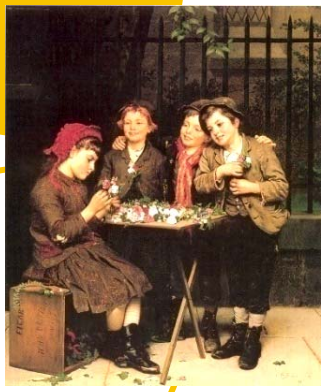
Addiction and Bipolar Disorder



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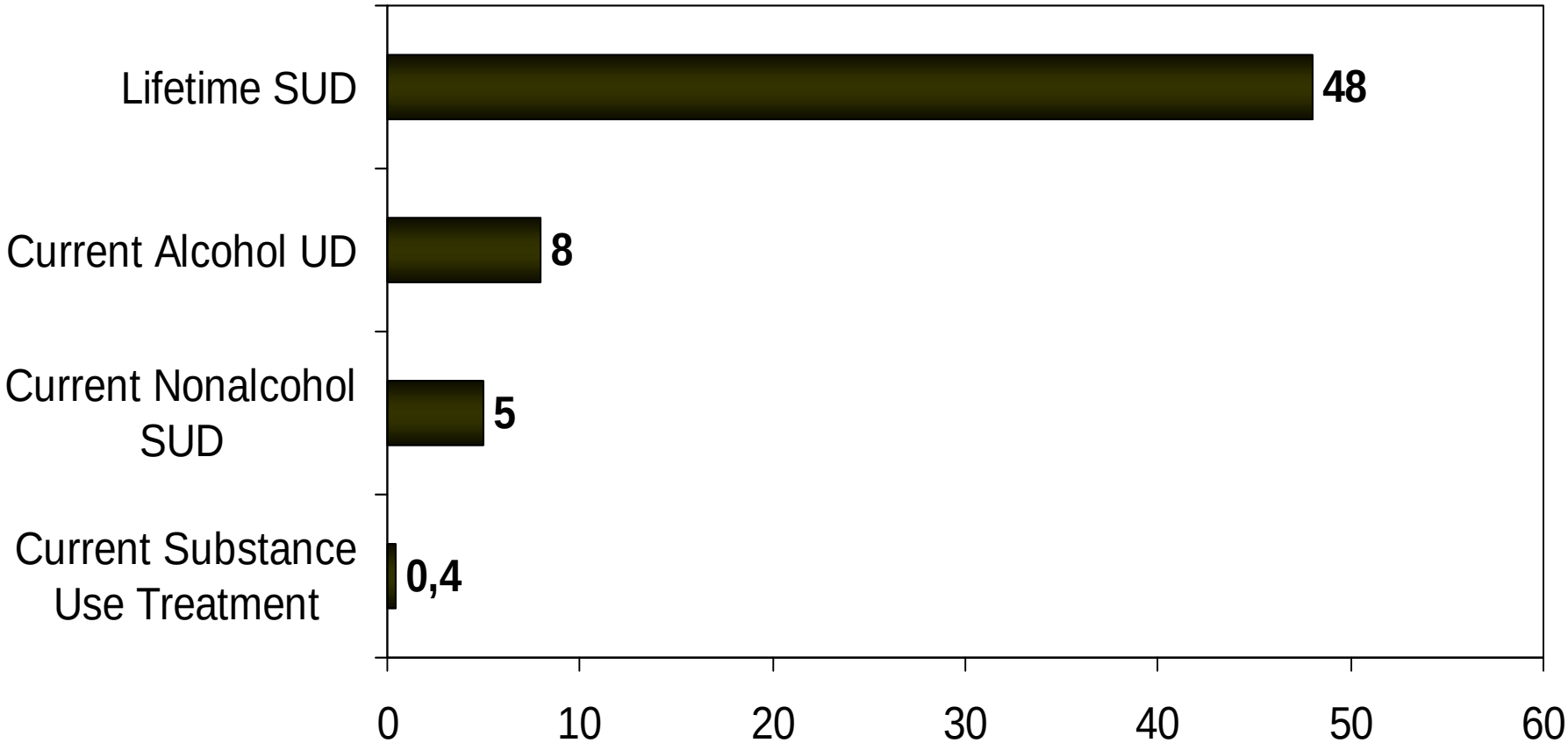
SCHEME

