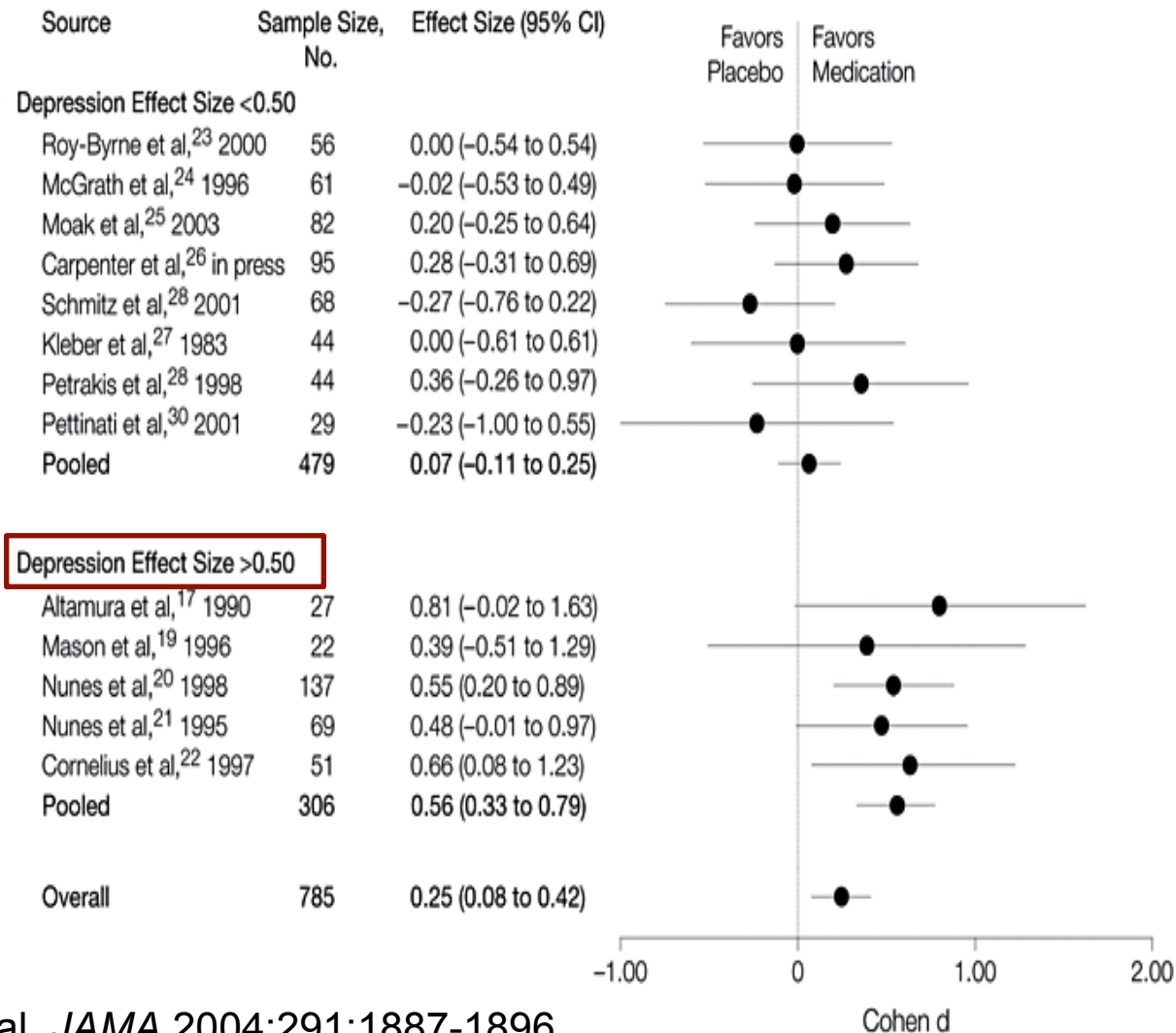
Salloum IM, Olagunju Y. *Current Psychiatry Reviews*. 2008;4:14-27.

Effect of Antidepressant Medication on Outcome of Depression (Hamilton Depression Scale)



Nunes EV. et al. *JAMA* 2004;291:1887-1896.

