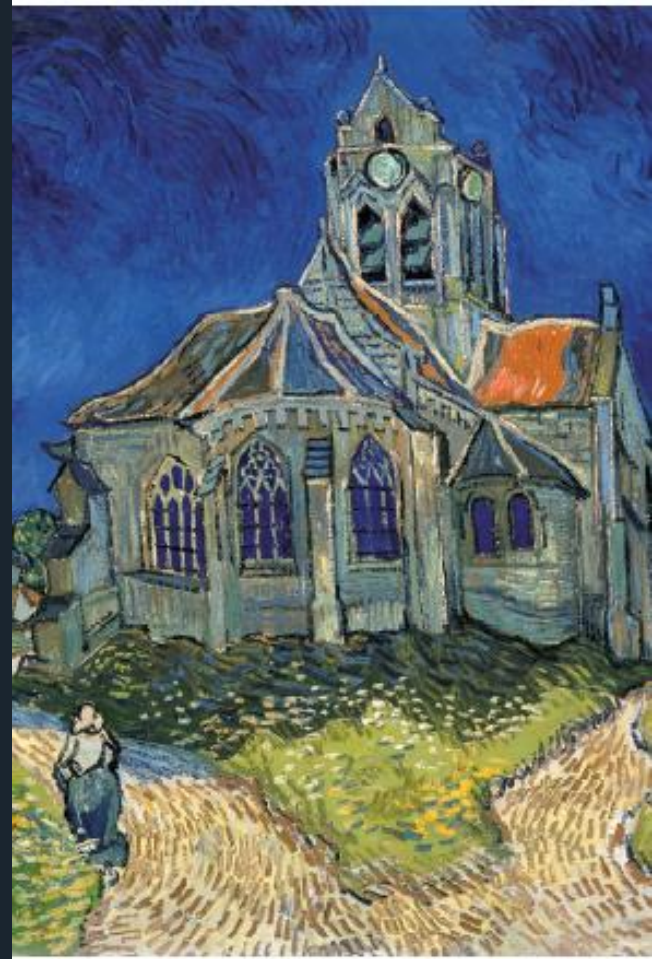


Bipolar and Alcohol Use Disorders: Not a simple coincidence



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06-05-2024 Maine SUD Learning Community

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Disclosures

I, Dr. Javier Ballester, have nothing to disclose. I have **no** relationships or conflicts of interest related to the subject matter of this presentation.

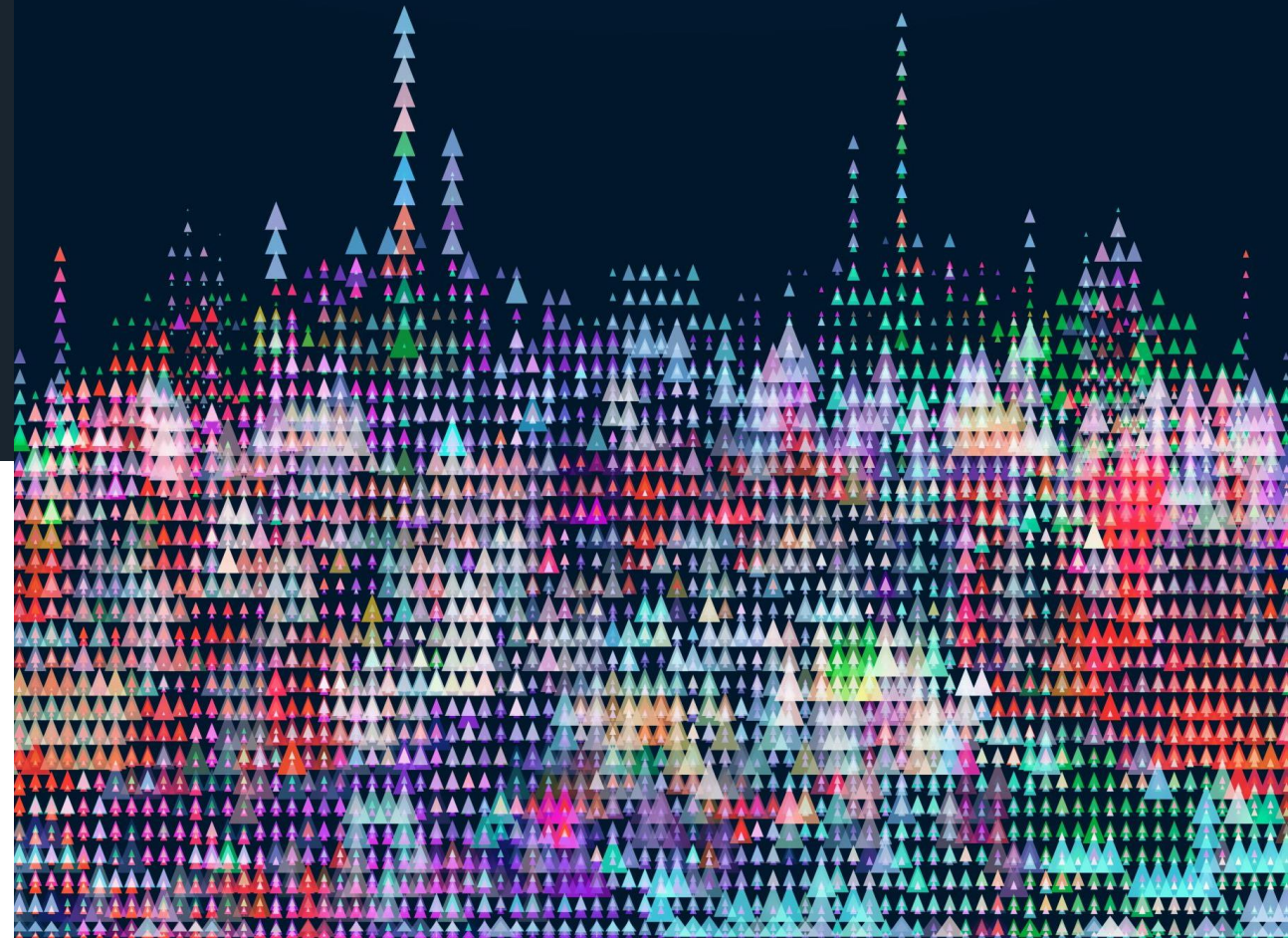
I, Dr. Javier Ballester, will be presenting my own opinions and views and do **not** represent the Veterans Health Administration's official position.