- Epidemiology
- Anxiety, and alcohol and drug abuse
- Polarity of episodes and alcohol and drug abuse
- Using and quiting alcohol and drug abuse, and relation with outcome
- Treating comorbidity
- Conclusions

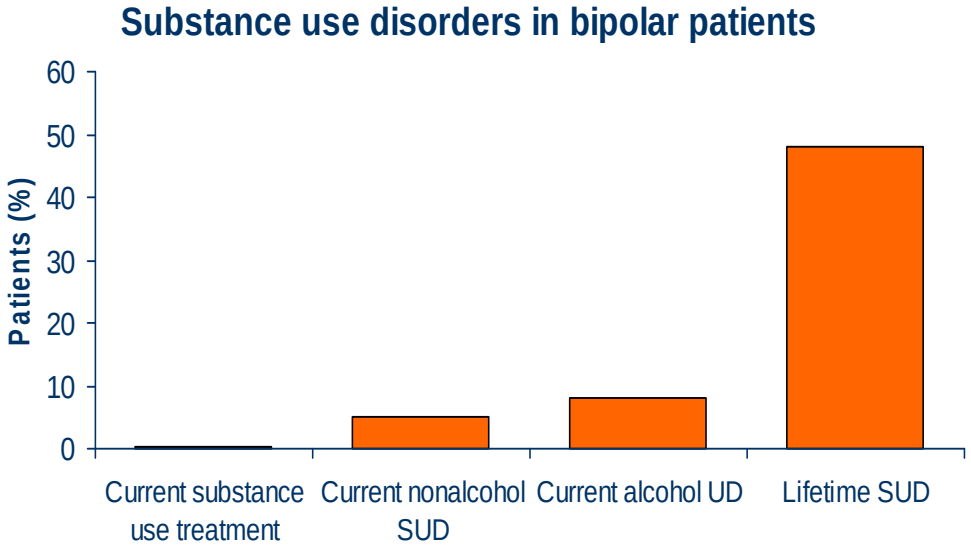
Comorbid conditions: baseline data from STEP-BD



Simon NM et al.J Clin Psychopharmacol 2004; 24(5): 512-20.

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



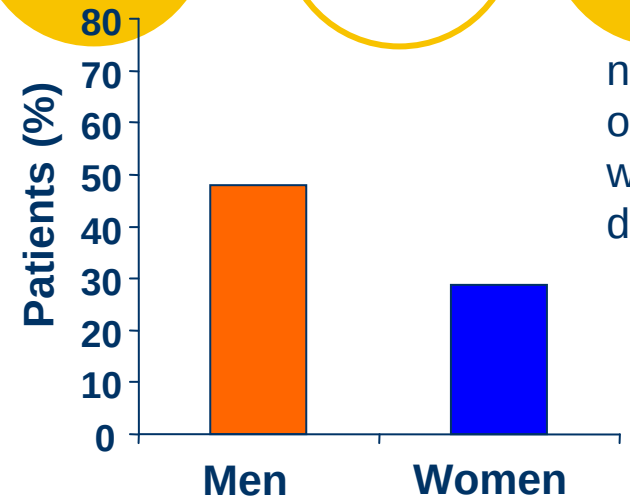
- Use of 'comorbidity-specific' pharmacotherapy for anxiety disorders, substance use disorders, and attention deficit disorder was limited, suggesting comorbidity in bipolar disorder may be under-treated

