«LA DEPRESSIONE IN COMORBILITÀ CON IL DISTURBO DA USO DI SOSTANZE»

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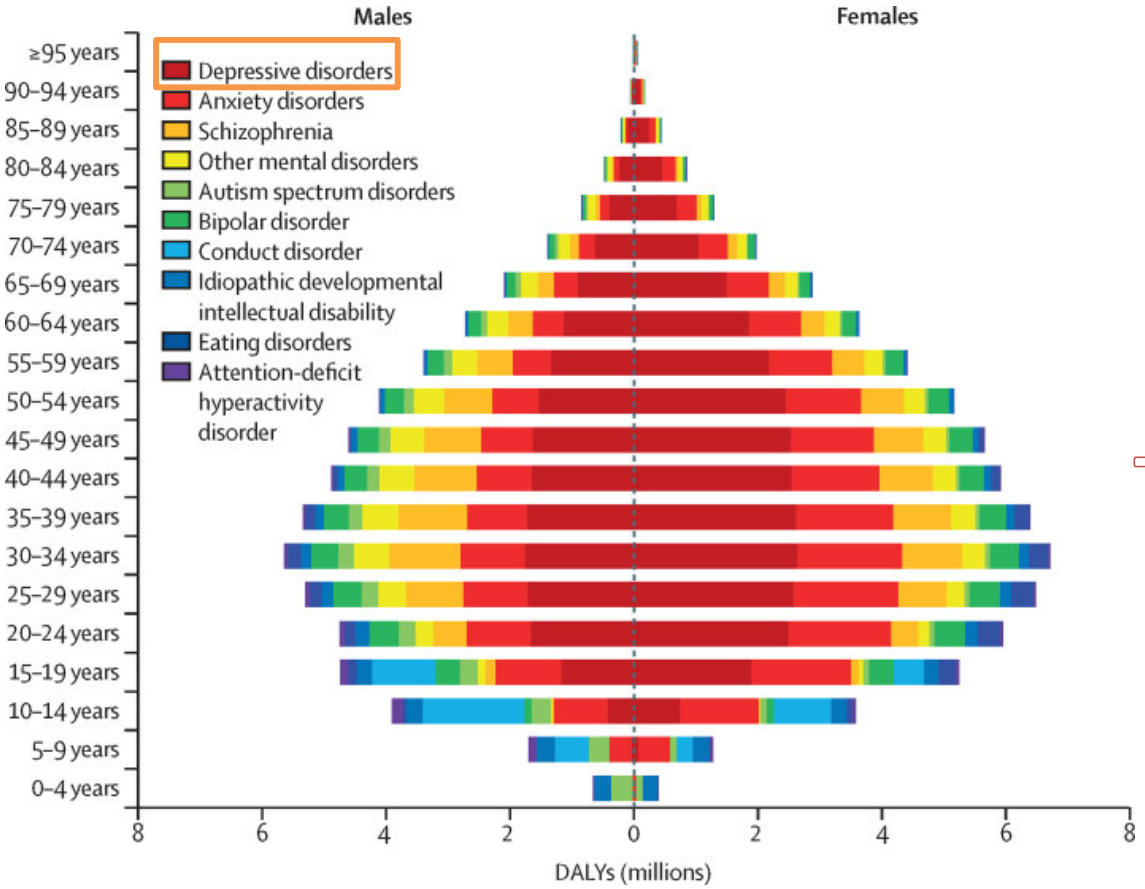
Global burden of mental disorders: an analysis from 1990 to 2019



Mental disorders remained among **the top ten leading causes** of **burden** worldwide **since 1990.**

44,5 million disability-adjusted life-years (DALYS)

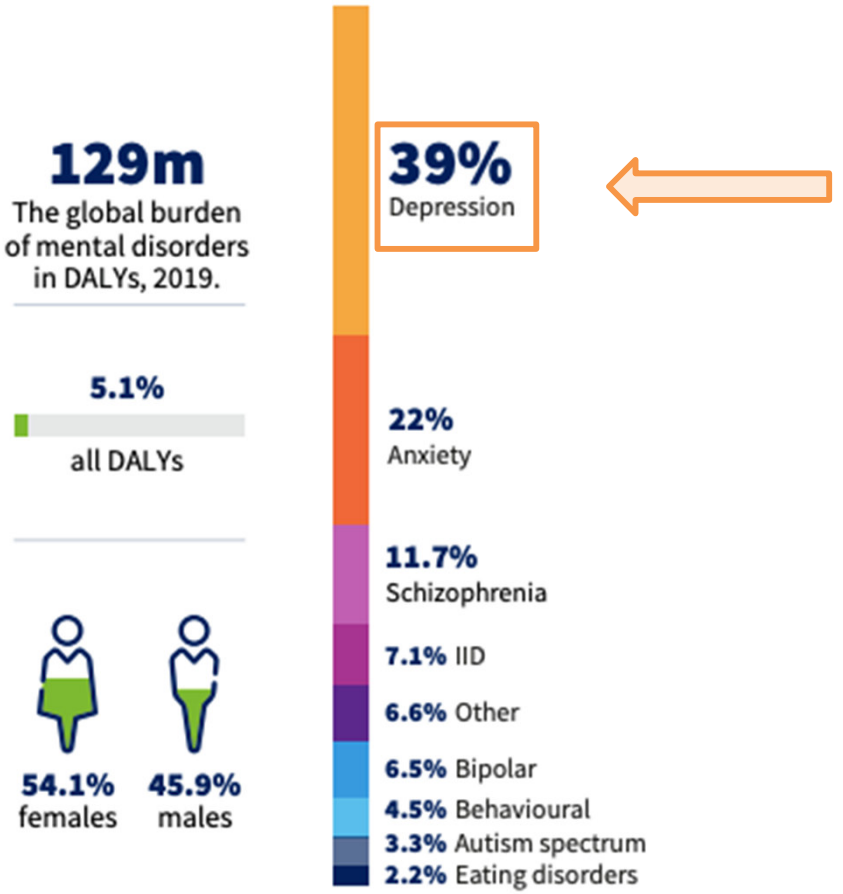
14,6% of global years lived with disability (YLDs)

GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry. 2022;9(2):137-150.; Institute of Health Metrics and Evaluation. Global Health Data Exchange (GHDx).

The impact of depression worldwide

280 million

People suffer from **DEPRESSION** worldwide (5% among adults, 5,7% among adults older than 60 years)



New GBD analyses show significant increases due to COVID-19

Read the full paper: Santomauro DF, Mantilla Herrera AM, Shadid J, et al. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. The *Lancet* 2021. Published online October 8.