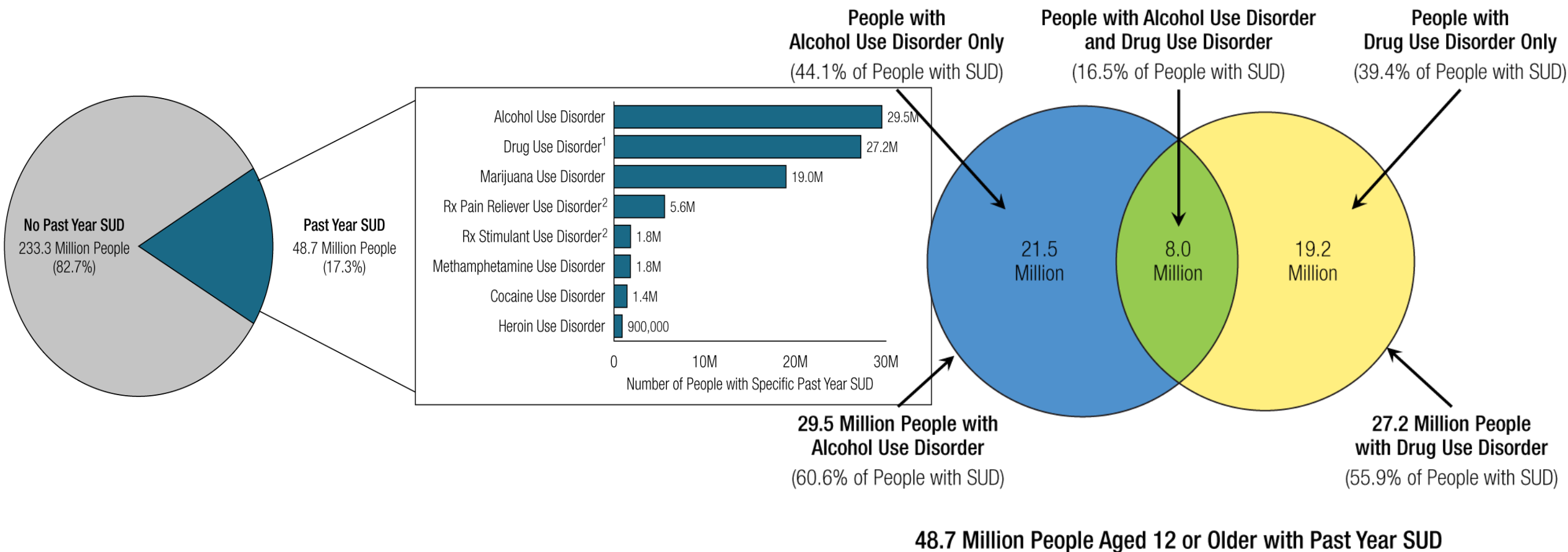
Learning Objectives

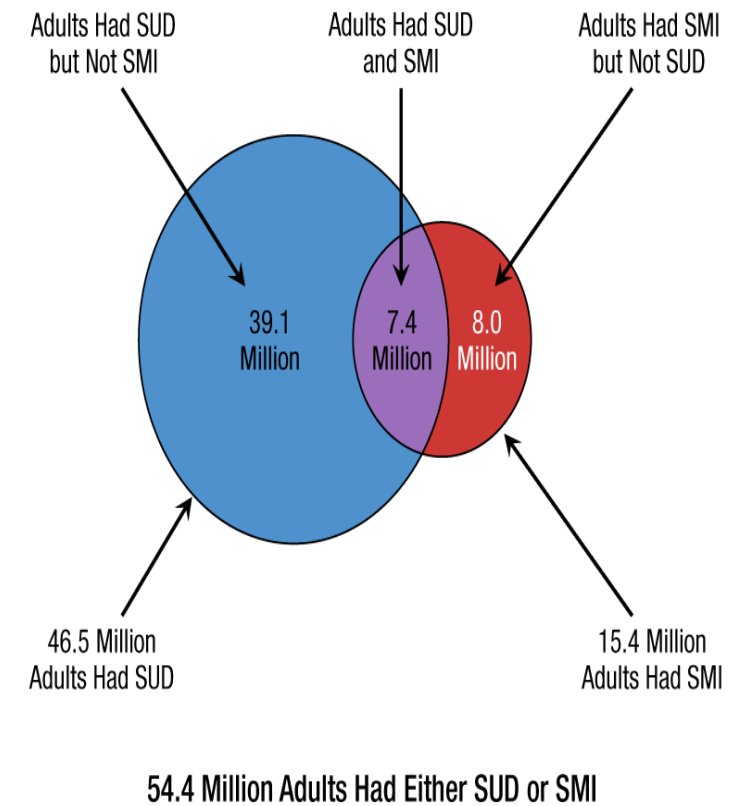
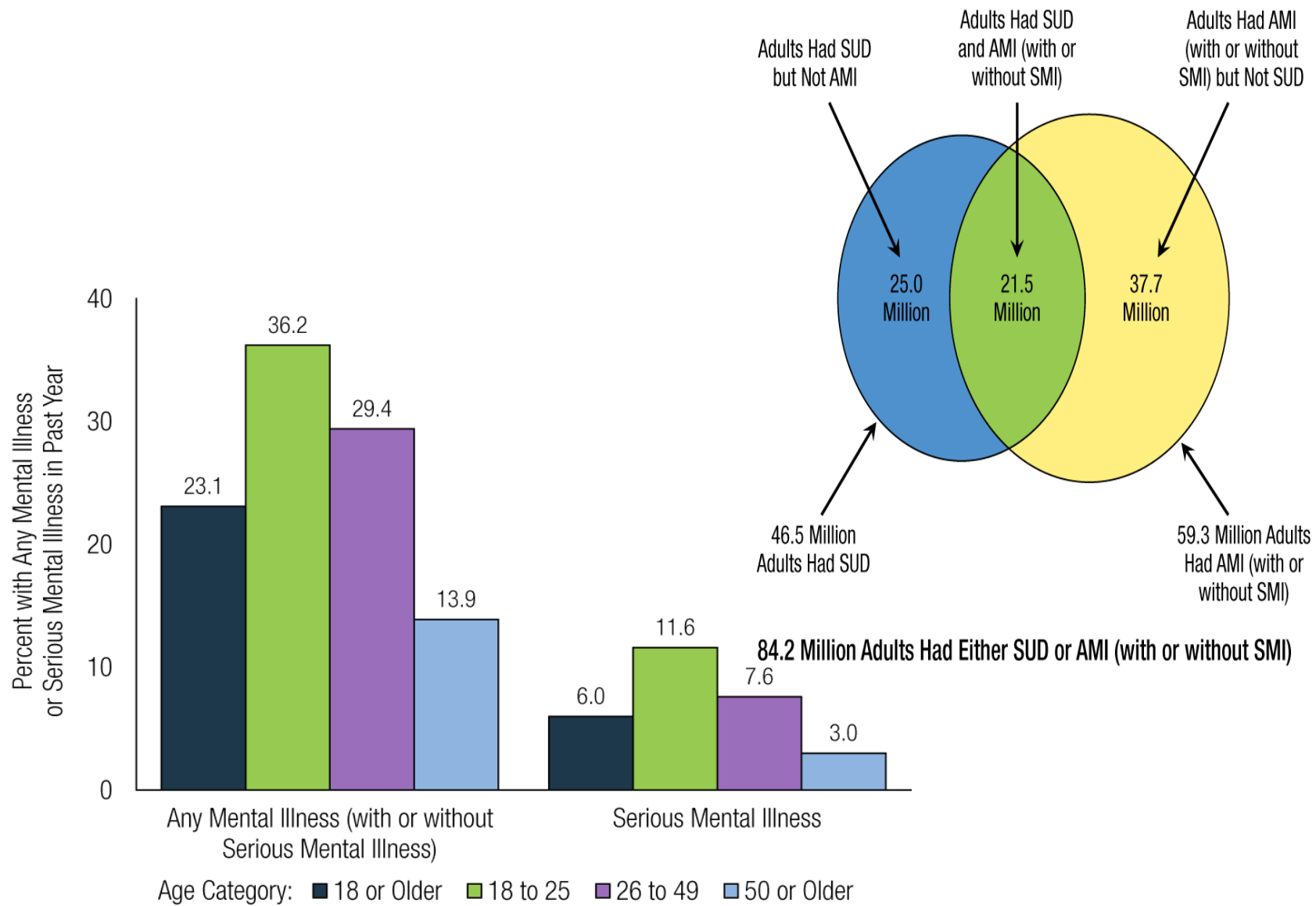
1. Describe the strength of the association between bipolar and alcohol use disorder.
2. Understand the clinical outcomes when this comorbidity is present.
3. Describe the most evidence-based pharmacological and psychotherapeutic interventions in this dual problem.

Section I

Epidemiological Data







Substance Abuse and Mental Health Administration, 2023.

Epidemiological Catchment Area study (1990). Bipolar disorder highest rate of substance use disorders among any other axis I disorders. 43% lifetime prevalence of AUD in any bipolar disorder ([Regier, 1990](#)).

1990

The latest national epidemiological survey on alcohol and related conditions-III (NESARC III wave 2012-2013) confirm these findings, exception of other SUD ([Grant, 2015](#)).

2012-2013

Clinical Studies

Systematic treatment enhancement program for bipolar disorder (1999-2005). Prevalence lower (ECA also included institutionalized) ([Bowden, 2012](#)).

Table 1 Psychiatric comorbidities among STEP-BD patients

	Lifetime	Current	Sample size
Anxiety disorder [5]	51.2	30.5	500
Alcohol use disorder [6]	32.2	11.8	4000
Drug use disorder [6]	21.7	7.3	4000
ADHD [7]	9.5	5.9	1000
Eating disorder [8,9]	7.9	2.0	1000

A recent systematic review of clinical studies (1990-2015) in clinical settings, both inpatient and outpatient settings, showed a prevalence of AUD of 40% in BD in the USA.

The same group performed another systematic review of national/international surveys of general populations, also between 1990 and 2015. In this case, the prevalence of AUD in BD was 24%.

Section I: Conclusions

Alcohol Use Disorder is the most prevalent substance use disorder in the population (>5% past year, NSDUH). Similar percentages are found for people with SMI.

Almost 2 out of 4 people with SMI suffer from an SUD (non-nicotine).

Bipolar Disorder is the most prevalent SMI with an AUD, up to 40% in population and clinical studies in the USA.

Section II

Clinical Characteristics and Consequences



Sex Differences

Frye (2006): 49% men vs 29% women.

Di Florio (2014): 40% in men and 20% in women.