SUD, substance use disorder; UD, use disorder

Simon NM, et al. J Clin Psychopharmacol 2004;24:512-520

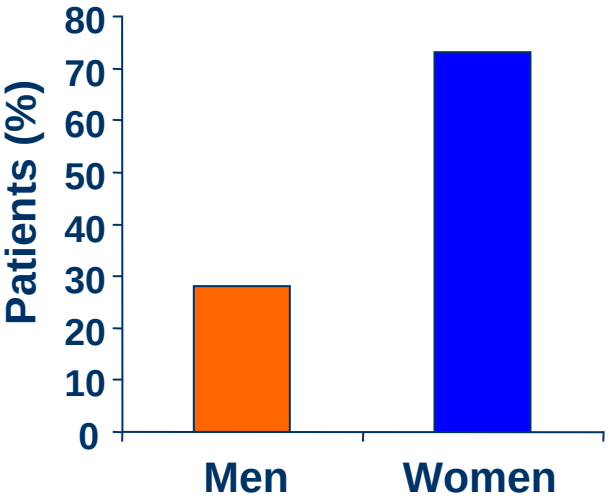
Alcohol abuse and gender in bipolar disorder

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



n=267 outpatients with bipolar disorder

- 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



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

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

EMBLEM
European Mania in Bipolar Longitudinal Evaluation of Medication

EMBLEM. N=3536 manic patients across Europe.
Haro et al, in 2006; Goetz et al, 2007; Vieta et al 2007.

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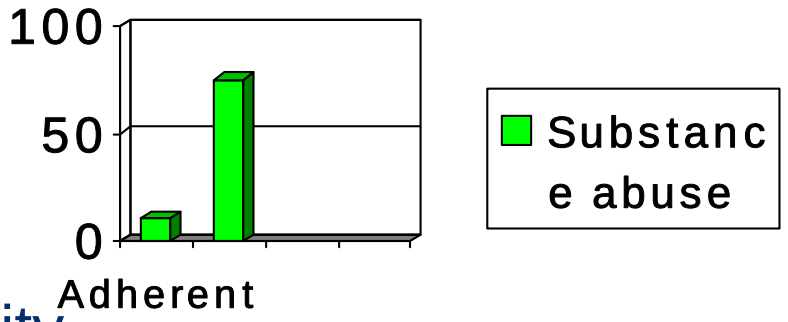
Clinical characteristics of bipolar patients with versus those without substance and/or alcohol abuse

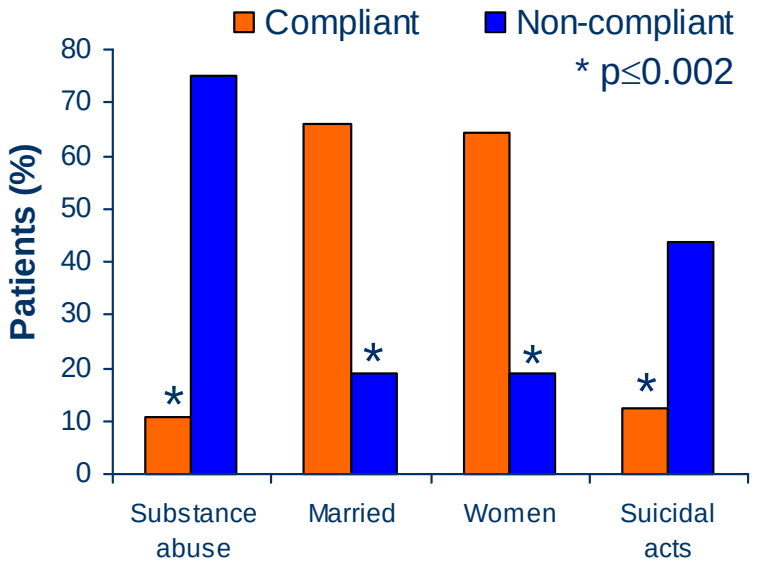
- More mixed episodes and rapid cycling
- Slower recovery
- More hospitalisations
- Earlier age of onset
- More suicide attempts
- Increased aggressivity/criminality
- Poor treatment adherence: 75% of non adherent patients were substace users (González-Pinto et al, 2006)