THE LANCET

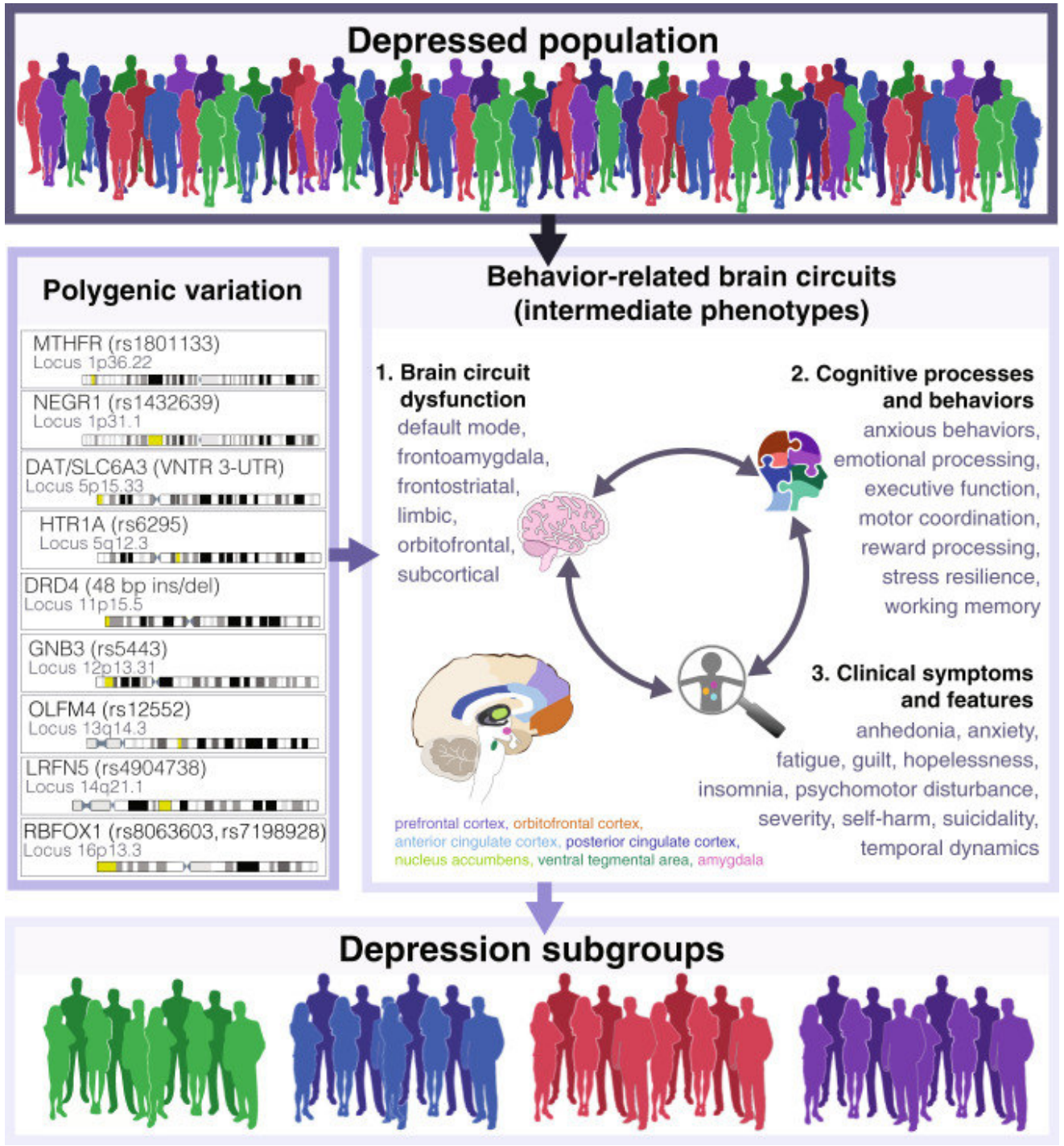
The University of Queensland AUSTRALIA

QCMHR

IHME

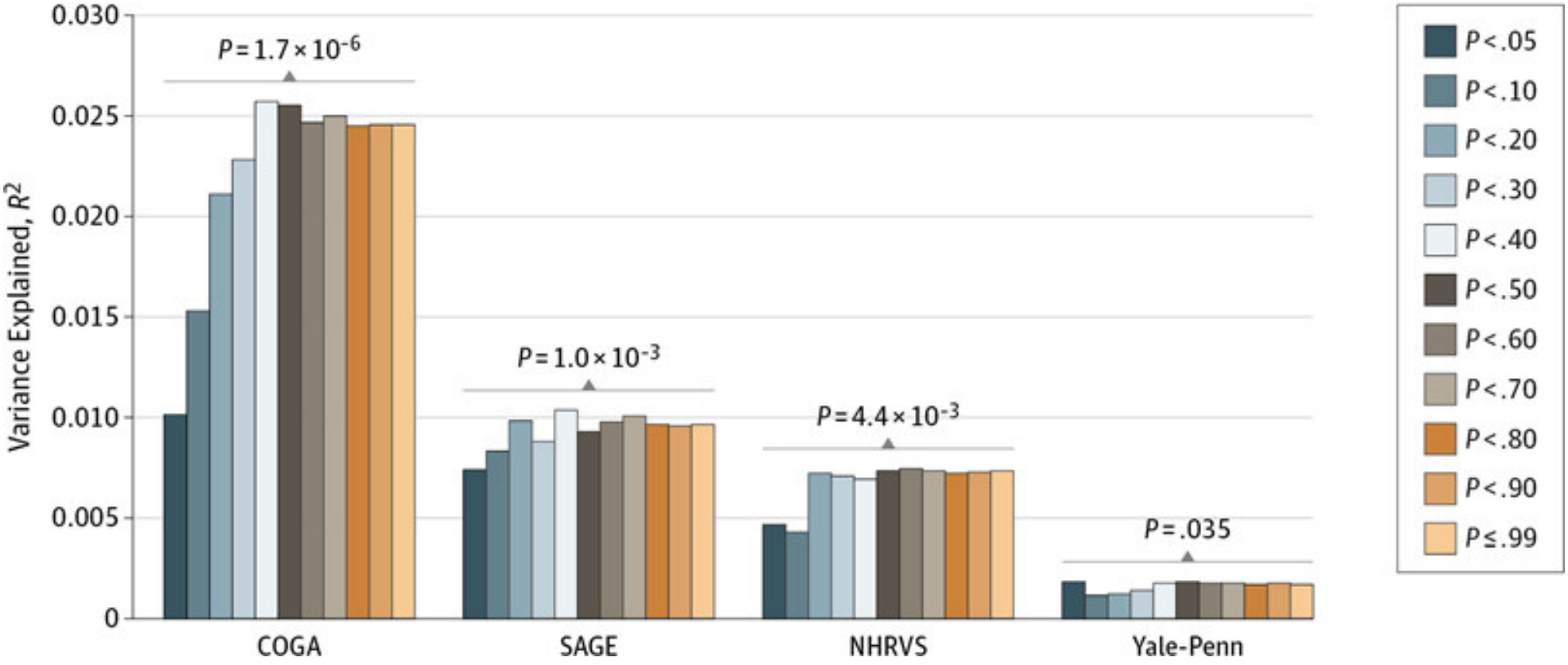
An **increase** of **27,6%** (25,1 to 30,3) of major depressive disorder cases globally due to the pandemic (total prevalence was 3152,9 cases per 100.000).

Altogether, major depressive disorder caused **49,4 million** (33,6 to 68,7) **DALYs.**