Xia (2020): AUD associated with

Male (OR = 2.08, 95% CI = 1.09-3.97, $p = 0.001$)

Other substance use disorders (OR = 10.81, 95% CI = 1.23-94.5, $p = 0.031$).

Bipolar Subtype Differences

Chengappa (2000):

Bipolar I 49% vs Bipolar II 39%

Frye (2006):

Bipolar I 41% vs Bipolar II 25%

Others not found (Xia, 2020).

Consequences

200 outpatients recruited in 6 centers in the USA. Four groups: Group 1 (BP II; n=20), Group 2 (BP II-AUD; n=56), Group 3 (BP I; n=36), Group 4 (BP I-AUD; n=116).

Measured at baseline and 5 years later.

Group 4 had more depressive and manic episodes, more suicidal behavior, and less social functioning.

Commutative Property does not apply: BD→AUD ≠ AUD→BD

Table 3. Course-of-Illness Characteristics of Patients Hospitalized for a First Manic Episode According to Whether They Have No Alcohol-Use Disorder or Whether the Onset of the Alcohol-Use Disorder Occurred Before or After the Onset of the Bipolar Disorder*

Characteristic	Comorbid Groups		
	No Alcohol (n = 83)	Bipolar First (n = 34)	Alcohol First (n = 27)
Follow-up time, mean ± SD, wk	120 ± 84	159 ± 81	147 ± 108
Time recovered, mean ± SD, % of wk	25 ± 32	30 ± 32	53 ± 34
Time in any affective episode, mean ± SD, % of wk†	21 ± 25	35 ± 26	15 ± 21
Manic	10 ± 18	16 ± 17	5 ± 8
Depressed	6 ± 14	10 ± 15	9 ± 20
Mixed‡	4 ± 13	9 ± 18	1 ± 3
Time with subsyndromal affective symptoms, mean ± SD, % of wk	54 ± 34	35 ± 23	33 ± 33
Time with symptoms an alcohol-use disorder, mean ± SD, % of wk§	2 ± 10	19 ± 19	11 ± 18
Time with full compliance with at least 1 mood stabilizer, mean ± SD, % of wk	70 ± 56	47 ± 41	52 ± 58
Rapid-cycling criteria met during follow-up, No. (%)	4 (5)	9 (26)	2 (7)

*Comparisons adjusted for age; age at bipolar onset; sex; education; and rates of psychosis, mixed states, and cannabis-use disorders at index.

†Significant group difference: $F_{9,134} = 4.6$, $P = .01$. The Bipolar First group had more time than both other groups.

‡Significant group difference: $F_{9,134} = 3.0$, $P = .05$; The Alcohol First group had less time than both other groups.

§Significant group difference: $F_{9,134} = 12.1$, $P < .001$. The Bipolar First group had more time than the Alcohol First group, which had more time than the No Alcohol group. Significant difference between Bipolar First and Alcohol First groups: $F_{8,52} = 14.8$, $P < .001$.

||Significant group difference: $\chi^2_1 = 5.8$, $P = .02$.

Two outpatient groups: SUBP (n=145) and NSUBP (n=144).

Similar proportion of BP-I and BP-II 60/40%.

The group with no substance abuse preceding the onset of BP had a higher number of hypomanic and depressive symptoms.

The AUD-BD group

- Comorbid sedative use
- Anxiety disorders
- Irritable temperament

-Depressive polarity at onset

The BD-AUD group

- Comorbid stimulant use
- Hyperthymic temperament

-Manic polarity at onset

Bipolar Disorder in Adolescents

One third of adolescents (12-17 y/o) developed a SUD within 4 years of intake.

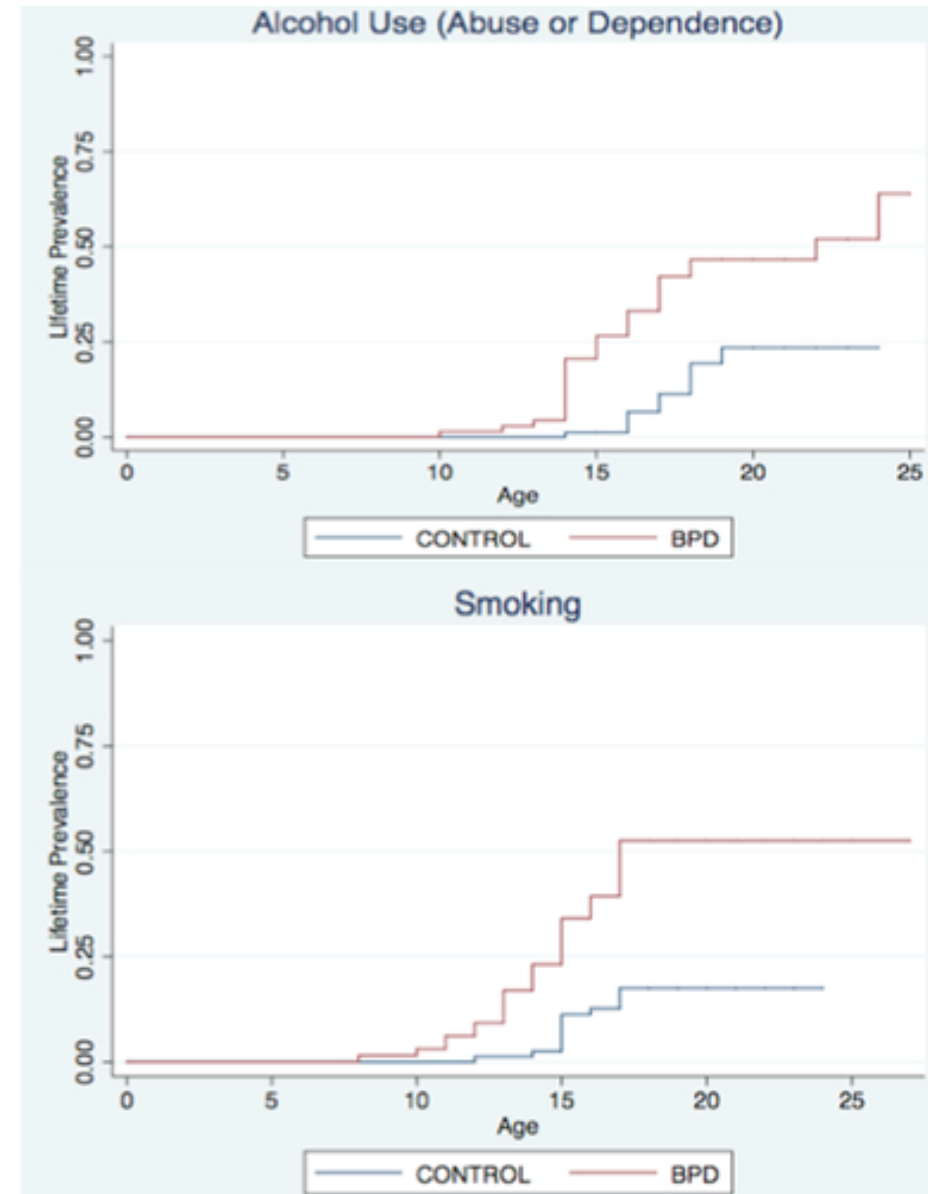
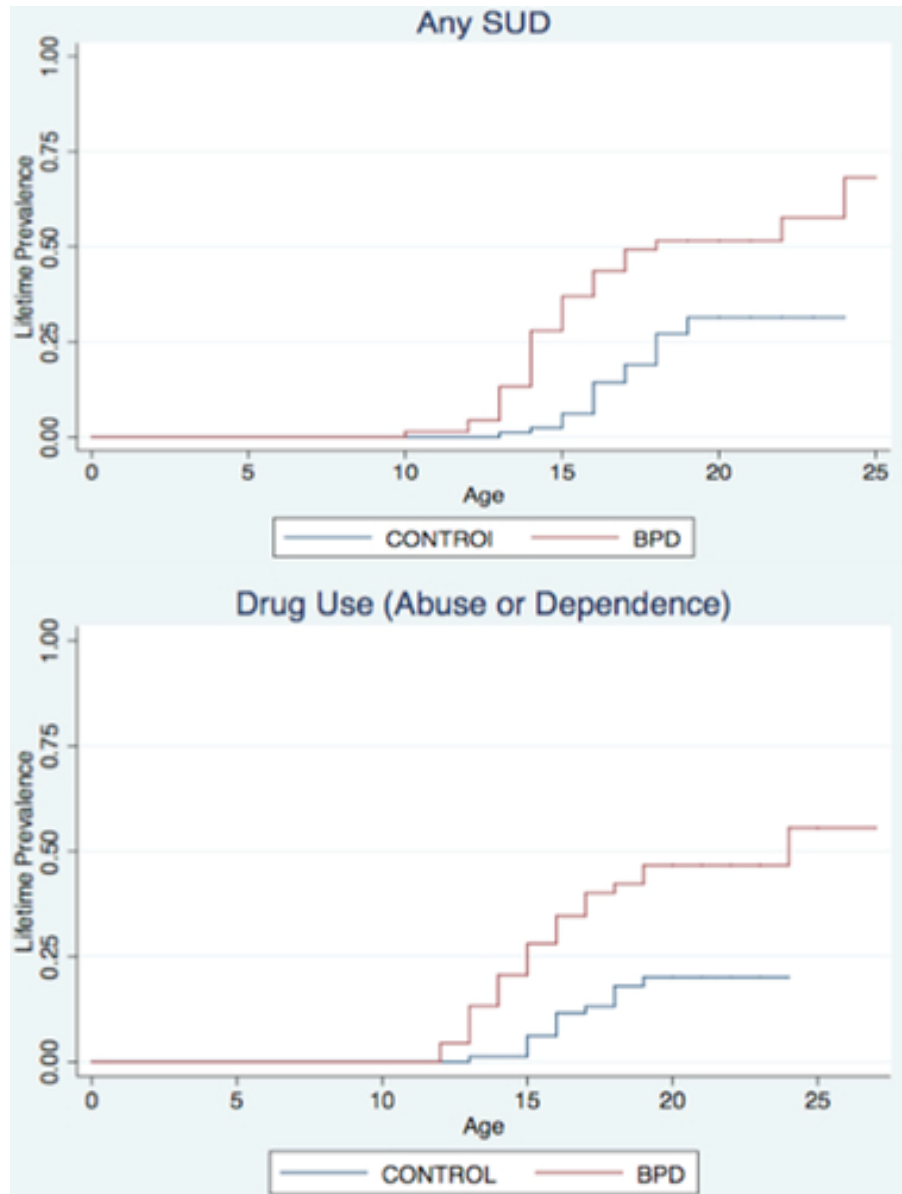
Mainly alcohol and/or cannabis use disorder.