Keller MB, et al. JAMA 1986;n
. Vieta E, et al. Bipolar Disord 2001;
. Colom F, et al. J Clin Psychiatry 2000;
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

Suicide attempts	p-value	OR	95% confidence interval	
			Inferior	Superior
Male	ns	0.857	0.129	5.674
Previous suicide attempts	ns	5.236	0.660	41.527
Alcohol abuse	ns	1.307	0.225	7.606
Tobacco abuse	ns	0.229	0.032	1.654
Cannabis abuse	ns	0.532	0.063	4.463
Stimulant abuse	<0.05	7.239	1.412	37.107
Age	<0.05	0.884	0.790	0.989

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

ns, not significant

González-Pinto A, et al. J Clin Psychiatry 2007;68:242-247

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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, Januar

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]

1. Mitchell JD, et al. J Affect Disord 2007;102:281-287
2. Goldstein BI, et al. J Affect Disord 2007;103:187-195

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Journal of Affective Disorders xx (2007) xxx–xxx

JOURNAL OF AFFECTIVE DISORDERS

www.elsevier.com/locate/jad

Research report

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

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Journal of Affective Disorders xx (2007) xxx–xxx

JOURNAL OF AFFECTIVE DISORDERS

www.elsevier.com/locate/jad

Brief report

Comorbid disorders in patients with bipolar disorder and concomitant substance dependence

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Received 28 July 2006; received in revised form 9 December 2006; accepted 4 January 2007

Abstract

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.

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Journal of Affective Disorders 101 (2007) 211–217

JOURNAL OF AFFECTIVE DISORDERS

www.elsevier.com/locate/jad

Research report

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 [e,f], Ralph Kupka [f], Paul E. Keck Jr. [b], Gabriele S. Leverich [g], Lori L. Altshuler [a], Sun Hwang [a], Jim Mintz [a], Robert M. Post [g]

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Received 9 September 2006; received in revised form 14 November 2006; accepted 28 November 2006

Available online 23 January 2007

Table 2
Lifetime prevalence of bipolar I disorder among adult males and females with versus without primary youth-onset anxiety disorders

	Subjects with lifetime bipolar I disorder, *N* (%)				$\chi 2$	Odds ratio (95% CI[a])
	Predictor variable present		Predictor variable absent			
	N	%	*N*	%		
Males						
Any anxiety disorder	91/572	15.9	488/17,946	2.7	318.4[b]	6.8 (5.3–8.6)
Social phobia	74/513	14.4	505/18,005	2.8	222.4[b]	5.8 (4.5–7.6)
Panic disorder	17/62	27.4	562/18,456	3.0	121.2[b]	12.0 (6.8–21.1)
Generalized anxiety disorder	18/51	35.3	561/18,467	3.0	174.7[b]	17.4 (9.7–31.1)
Females						
Any anxiety disorder	138/999	13.8	694/23,576	2.9	346.2[b]	5.3 (4.3–6.4)
Social phobia	118/873	13.5	714/23,702	3.0	284.0[b]	5.0 (4.1–6.2)
Panic disorder	20/122	16.4	812/24,453	3.3	63.4[b]	5.7 (3.5–9.3)
Generalized anxiety disorder	29/127	22.8	803/24,448	3.3	147.6[b]	8.7 (5.7–13.3)

[a] 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

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

- 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)

Reproduced with permission
Goldberg JF, Whiteside JE. J Clin Psychiatry 2002;63:791-795

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 tretament

Colom F, Vieta E, Daban C, Pacchiarotti I, Sánchez-Moreno J. Clinical implications of predominant polarity in bipolar disorder. J Affect Disord. 2006

- Ten years follow-up of 169 bipolar patients.

Depressive polarity:

More relapses.