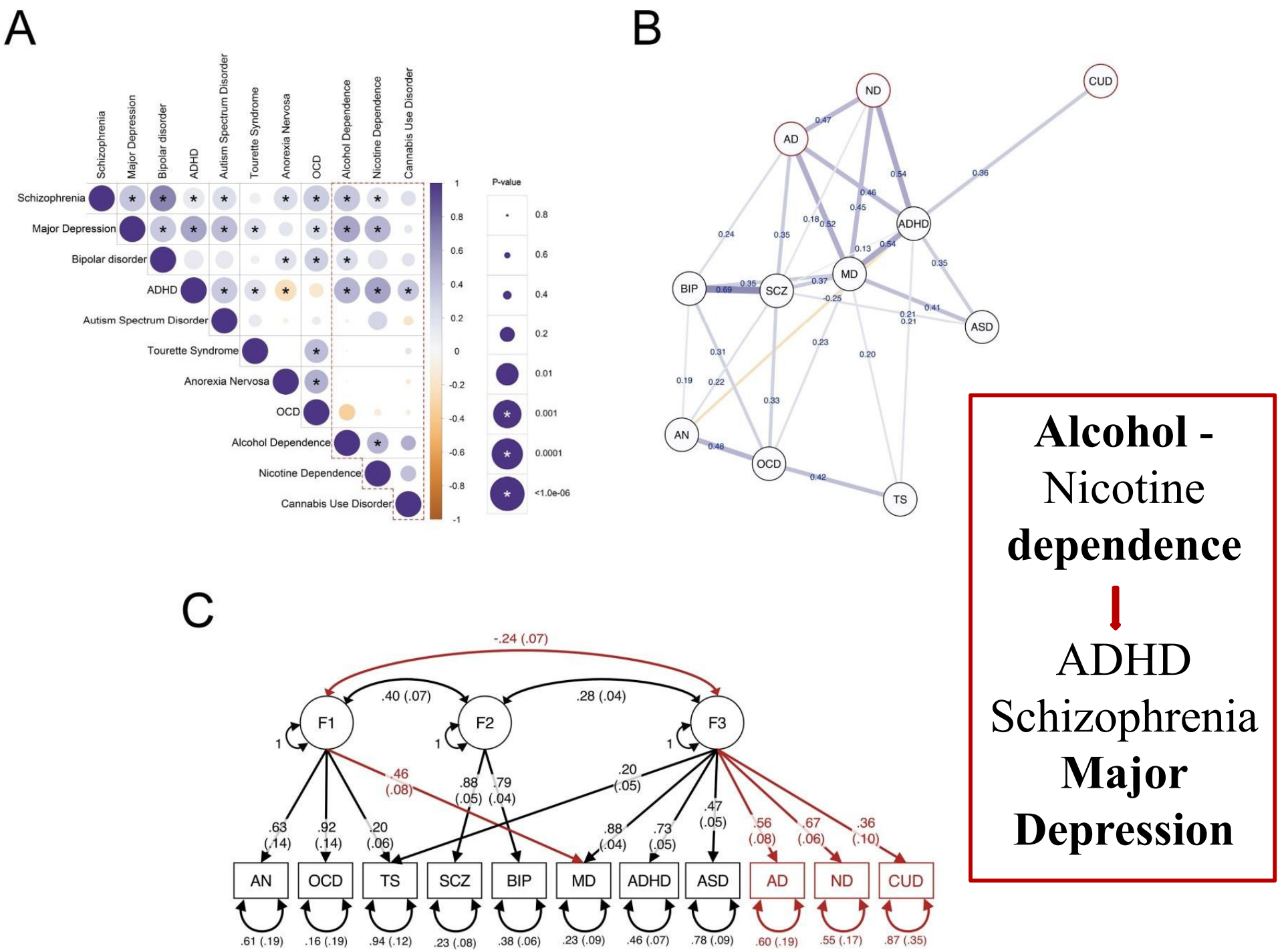


Buch AM, Liston C. Neuropsychopharmacology. 2021;46(1):156-175

Polygenic Scores for Major Depressive Disorder and Risk of Alcohol Dependence

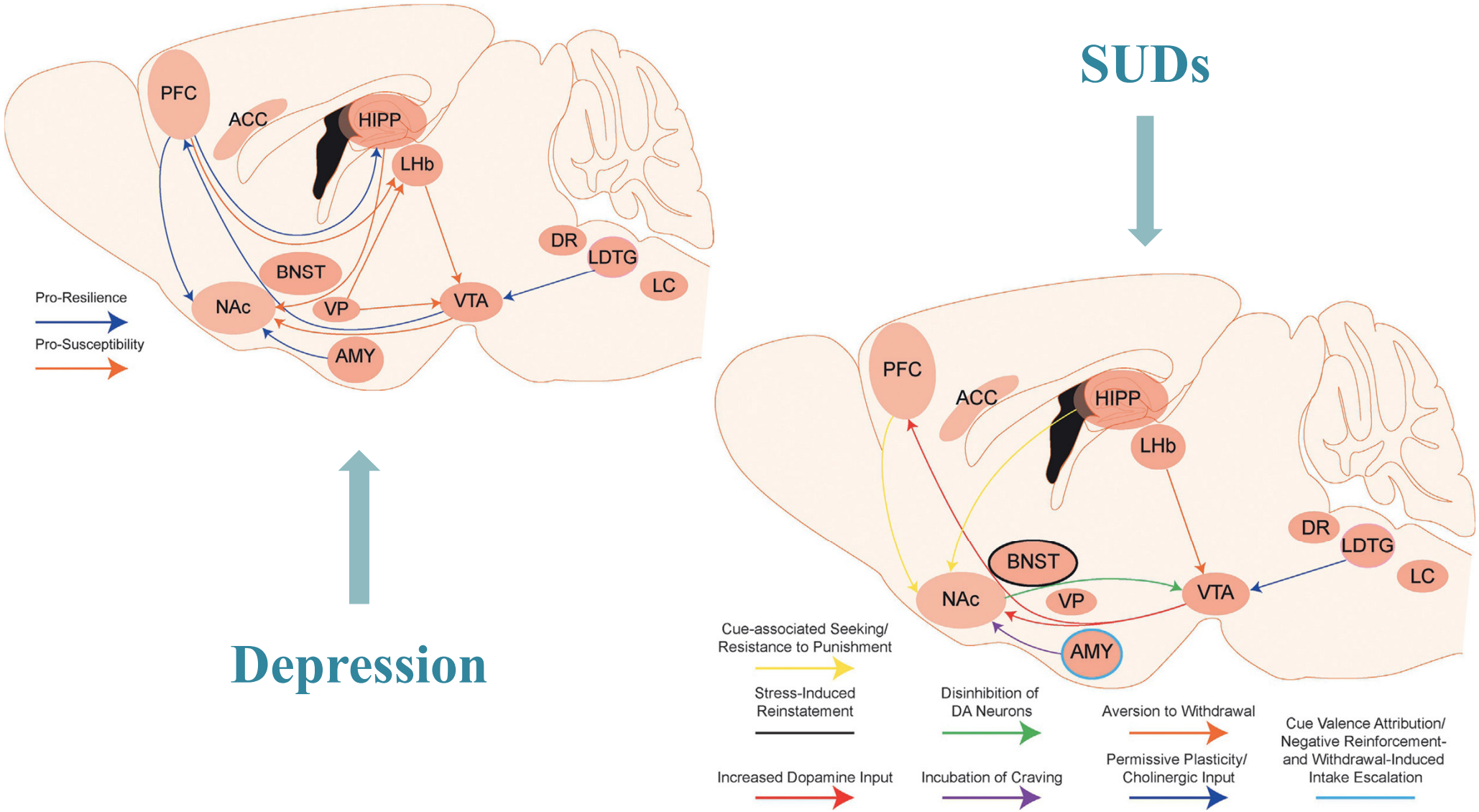


Andersen AM, et al. Polygenic Scores for Major Depressive Disorder and Risk of Alcohol Dependence. *JAMA Psychiatry*. 2017.



Abdellaoui A, et al. Genomic relationships across psychiatric disorders including substance use disorders. *Drug Alcohol Depend*. 2021.

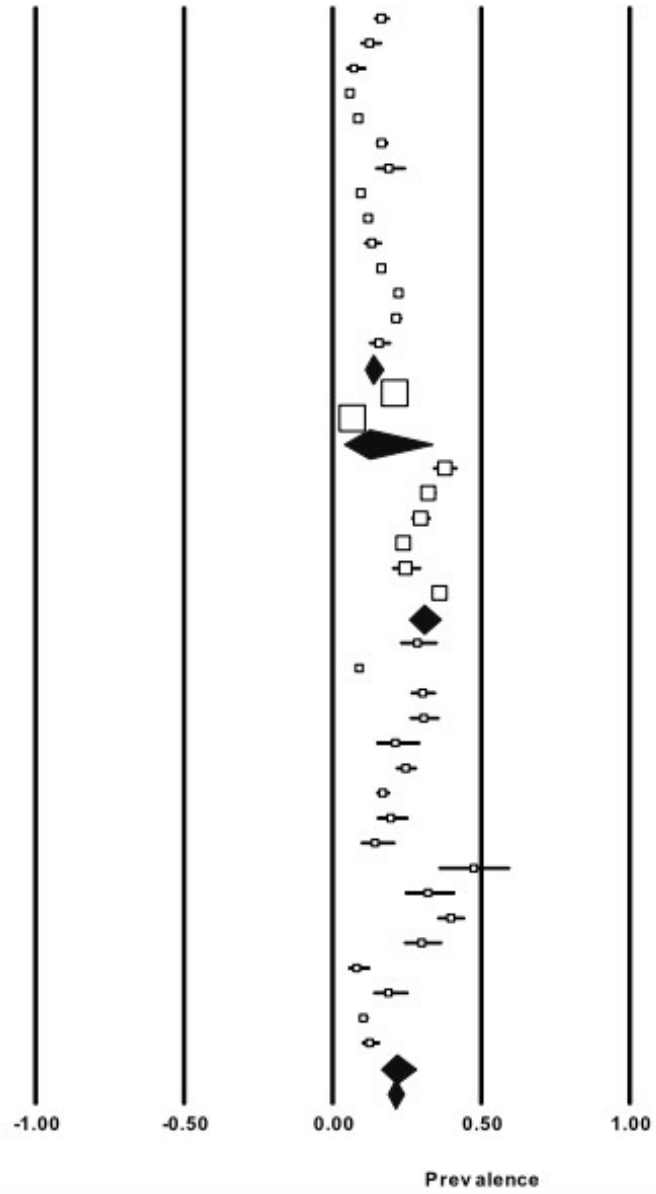
Shared neurobiology



Calarco CA, Lobo MK. Depression and substance use disorders: Clinical comorbidity and shared neurobiology. *Int Rev Neurobiol*. 2021;157:245-309