Incidence similar in BP-I, BP-II

Experimentation with alcohol was robust predictor of SUD.

Lifetime prevalence of ODD, panic disorder, family history of SUD, low family cohesiveness.

If 3 or more: 50% developed a SUD.



Consequences

Higher rates of mixed mania, rapid cycling, increased severity of manic and depressed symptoms ([Frye MA, 2006](#)), higher levels of suicidality ([Dalton 2003](#), [Cardoso 2008](#), [Oquendo 2010](#)), aggression ([Salloum IM, 2002](#)).

Step-BD. Earlier age of onset of bipolar disorder, more suicide attempts, poorer functional outcomes, adherence. No association with mood outcomes.

Increased risk of depressive relapse in BP-I ([Simhandl, 2016](#)).

Section II: Conclusions

Comorbid AUD-BD more than double men>women.

Bipolar I-AUD seems more prevalent than Bipolar II and may have worse course.

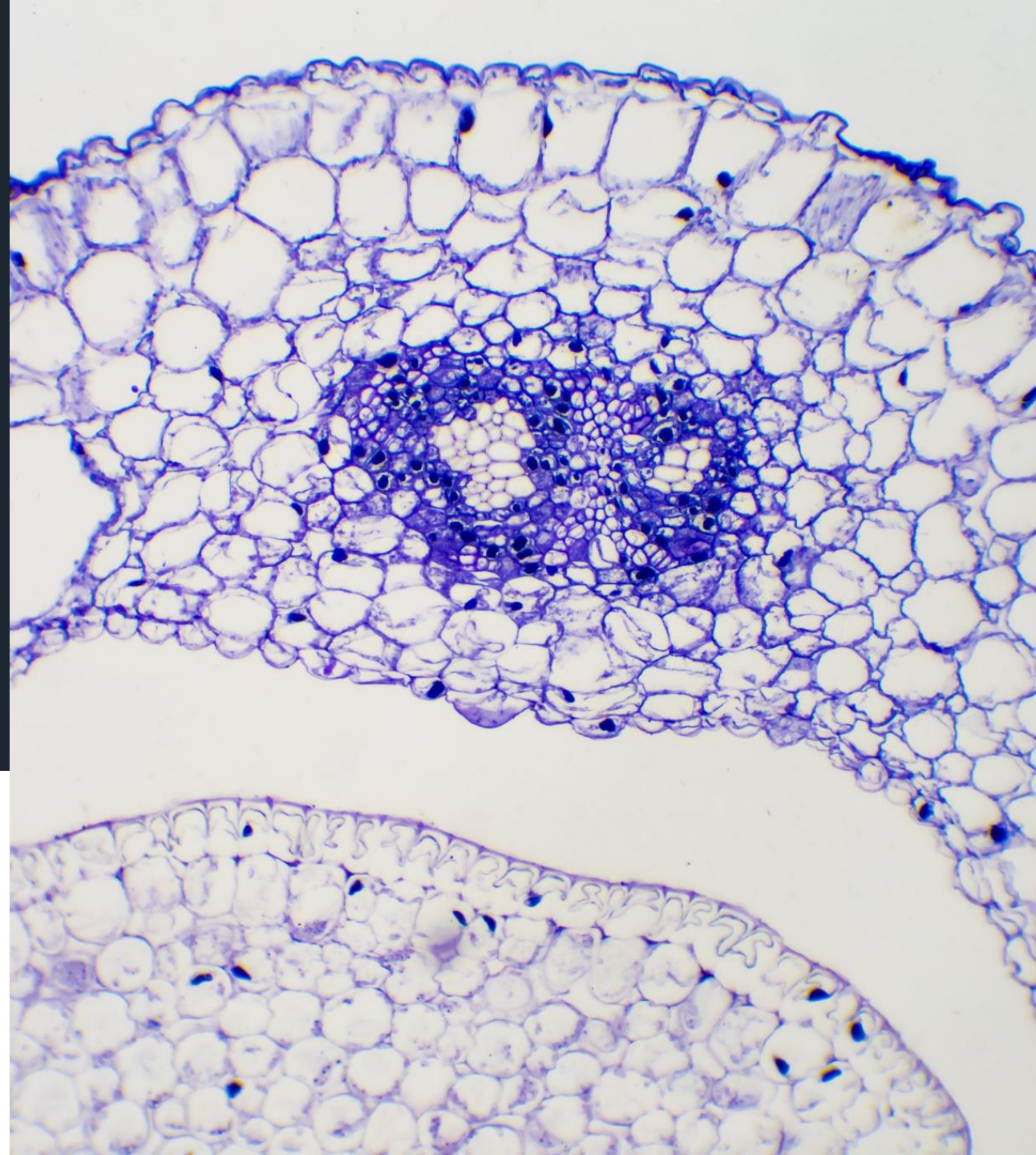
Adolescents with BD are at very high risk for a SUD (30-50%).

BD-AUD more severe than AUD-BD.

Comorbidity: More mixed, rapid cycling episodes, suicidality, aggression.
Less functioning and adherence to treatment.