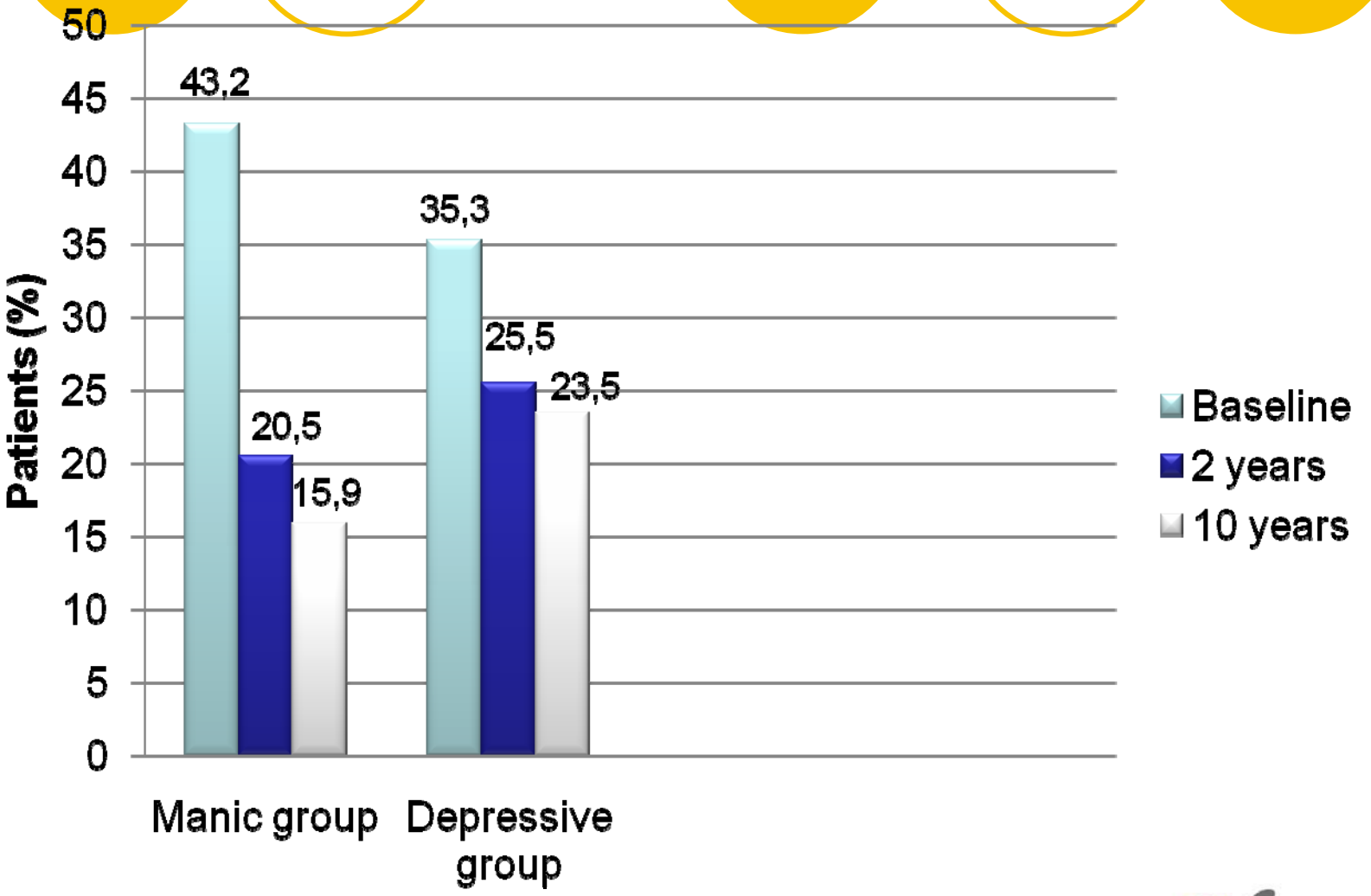
More hospitalizations.

More suicide attempts

More difficulties in quitting .