Alcohol use and major depression

Group by population	Study name	Event rate	Lower limit	Upper limit	Events/Total
1-Epidemiology	01 NSMHWB	0.164	0.137	0.195	101 / 617
1-Epidemiology	02 Brazil	0.125	0.091	0.168	36 / 289
1-Epidemiology	03 BPMS	0.072	0.044	0.116	15 / 209
1-Epidemiology	04 CCHS	0.058	0.047	0.071	86 / 1479
1-Epidemiology	05 CNPHS	0.086	0.077	0.097	270 / 3133
1-Epidemiology	06 ECA	0.165	0.143	0.189	164 / 994
1-Epidemiology	08 Israel	0.189	0.141	0.249	39 / 206
1-Epidemiology	09 MHGP	0.095	0.087	0.104	413 / 4339
1-Epidemiology	10. NCS	0.120	0.104	0.137	183 / 1530
1-Epidemiology	11. NEMESIS	0.132	0.103	0.168	55 / 417
1-Epidemiology	12 NESARC	0.164	0.151	0.178	507 / 3090
1-Epidemiology	12 NESARC-III	0.222	0.209	0.235	838 / 3776
1-Epidemiology	13. NLAES	0.214	0.193	0.236	302 / 1414
1-Epidemiology	15. OHS	0.156	0.121	0.199	52 / 333
1-Epidemiology		0.133	0.106	0.166	
2-Case registry	16. Denmark	0.209	0.207	0.211	41184 / 197057
2-Case registry	17. Norway	0.066	0.065	0.068	5911 / 89033
2-Case registry		0.121	0.036	0.332	
3-Cohort	19. MIDAS	0.378	0.336	0.422	181 / 479
3-Cohort	20. NESDA	0.322	0.295	0.350	359 / 1115
3-Cohort	21. NIMH-CDS	0.296	0.263	0.332	201 / 678
3-Cohort	22. STAR*D	0.238	0.222	0.254	674 / 2835
3-Cohort	23. VDS	0.245	0.198	0.300	66 / 269
3-Cohort	25. VTS	0.360	0.343	0.377	1069 / 2972
3-Cohort		0.305	0.255	0.360	
4-Clinical	Arias-13	0.286	0.225	0.356	52 / 182
4-Clinical	Cornelius-95	0.090	0.080	0.101	239 / 2660
4-Clinical	Fava-96	0.303	0.260	0.350	120 / 396
4-Clinical	Fischer-98	0.307	0.257	0.362	90 / 293
4-Clinical	Hapangama-13	0.211	0.144	0.298	23 / 109
4-Clinical	Hobden-17	0.247	0.211	0.286	124 / 503
4-Clinical	Loo-90	0.169	0.145	0.196	138 / 817
4-Clinical	Maier-95	0.196	0.147	0.257	39 / 199
4-Clinical	Merikangas-94	0.143	0.093	0.213	19 / 133
4-Clinical	Mueser-00	0.475	0.354	0.600	29 / 61
4-Clinical	Mulder-94	0.321	0.240	0.414	35 / 109
4-Clinical	Olvera-11	0.398	0.350	0.448	154 / 387
4-Clinical	Rae-02	0.300	0.238	0.371	54 / 180
4-Clinical	Sanderson-90	0.081	0.050	0.128	16 / 197
4-Clinical	Subramaniam-17	0.188	0.134	0.258	29 / 154
4-Clinical	Watkins-06	0.104	0.087	0.124	110 / 1061
4-Clinical	Yen-08	0.125	0.095	0.162	48 / 385
4-Clinical		0.213	0.161	0.276	
Overall		0.208	0.183	0.235	



Hunt GE, et al. Prevalence of comorbid substance use in major depressive disorder in community and clinical settings, 1990-2019: Systematic review and meta-analysis. *J Affect Disord*. 2020

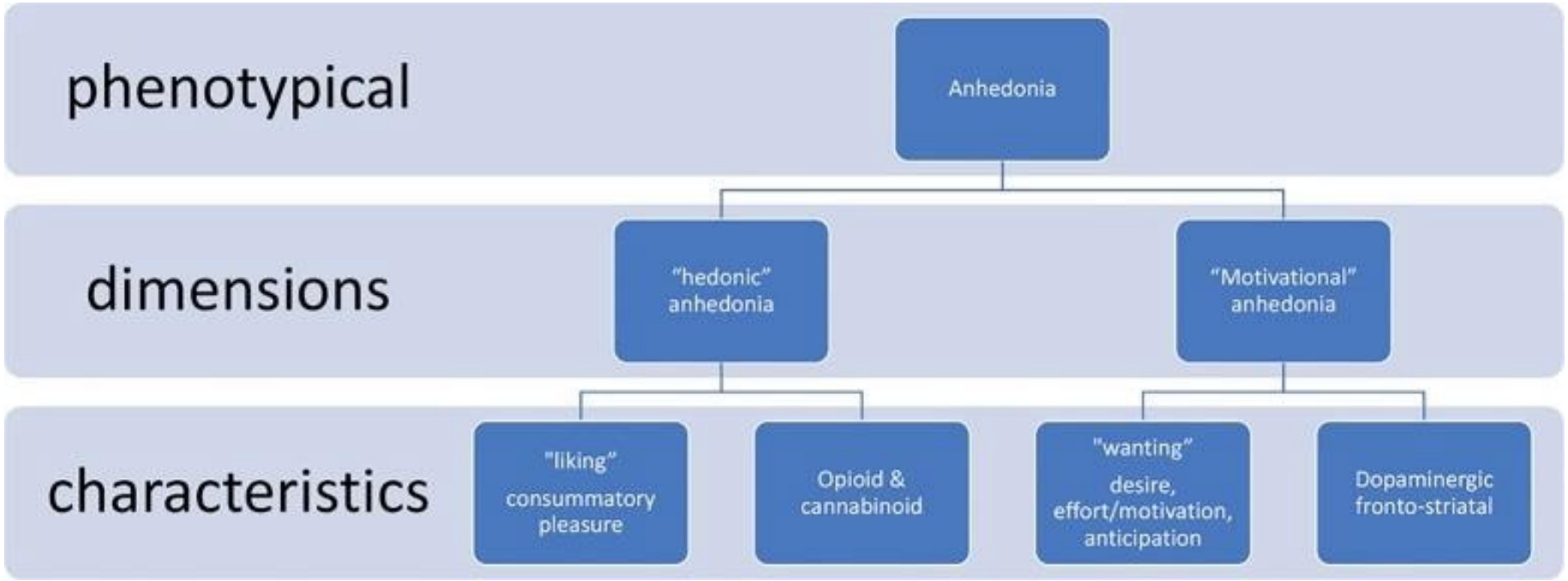
Depression and Substance Use Disorders (SUDs)

Table 1 Lifetime prevalence of comorbid MDD with substance abuse or dependence by substance class.

Drug use disorder	% with any mood disorder	% with depression
Any drug use disorder	21.6	20.7
Any drug abuse	13.5	13.1
Any drug dependence	8.2	7.7
Marijuana use disorder	17.1	16.3
Marijuana abuse	13.1	12.6
Marijuana dependence	4.0	3.7
Cocaine use disorder	6.5	6.1
Cocaine abuse	3.3	3.2
Cocaine dependence	3.1	2.8

Calarco CA, Lobo MK. Depression and substance use disorders: Clinical comorbidity and shared neurobiology. *Int Rev Neurobiol*. 2021;157:245-309.