Section III

Etiology



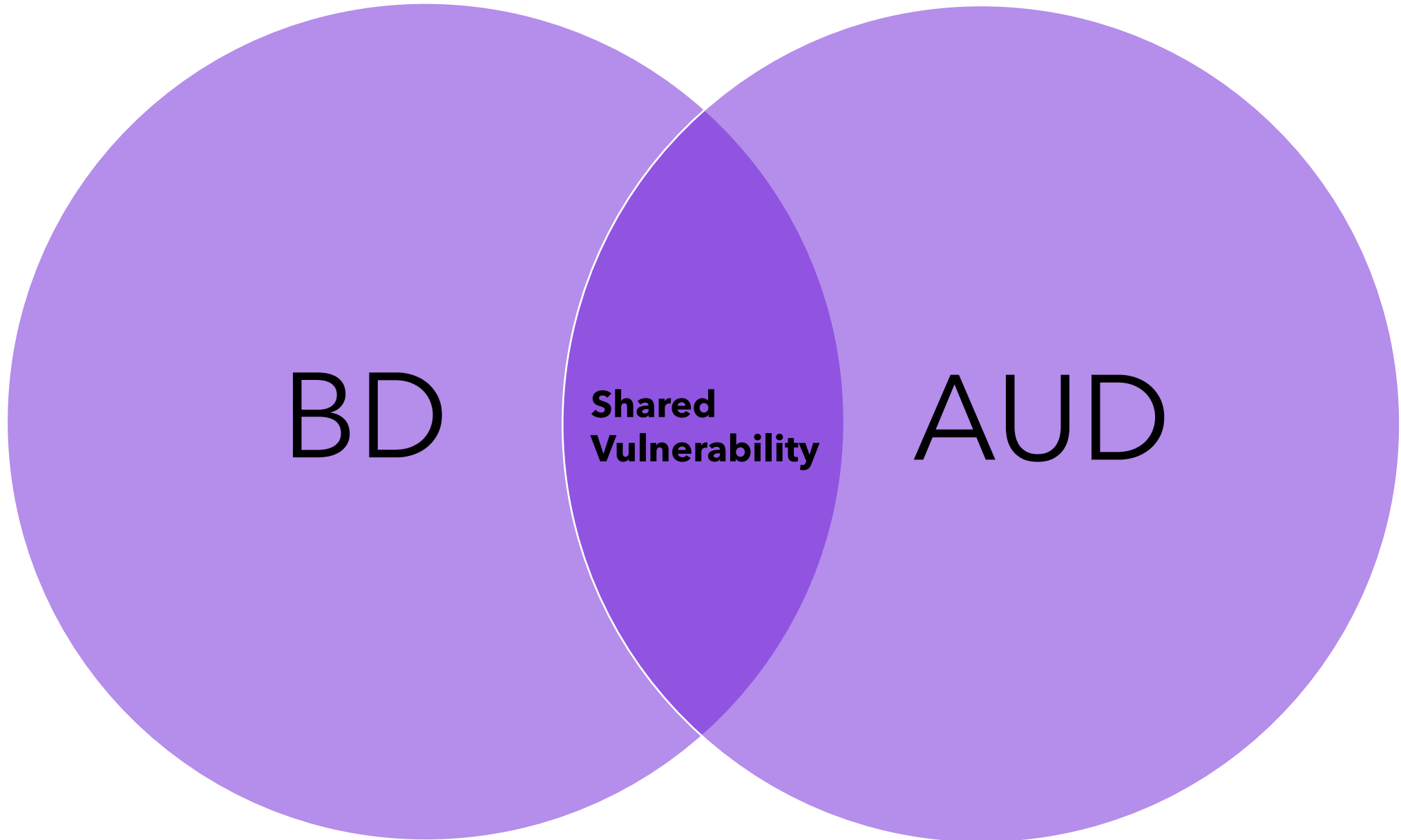


Bipolar Disorder increasing risk of alcohol use

- Symptoms of BD (impulsivity and sensation seeking in mania) leads to increase alcohol use.
- Self-medication hypothesis, especially insomnia, depression or anxiety.

Alcohol Use Disorder increasing risk of mood episode

- Symptoms of AUD (withdrawal, insomnia) increases risk of manic or depressive episode



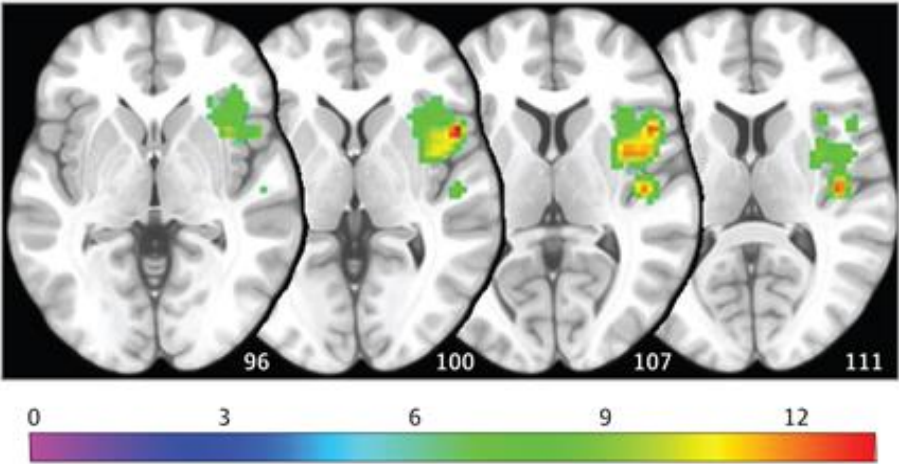
Reward Hypersensitivity Model

Dysregulation of the Behavioral Approach (Activation) System ([Urosevic, 2008](#)): Extreme fluctuations of the BAS (system related to goals and reward).

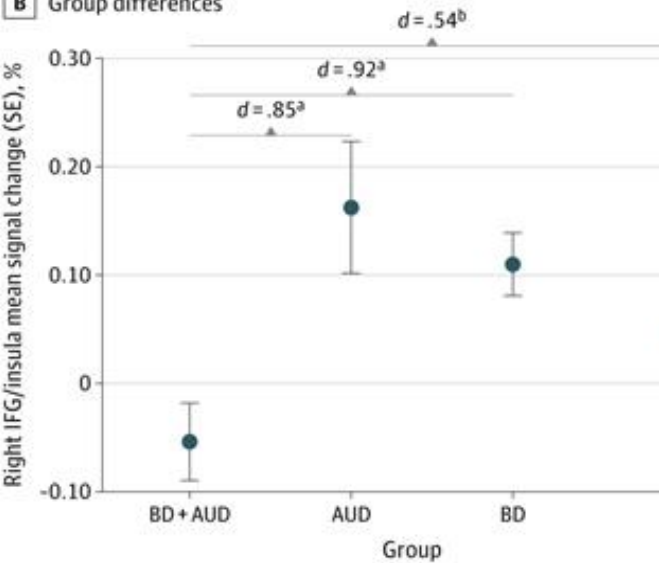
Mood Instability and Reward Dysregulation ([Mason, 2017](#)): Mood biasing reward perception and vice versa.