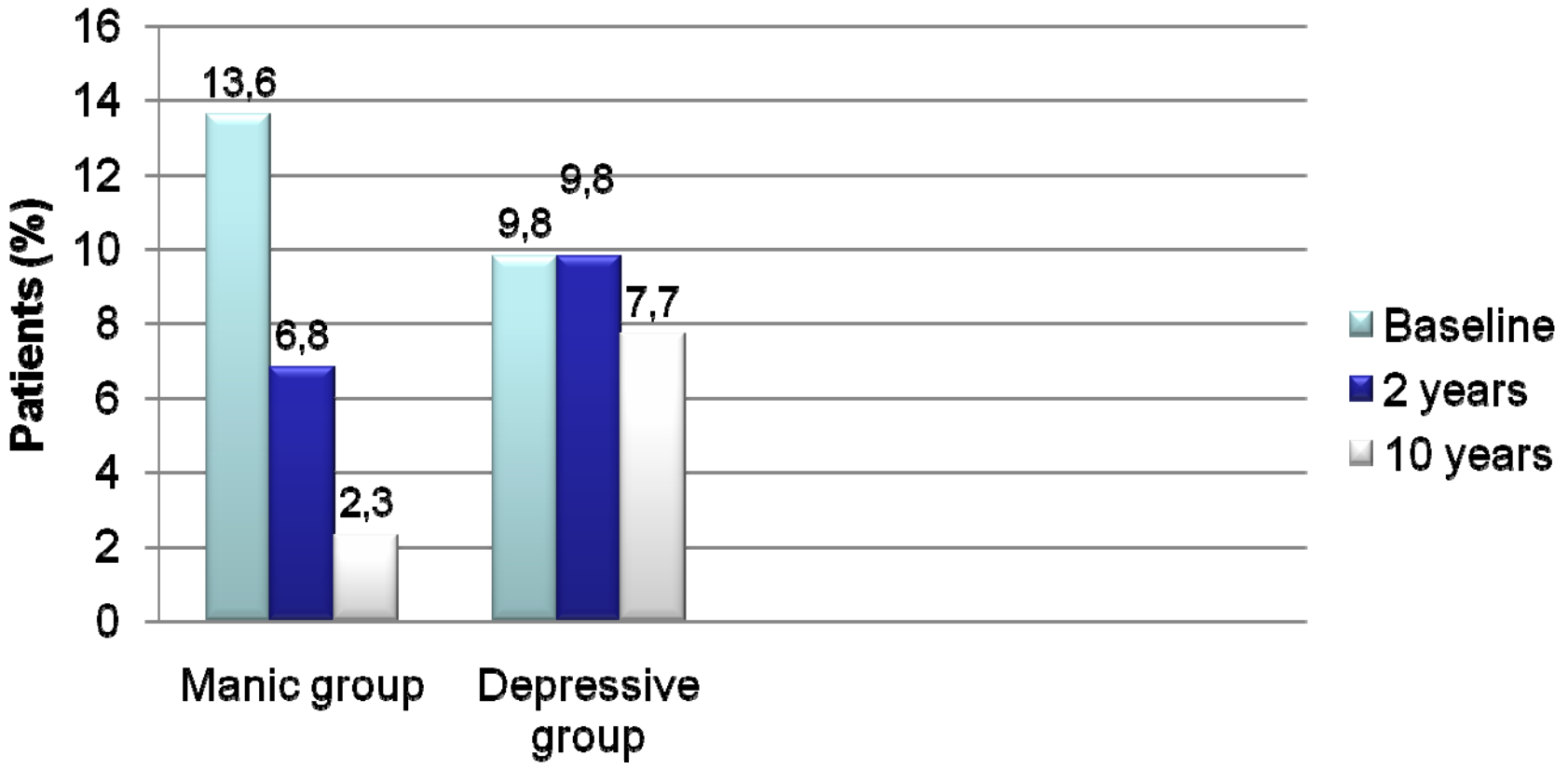
González-Pinto y cols., J Affect Dis 2009