Addiction, Anhedonia, and Comorbid Mood Disorder



Destoop M, et al. Addiction, Anhedonia, and Comorbid Mood Disorder. A Narrative Review. *Front Psychiatry*. 2019

Clinical characterization of MDD in patients with comorbid AUD

- General population survey of 38.694 French individuals
- 4339 subjects (11.2%) met the criteria for MDD
- Among them, 413 (9.5%) AUD subjects were identified

	Alcohol Abuse Group		Alcohol Dependence Group	
	%	OR [95 % CI]	%	OR [95 % CI]
MDD symptoms				
Sadness	81.0	0.43 [0.27-0.72]***,+	87.3	0.77 [0.49-1.26]
Anhedonia	80.1	1.46 [0.91-2.44]	81.2	1.30 [0.90-1.94]
Fatigue or loss of energy	87.0	1.20 [0.70-2.18]	84.6	1.10 [0.73-1.73]
Weight or appetite variations	72.4	1.67 [1.11-2.58]*	66.5	1.33 [0.97-1.85]
Sleep disorders	72.4	1.34 [0.88-2.08]	77.6	1.87 [1.31-2.74]***,+
Psychomotor retardation or agitation	56.0	1.12 [0.76-1.65]	57.9	1.17 [0.86-1.59]
Feelings of worthlessness	67.2	1.06 [0.71-1.61]	74.1	1.40 [1.01-1.99]*
Feelings of guilt	65.5	1.19 [0.80-1.81]	71.4	1.44 [1.04-2.01]*
Diminished concentration/indecisiveness	67.2	1.06 [0.71-1.61]	74.1	1.40 [1.01-1.99]*
Thoughts of death	39.7	1.10 [0.74-1.63]	52.8	1.92 [1.42-2.62]***,+

Carton L, et al. Influence of comorbid alcohol use disorders on the clinical patterns of major depressive disorder: A general population-based study. *Drug Alcohol Depend*. 2018.

MDE is associated with cognitive impairment in subjects with AUD

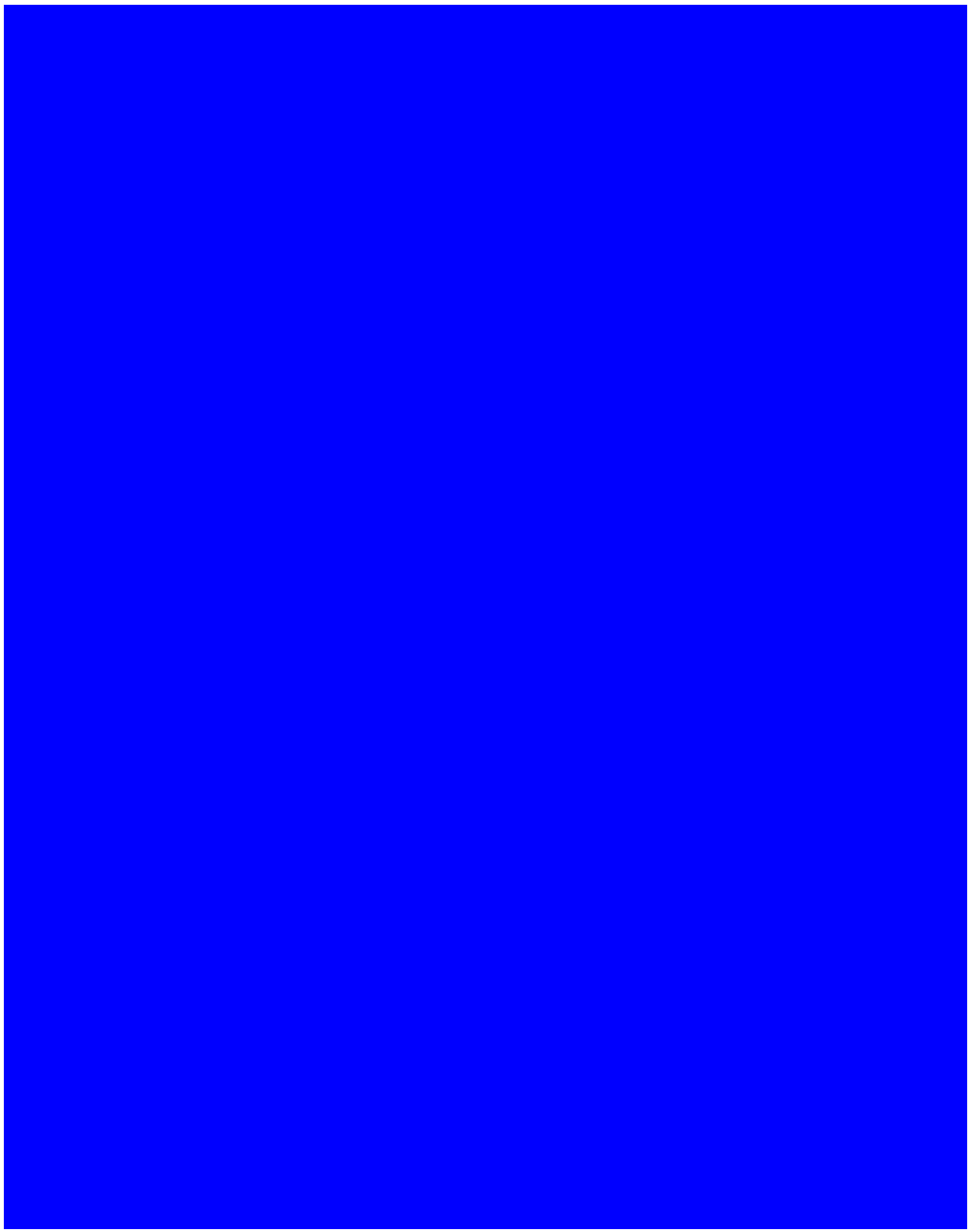
Results of the logistic regression modeling based on the parameters associated with a positive MoCA test in the bivariable comparisons.

	B (SE)	95% CI for odds ratio		
		Lower	Odds ratio	Upper
Included				
Constant	−1.72 (1.41)			
ADHD	0.60 (0.56)	0.61	1.83	5.51
Agoraphobia	1.47 (0.72)*	1.16	4.36	21.56
BIS-11	0.01 (0.02)	0.97	1.01	1.06
Current depressive episode	1.53 (0.58)**	1.55	4.60	15.75

Note. $R^2 = 0.18$ (Hosmer–Lemeshow), 0.22 (Cox–Snell), 0.30 (Nagelkerke). Model $\chi^2(1) = 25.26$, $p < 0.001$. ** $p < 0.01$; * $p < 0.05$.

D'Hondt F et al. Psychiatric comorbidities associated with a positive screening using the Montreal Cognitive Assessment (MoCA) test in subjects with severe alcohol use disorder. *Drug and Alcohol Dependence* 191 (2018) 266–269.