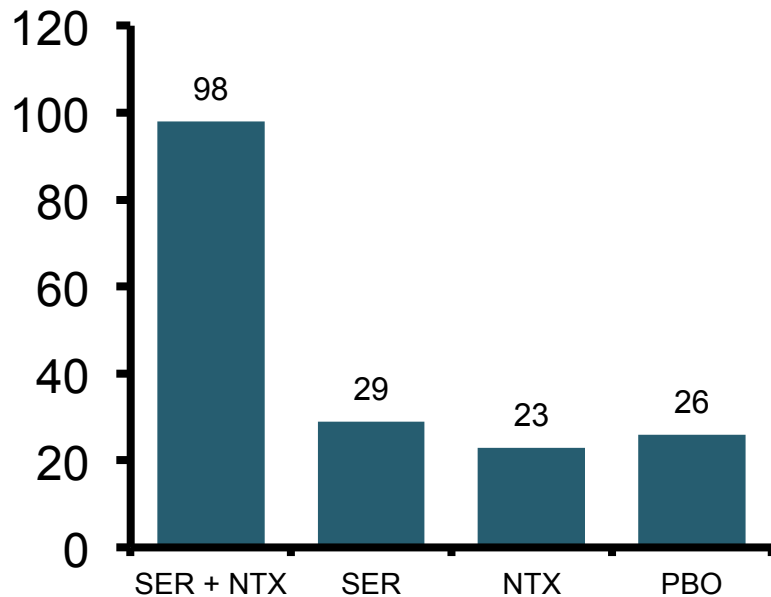
Effect of Antidepressant Medication on Outcome of Substance Use



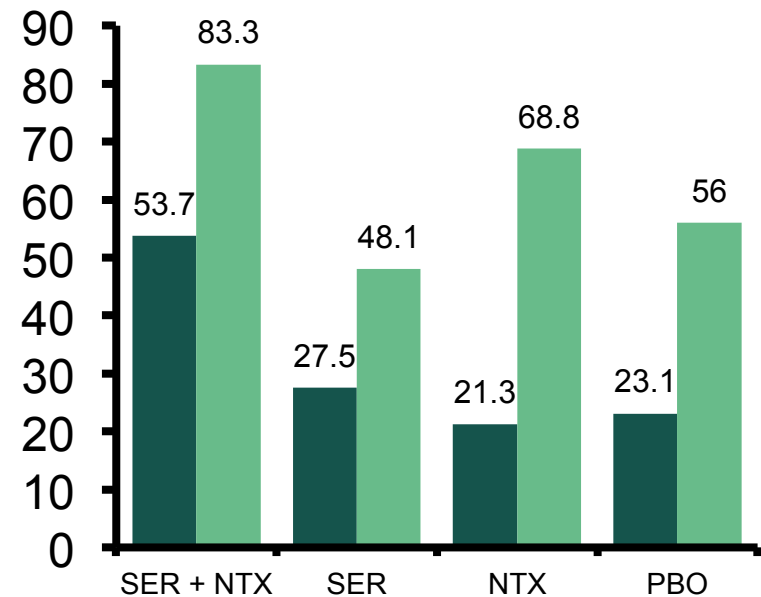
Nunes EV. et al. *JAMA* 2004;291:1887-1896.

Combined Sertraline and Naltrexone in MDD + Alcoholism

Time to Relapse to Heavy Drinking (days)



■ Abstinence Rate ■ Not Depressed



N = 170, 14 wks, 4 grps (Sertraline (SER) 200 mg, Naltraxone (NTX) 100 mg, Placebo (PBO), SER + NTX)

Pettinati HM, et al. *Am J Psychiatry*. 2010;167(6):668-675.

Summary



- Bipolar disorder with comorbid alcoholism is still an area of treatment needs
- No clear medication of choice although published data so far favors anticonvulsants use
- Naltrexone may be a promising adjunctive medication
- Multisite trials are needed for this population
- Innovative technologies and methods may enhance identification of markers of treatment response

Summary



- Antidepressants in general decrease depression but are less effective for SUD in comorbid MDD+SUDs pts
- There are no clear antidepressants of choice for DD
- Lack of response is likely due to SUD-related behavior vs. true treatment resistance
- Maximizing MDD treatment helps prevent SUD relapse
- Clarifying the nature of depression still relies on historical information
 - structured clinical assessment is more helpful than self-report
- Psychotherapy for DD is important ingredient of clinical care

DD=Dual diagnosis

Audience Response



What percentage of people with alcohol dependence report having depressive symptoms?

- A. 40%
- B. 50%
- C. 70%
- D. 80%

Audience Response



Which of the following are common measures used in addiction for withdrawal symptoms?

- A. CIWA, COWS
- B. CIWA, OCDS
- C. COWS, CAGE
- D. OCDS, CAGE



Thank You