Alcohol abuse



González-Pinto y cols., J Affect Dis (2009)

Other substance abuse



González-Pinto y cols., J Affect Dis 2009

LONG TERM IMPROVEMENT AFTER CANNABIS WITHDRAWAL

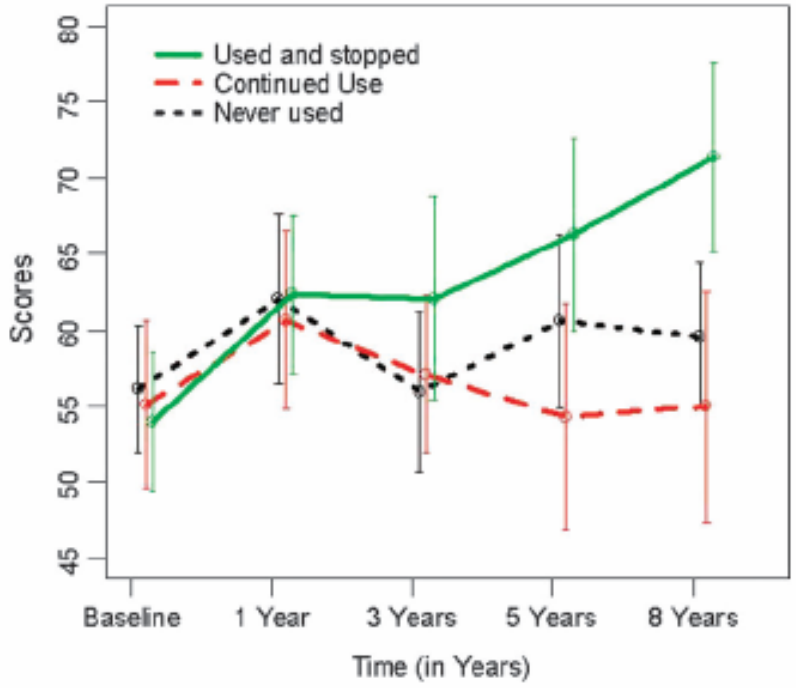


Fig. 1. Global Assessment of Functioning (GAF) Outcome by Cannabis Use Group.

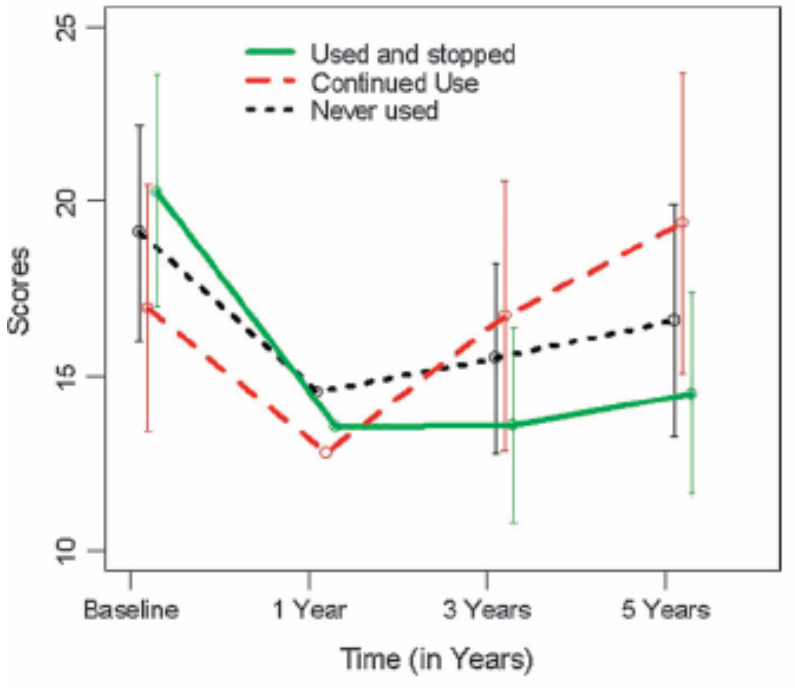


Fig. 3. Positive and Negative Symptoms Scale (PANSS) Negative Outcome by Cannabis Use Group.