MDD in comorbidity with SUD: patients' features



Patients with MDD+SUD often show increased anhedonia, emotional blunting, impaired cognitive function

↓

inability to control cravings, more substance use, increased relapse rates, and poor treatment adherence

↓

detrimental cycle with more severe depressive symptoms, functional impairment, and chronicity, culminating in heightened morbidity, mortality, and healthcare resource utilization

De Filippis S., Martinotti G., Nicoletti F., Mastrostefano A., Trovini G., Pugliese A., Di Nicola M. Current Neuropharmacology. 2024. *In press*

The effect of psychiatric disorders on alcohol consumption levels

Daily limits: > 4/3 drinks/d for Men/Women
Weekly limits: > 14/7 drinks/wk for Men/Women

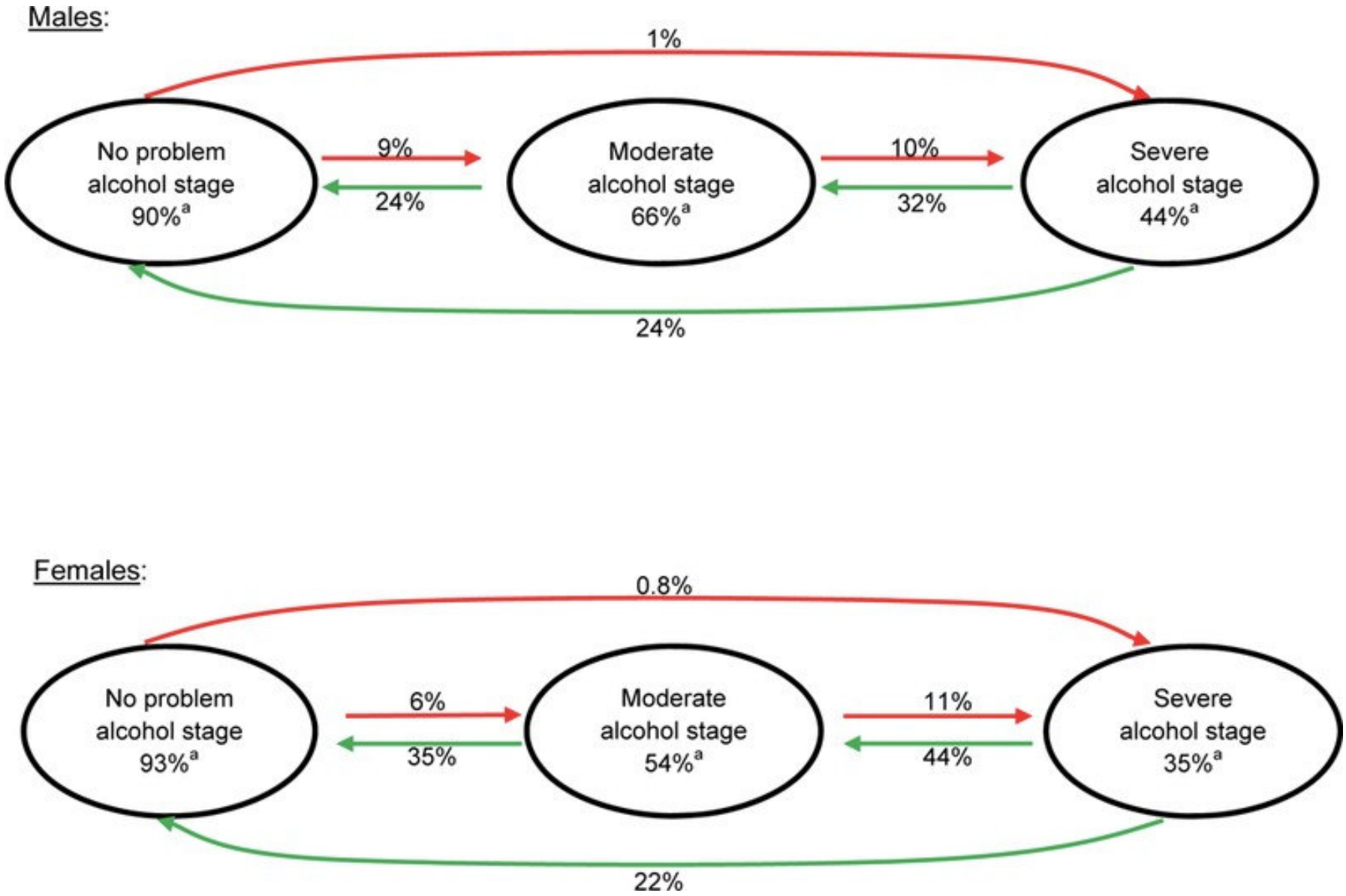
Table 2. Unadjusted Prevalence of Psychiatric Disorders[a] by Alcohol Consumption Level[b], Kaiser Permanente Northern California, 2014 to 2017

		Alcohol consumption level[b], *n* (%)				
Psychiatric disorder[a]	Overall (*n* = 2,720,231)	No Use (*n* = 1,858,804)	Low-risk (*n* = 592,048)	>Daily (*n* = 165,581)	>Weekly (*n* = 62,349)	>Both (*n* = 41,449)
Anorexia nervosa	624 (<0.1)	487 (<0.1)	94 (<0.1)	27 (<0.1)	9 (<0.1)	7 (<0.1)
Anxiety disorder	203,242 (7.5)	143,045 (7.7)	40,037 (6.8)	11,267 (6.8)	5,191 (8.3)	3,702 (8.9)
Bipolar disorder	21,150 (0.8)	16,373 (0.9)	3,231 (0.5)	861 (0.5)	366 (0.6)	319 (0.8)
Bulimia nervosa	1,329 (<0.1)	933 (0.1)	236 (<0.1)	97 (0.1)	29 (<0.1)	34 (0.1)
Depression	225,185 (8.3)	164,236 (8.8)	41,540 (7.0)	9,851 (5.9)	5,917 (9.5)	3,641 (8.8)
Obsessive–compulsive disorder	4,980 (0.2)	3,783 (0.2)	795 (0.1)	271 (0.2)	69 (0.1)	62 (0.1)
Schizoaffective disorder	3,260 (0.1)	2,886 (0.2)	263 (<0.1)	59 (<0.1)	21 (<0.1)	31 (0.1)
Schizophrenia	2,660 (0.1)	2,330 (0.1)	239 (<0.1)	57 (<0.1)	19 (<0.1)	15 (<0.1)

"**Low-risk**": exceeding neither daily nor weekly limits;
"**>Daily**": exceeding only daily limits; "**>Weekly**": exceeding only weekly limits;
"**>Both**": exceeding both daily and weekly limits.

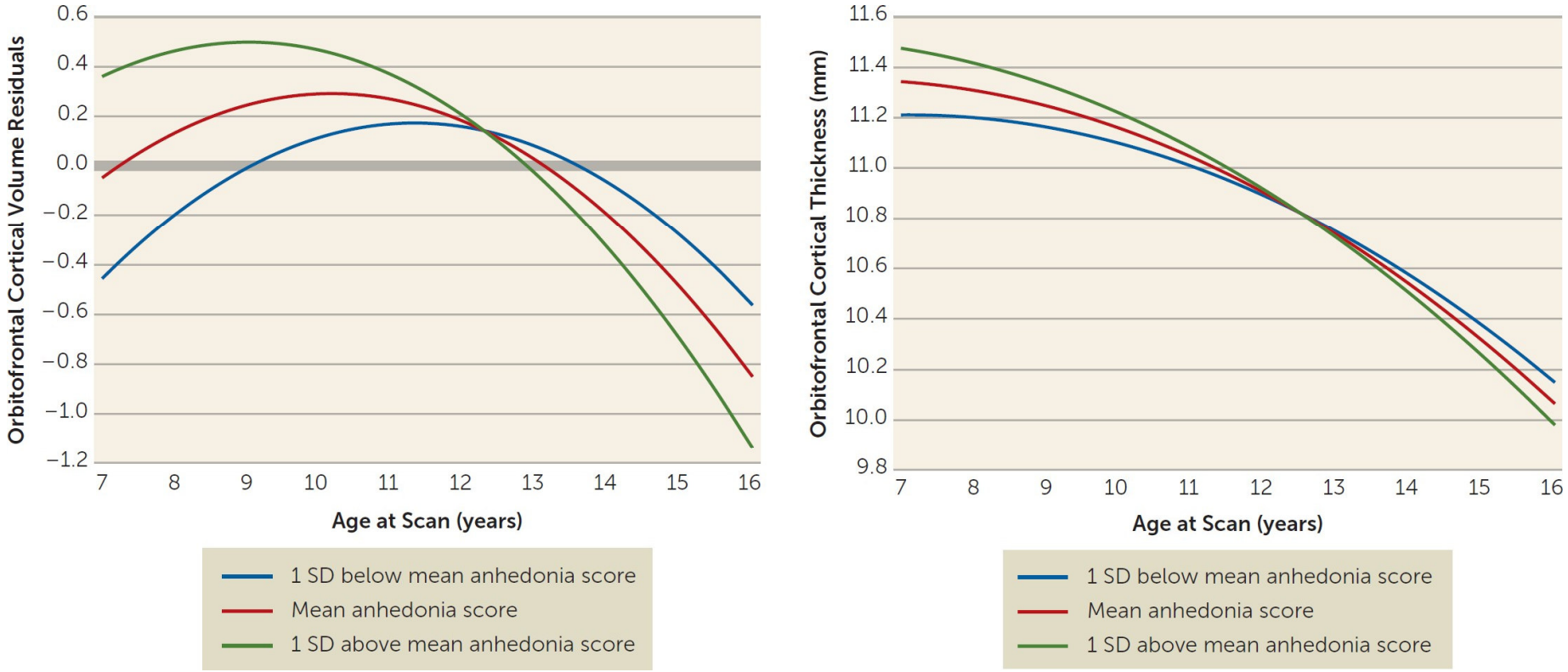
Palzes VA, et al. Associations Between Psychiatric Disorders and Alcohol Consumption Levels in an Adult Primary Care Population. *Alcohol Clin Exp Res*. 2020.