Failure of top-down and bottom-up dysregulation

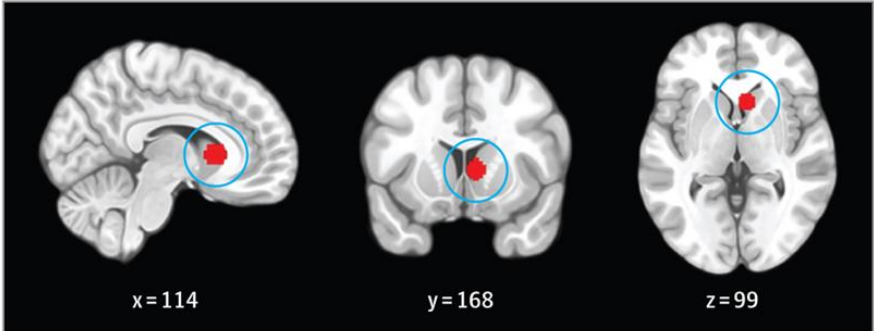
A ALC-BEV contrast in BD+AUD



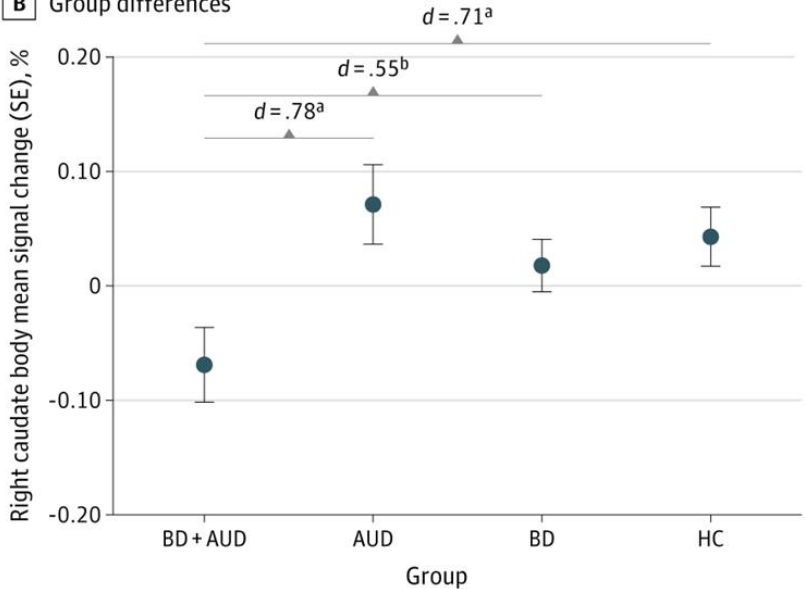
B Group differences



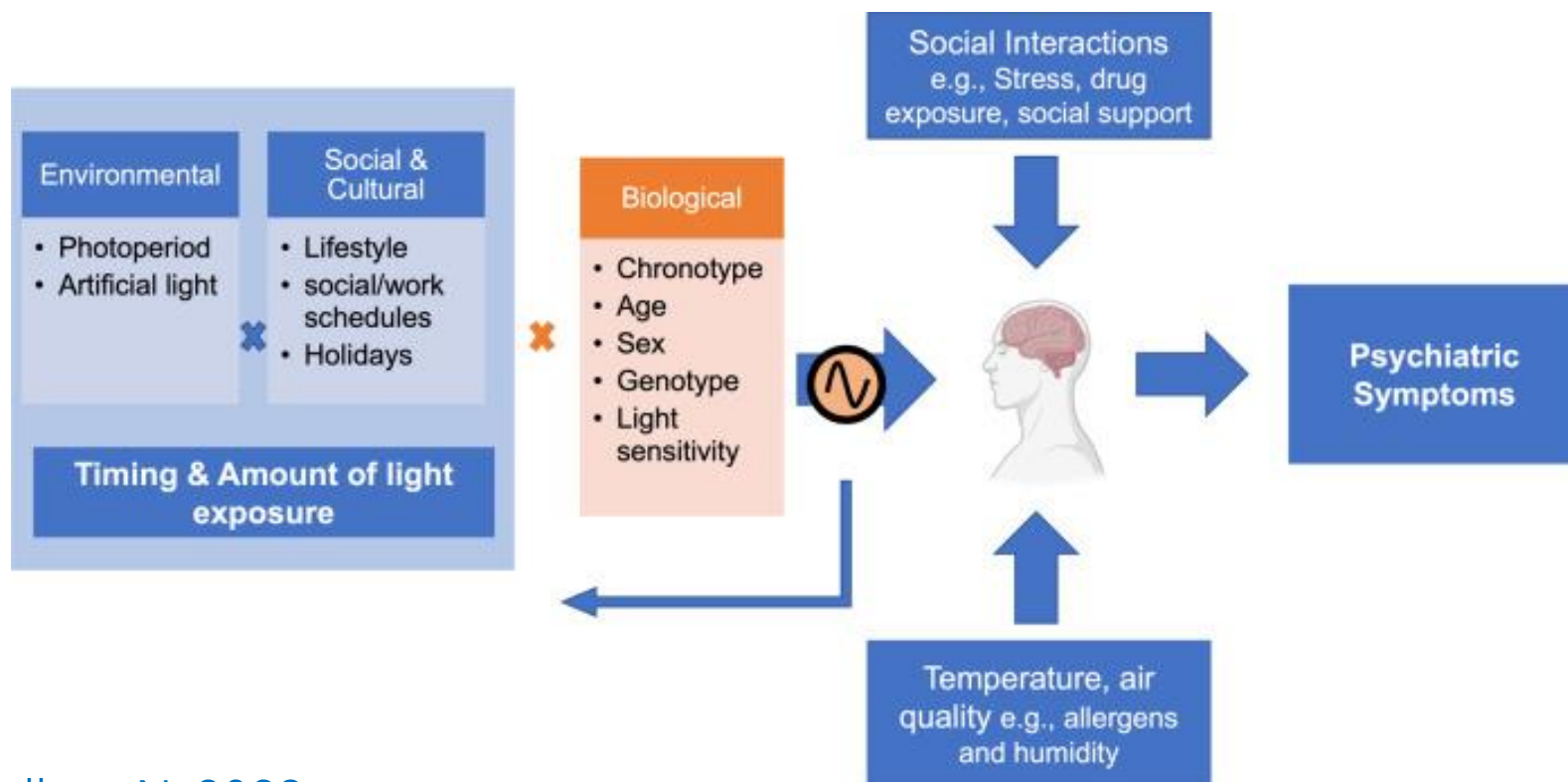
A Right caudate body region of interest

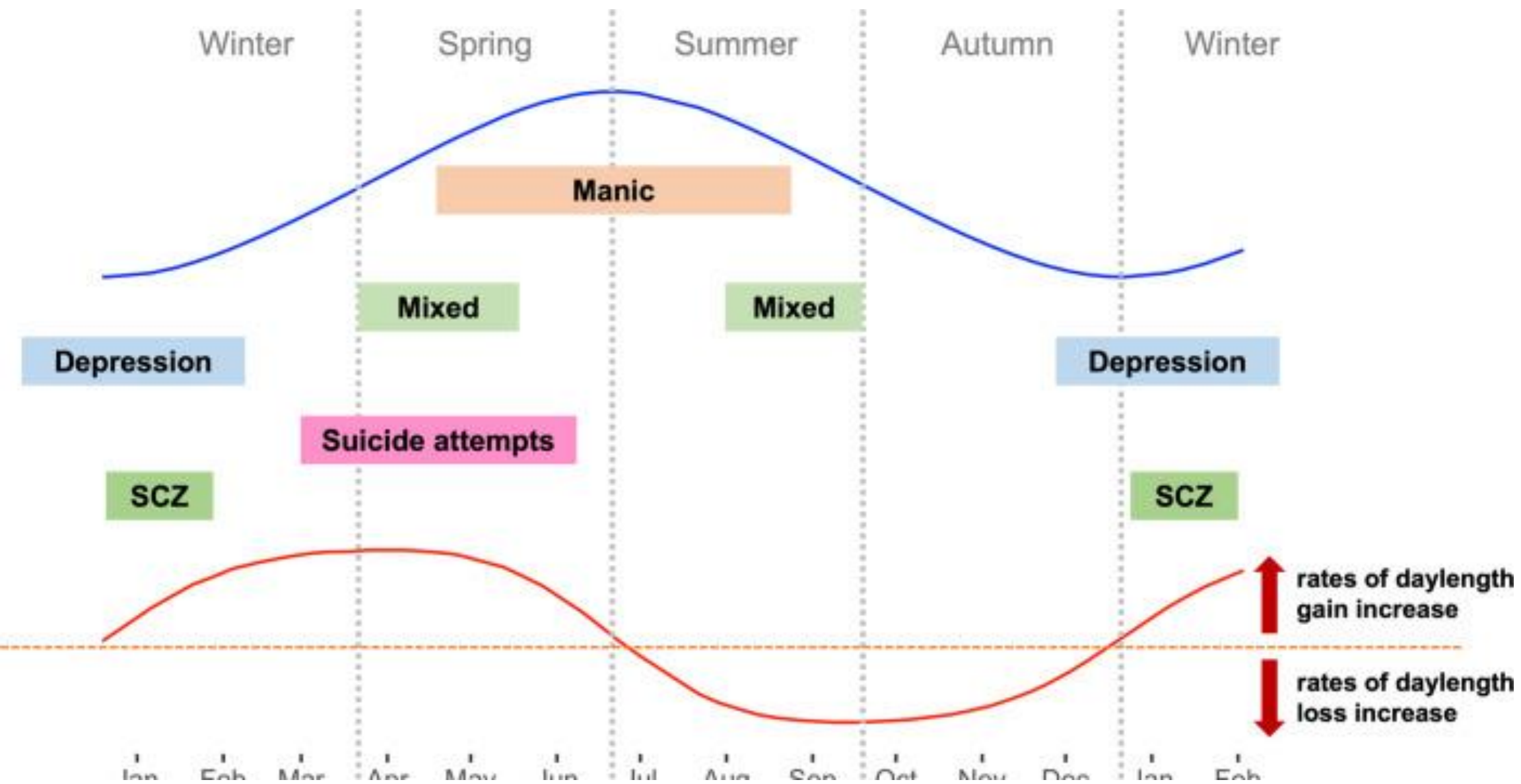


B Group differences



Chronobiology in BD and AUD



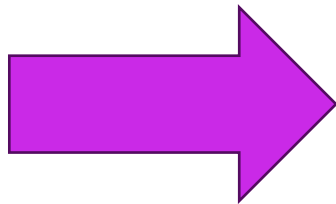


Evening chronotype associated with the use of stimulants and alcohol ([Adan, A 1994](#))

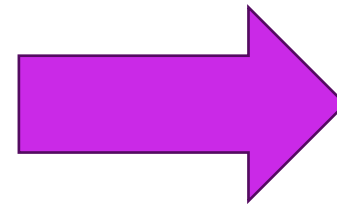
Social jet-lag and evening chronotype associated to alcohol use: systematic review ([Nelson, M et al 2024](#)).

Alcohol disrupts circadian rhythms and circadian gene expression. Circadian genes regulate responses to alcohol use and have an effect on DA circuit ([Parekh P, et al. 2015](#)).