G Pinto et al. Schizophrenia Bull., 2009

Lithium for adolescent bipolar disorders with secondary substance dependency

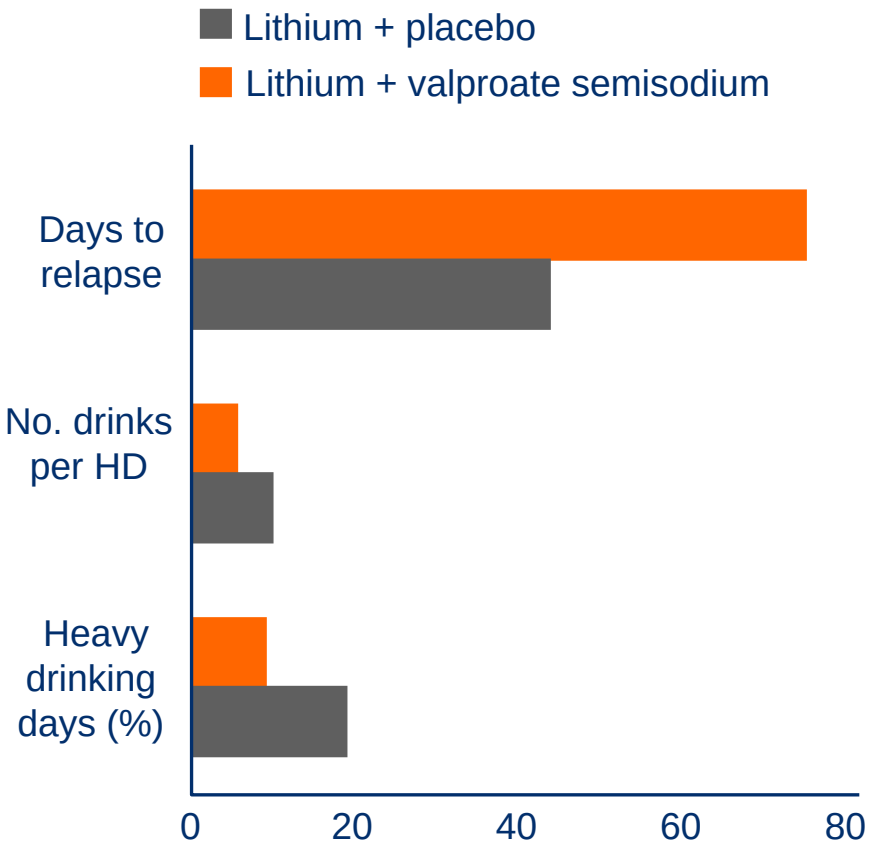
- 25 adolescent patients with bipolar disorder and SSD received lithium or placebo
  - Randomised, double-blind, placebo-controlled pilot study
- Addiction to both alcohol and cannabis was the most frequent category of SSD
- The mean scheduled weekly serum lithium level of active responders was 0.9 mEq/L
- 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

Geller B, et al. J Am Acad Child Adolesc Psychiatry 1998;97:171-178

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

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

Valproate

- 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
  - Fewer drinks per drinking day
- Outcome was correlate with compliance
- Divalproex group had better liver function test scores

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

DEPRESSION AND ANXIETY 23:492–495 (2006)

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.

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
- 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

Weiss RD, et al. Am J Psychiatry 2007;164:100-107

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.

J Clin Psychiatry 2000; 61: 361-367.

Article

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.

Am J Psychiatry 2007; 164:100–107.

Group Therapy

- Population
  - 21 adults received integrated group therapy
  - 24 adults received usual care
- Integrated group therapy was associated with
  - Significantly ($p \leq 0,02$) greater decrease in Addiction Severety 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
- Psycoeducation and psychosocial interventions are crucial for patients with comorbidity

CHRISTMAS LUNCH