Mood disorders impact transition through stages of alcohol involvement



Crum RM, et al. Transitions through stages of alcohol involvement: The potential role of mood disorders. *Drug Alcohol Depend*. 2018.

Developmental trajectories of OF cortex and anhedonia and risk for substance use



Luby JL, et al. A Randomized Controlled Trial of Parent-Child Psychotherapy Targeting Emotion Development for Early Childhood Depression. *Am J Psychiatry*. 2018

Developmental transitions of co-occurring depression and alcohol use

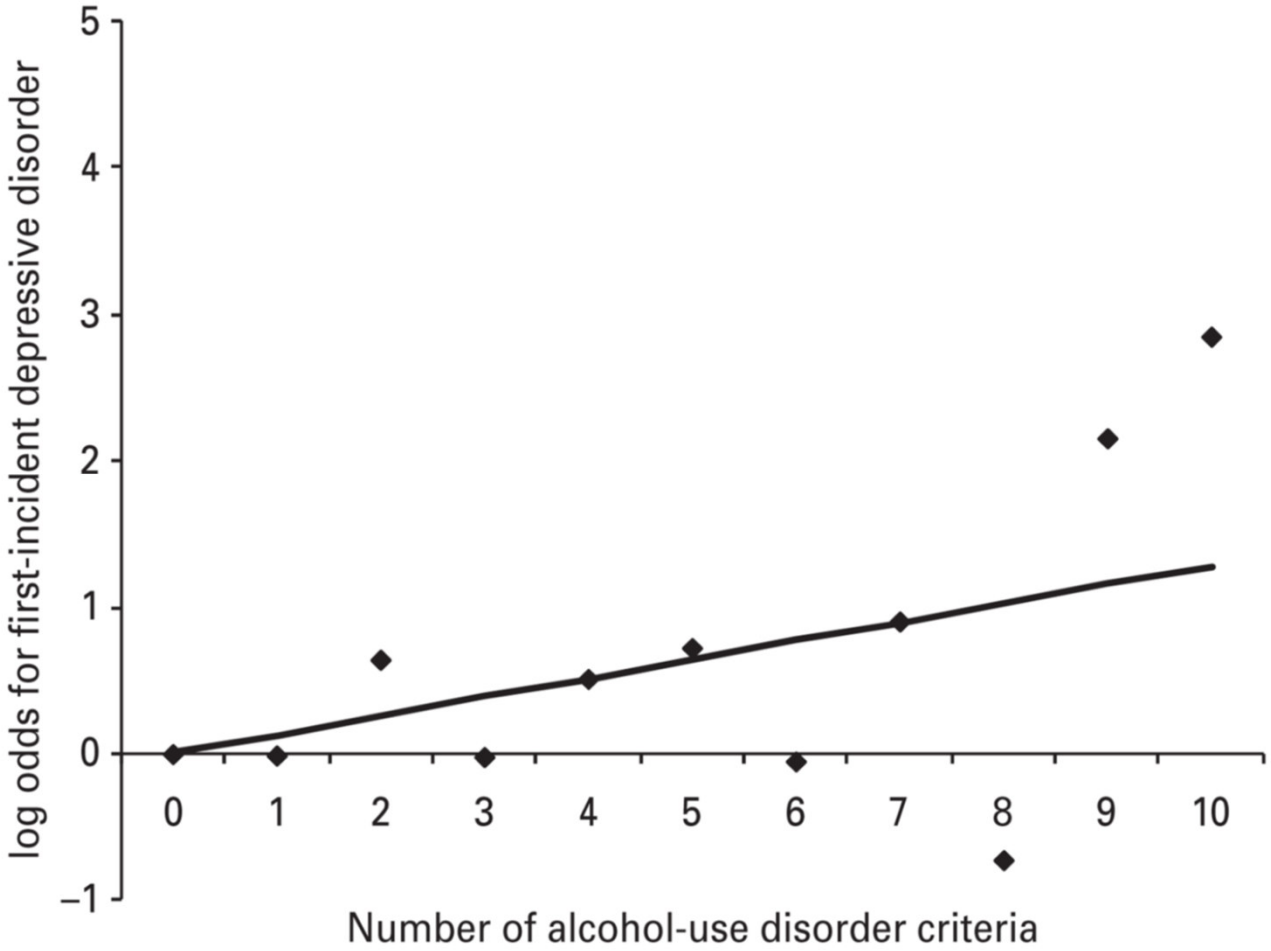
- Longitudinal study
- **N= 498**
- Late adolescents and early adults

Substance use coping: an intervening pathway both at the symptom level, from 17 to 23 ys, and in predicting **longer term diagnostic outcomes** at 28-30 ys.

Promising intervention target for preventive strategies

Magee KE, Connell AM. The role of substance use coping in linking depression and alcohol use from late adolescence through early adulthood. *Exp Clin Psychopharmacol*. 2021.

Alcohol-use disorder severity predicts first-incidence of depressive disorders



- ✓ N=27.571
- ✓3-years follow-up study
- ✓The number of DSM-5 AUD criteria predicts first-incident depressive disorders (MDD or dysthymia) (0 to all criteria: 4.20% vs. 44.47%)

Boschloo L, et al. Alcohol-use disorder severity predicts first-incidence of depressive disorders. *Psychol Med*. 2012.