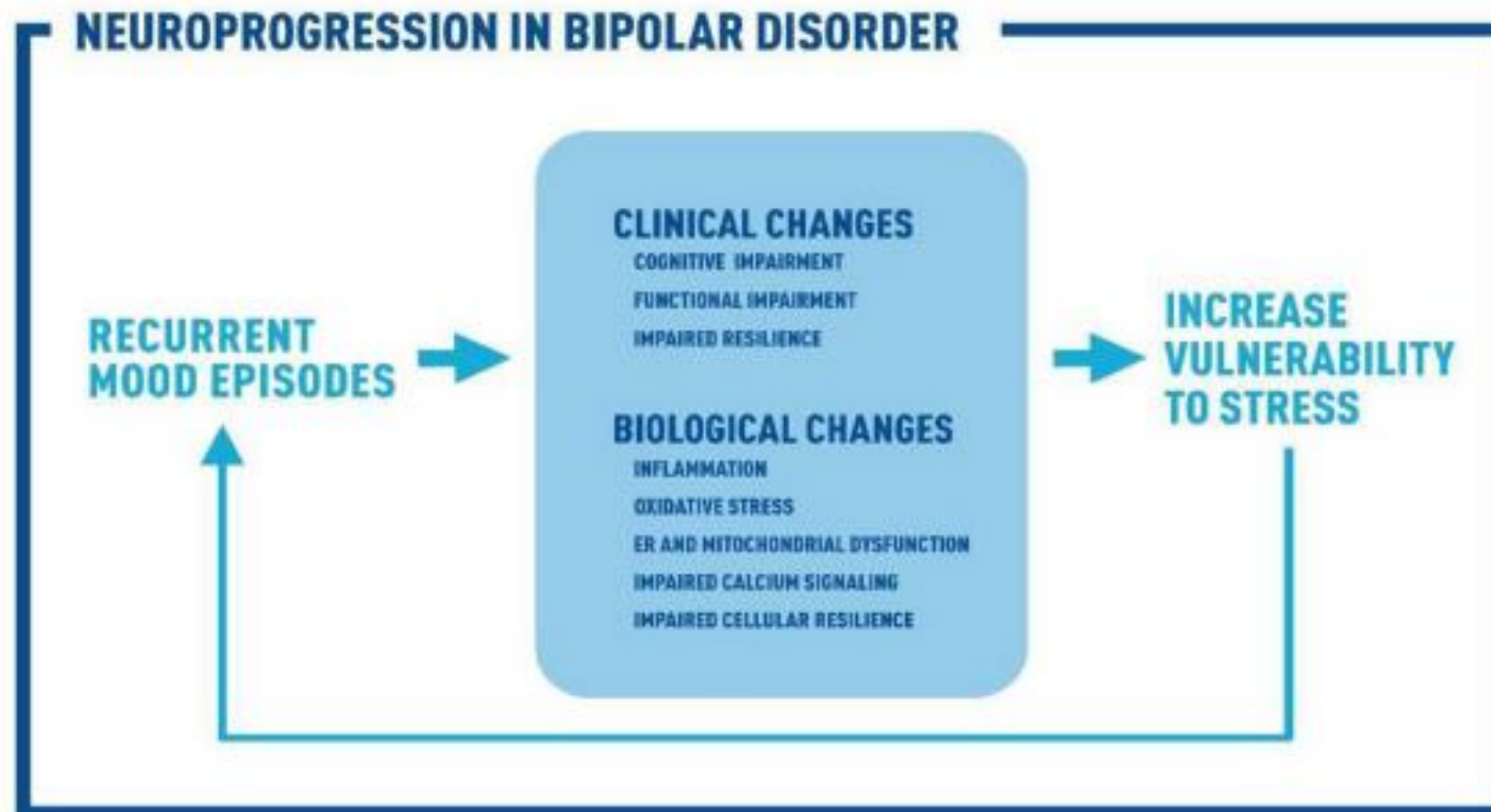
Susceptibility

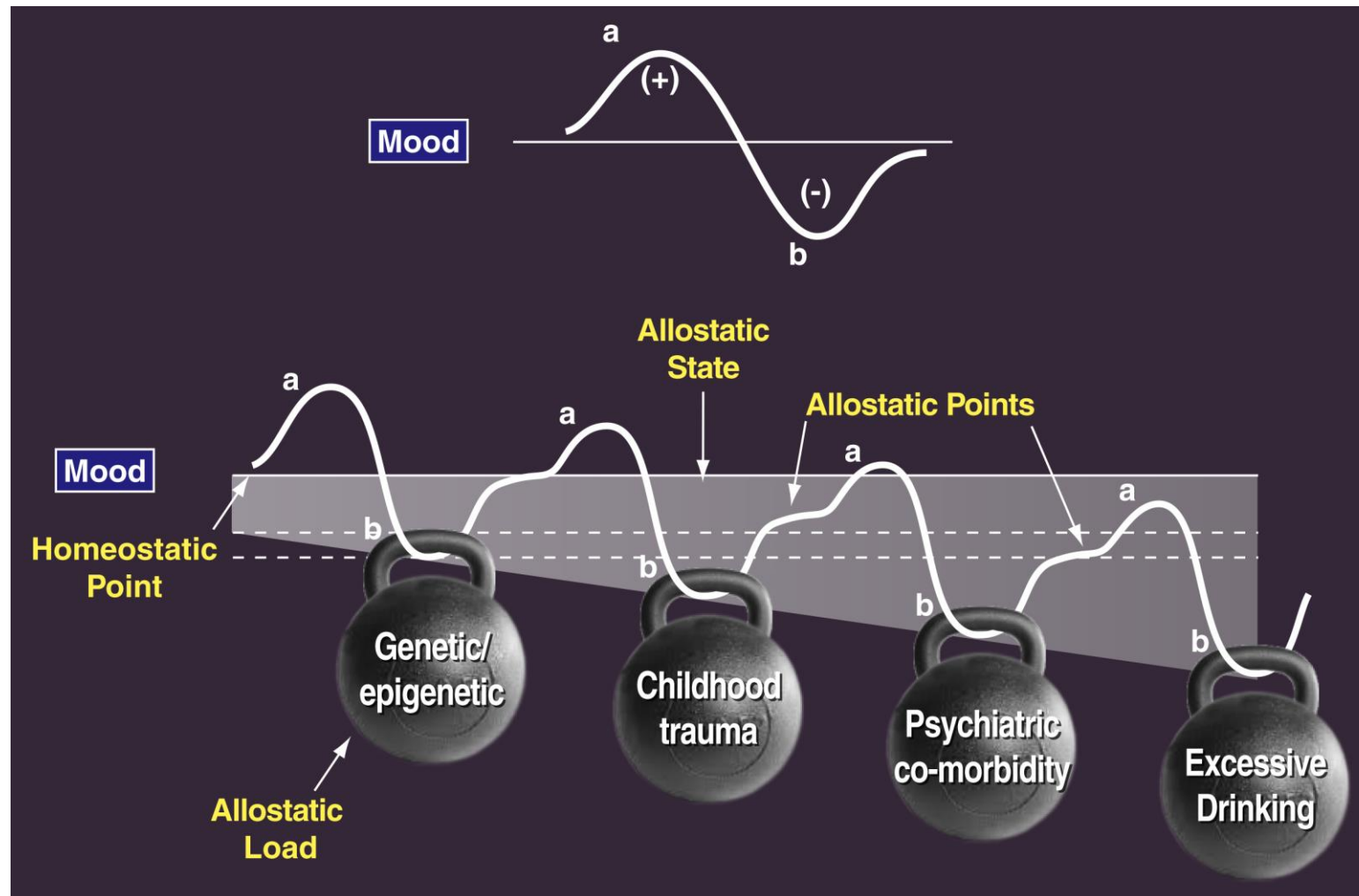


BD+AUD



Neuroprogression





Koob GF and Le Moal M, 2001

Section III: Conclusions

Conceptualization of BD-AUD comorbidity may influence treatment.

Bipolar Disorder, classical presentations and spectrum. Added AUD, even more variability.

Every patient unique. However, might be able to categorize into groups for a more personalized treatment.

Section IV

Treatment



Principles

Integrated model of care by the same treatment team ([Salloum, 2017](#)).

More medical comorbidities. Primary and specialty care.

Acute inpatient care will be needed more often: bipolar decompensation (mania, psychotic features, depression with suicide ideation), medical management of withdrawal symptoms.

Consider adding psychosocial treatment as soon as possible. Ideal family.



Old axiom: treating alcohol use disorder first is not valid.



Despite lack of studies, consider adding "maintenance" psychopharmacological treatment for alcohol use disorder soon (naltrexone, disulfiram, acamprosate).



Long acting injectables (antipsychotics, naltrexone LAI) could improve adherence/outcomes but this has not been studied in this population.

Approaches

Two different pharmacological approaches:

1) A medication used in BD tested to see if it helps not only mood but alcohol outcomes: lithium, valproate, quetiapine.

2) A medication used in AUD tested as an add-on to regular BD treatment: naltrexone, acamprosate

Psychotherapy approaches: Integrated Group Therapy, Family Focused Therapy (adolescents), CBT+psychoeducation in inpatient.

Salloum, 2017

Valproate

24-week randomized, double blind, placebo controlled done in 59 BP-I patients with AUD moderate/severe. Inpatients and follow-up.

Patients receive TAU with lithium and psychosocial interventions and valproic vs placebo was added on top of it.

No differences in manic/depressive symptoms. Patients on valproate had less proportion of heavy drinking days (HDD) and less drinks per HDD. Valproate serum correlated with better alcohol outcomes

[Salloum, 2005](#)

Quetiapine

115 outpatients with BD-I or BD-II assigned to quetiapine or placebo as add-on to TAU (lithium, anticonvulsants, AD). Mostly depressed. Half of the sample not taking medications. Quetiapine improved depressive symptoms (HAM-D) for 12 weeks. No alcohol changes ([Brown, 2008](#)).

Multicenter study in 362 Bipolar-I-AUD outpatients. Quetiapine (up to 400mg) as add-on to lithium or valproate vs placebo. No changes in alcohol use ([Stedman, 2010](#)).

90 outpatients with BD-I or BD-II, depressed/mixed. 12 weeks of add-on quetiapine XR (600 mg) or placebo. No changes in alcohol ([Brown, 2014](#)).

Naltrexone

50 outpatients with AUD-BD I/II 12 weeks of naltrexone (50 mg) add-on (valproate, lithium, APs) or placebo and CBT. Only 26 completed treatment. No statistical significant changes in any drinking day each week but a trend. However moderate effect size in alcohol craving, liver enzymes ([Brown, 2009](#)).

Two other open label, small randomized studies.

A large VA based study, in 254 patients with Axis-I and AUD showed naltrexone or disulfiram to be safe and effective in craving. Results in each specific Axis-I disorder not shown ([Petrakis, 2005](#)).

Psychotherapy

Integrated Group Therapy. Two RCTs:

1) 62 patients (80% BDI, valproate/lithium or both, 60% both alcohol and drug use disorder), 20 weeks, IGT vs group drug counseling. IGT less number of days of any substance use (mainly alcohol). No mood differences.

2) 61 patients (similar clinical features), 12 weeks, community friendly. IGT showed a trend ($p < 0.1$) with less days of substance use during follow-up (month 6) and less mood episodes during treatment (month 3).

[Weiss, 2007](#); [Weiss, 2009](#)

Section IV: Conclusions

Lack of studies in psychopharmacological and psychosocial treatments.

Data only on valproate added to lithium, naltrexone (added to mood stabilizers) and integrated group therapy.

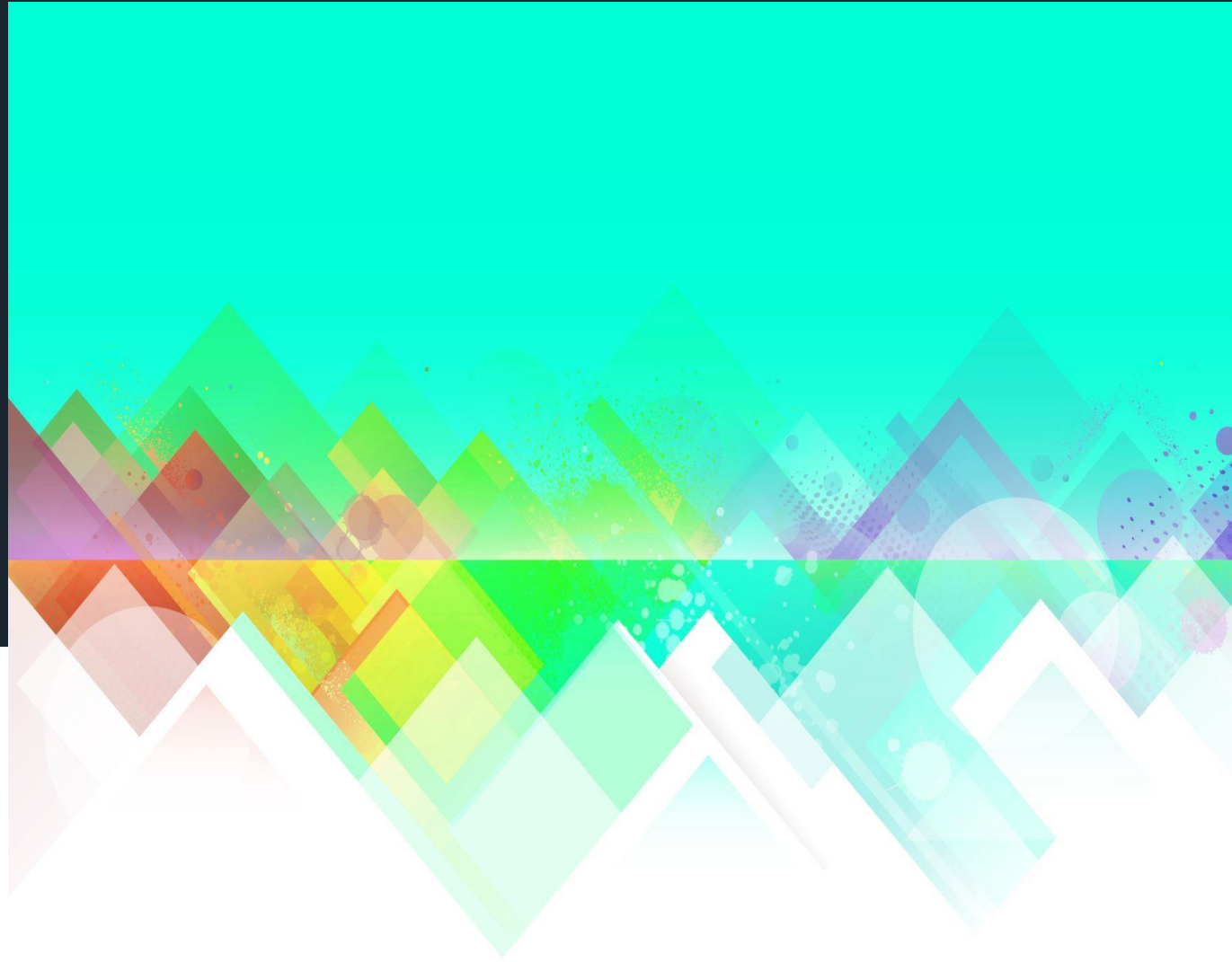
Disulfiram and naltrexone are safe to use in population with SMI.

Integrated medical model of care, same setting, good collaboration with primary, specialty care and acute inpatient units.

Early psychosocial treatment (i.e family), start treatment for AUD soon.

Section V

Treatment in Minoritized Groups



Black Individuals and Bipolar Disorder

No significant differences in rates of BD by race found in the ECA (Regier DA, 1984).

AA in comparison with Caucasian, 4 times more chances to receive a schizophrenia diagnosis (Blow FC, 2004).

AA prescribed AP at a higher rate compared to Caucasians (92% vs 62%) (Szarek BL, 2003).

Recent review (Akinhanmi MO, 2018): Systematic issues-Historical mistrust (slavery, institutional racism, discrimination, poverty, segregation).

Hispanic Individuals and SUD treatment

Hispanic individuals less likely to complete substance abuse treatment, underutilize treatment, perceived lack of treatment efficacy ([Pinedo, 2019](#)).

Hispanic individuals participating in NIDA Clinical Trials Network studies over the past 20 years: lower employment rates, having insurance, increased travel time to SUD treatment, geographical inaccessibility, citizenship status, level of acculturation ([Eghaneyan, 2020](#)).

Section V: Conclusions

Lack of Research in Racial and Ethnic Minorities.

An Uncomfortable Truth: Diagnosis and Treatment of Bipolar Disorder and Substance Use Disorder is Suboptimal.

Need of cultural competency training, multi-minority teams.

Social determinants might be more powerful than biological ones.

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