Sleep disruption and depressive symptoms in early alcohol recovery

Baseline sleep disturbance →

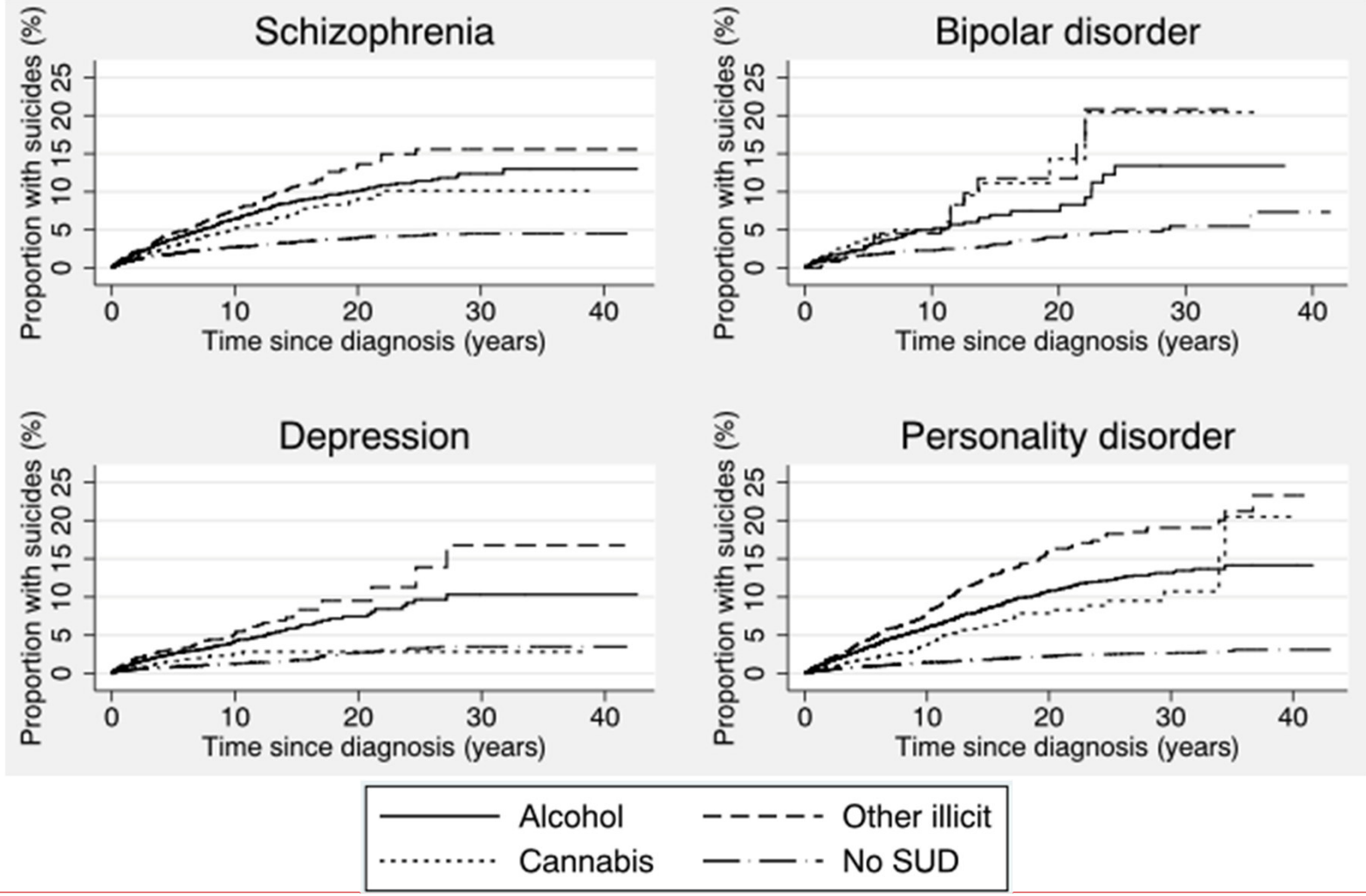
depressive symptoms (< .0001),
craving (< .0001),
propensity to drink when experiencing unpleasant emotions (< .0001),
number of drinks consumed (0.004),
drinking days (0.004)
hazardous drinking days (0.03)

Table 4
Correlation matrix examining pairwise correlations between predictor variables included in the multivariate regression model and PSQI total score.

	PHQ-9	PACS	GAD-7	IDTS Unpleasant Emotions	IDTS Urges Temptations	IDTS Physical Discomfort	TLFB Heavy Drinking Days	TLFB Days Drinking	TLFB Hazardous Drinking Days	PSQI Total Score
PHQ-9	1	0.46	0.77	0.34	0.18	0.30	0.20	0.18	0.16	0.55
PACS	0.46	1.00	0.40	0.25	0.30	0.20	0.19	0.30	0.26	0.29
GAD-7	0.77	0.40	1.00	0.34	0.18	0.22	0.06	0.07	0.05	0.47
IDTS Unpleasant Emotions	0.34	0.25	0.34	1.00	0.59	0.66	0.20	0.03	0.05	0.19
IDTS Urges Temptations	0.18	0.30	0.18	0.59	1.00	0.60	0.22	0.05	0.08	0.09
IDTS Physical Discomfort	0.30	0.20	0.22	0.66	0.60	1.00	0.33	0.16	0.18	0.27
TLFB Heavy Drinking Days	0.20	0.19	0.06	0.20	0.22	0.33	1.00	0.72	0.77	0.16
TLFB Days Drinking	0.18	0.30	0.07	0.03	0.05	0.16	0.72	1.00	0.95	0.17
TLFB Hazardous Drinking Days	0.16	0.26	0.05	0.05	0.08	0.18	0.77	0.95	1.00	0.12
PSQI Total Score	0.55	0.29	0.47	0.19	0.09	0.27	0.16	0.17	0.12	1.00

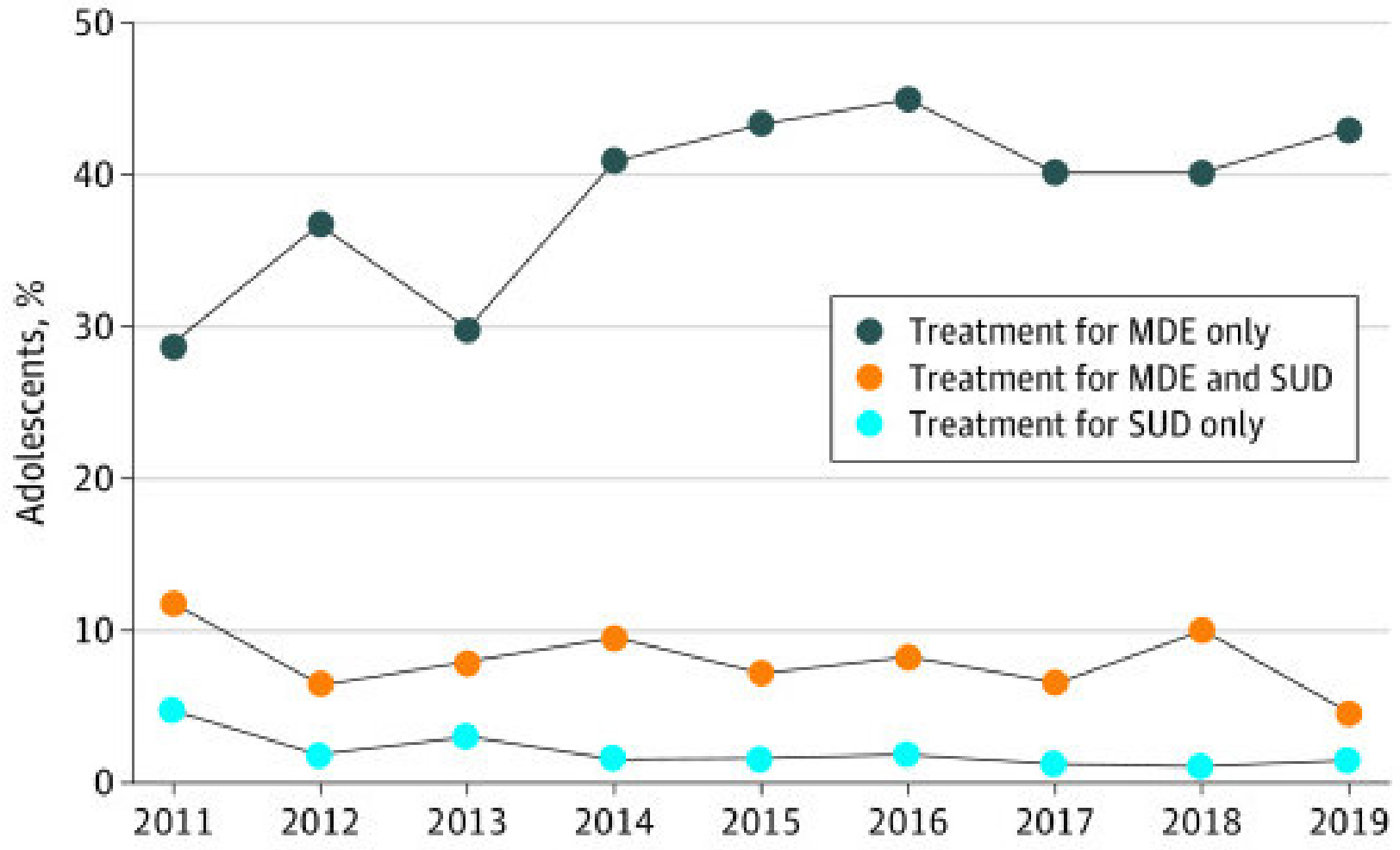
Kolla BP, et al. Sleep disturbances in early alcohol recovery: Prevalence and associations with clinical characteristics and severity of alcohol consumption. *Drug Alcohol Depend*. 2020

Alcohol misuse increases risk of completed suicide in psychiatric patients



Østergaard MLD, Nordentoft M, Hjorthøj C. Associations between substance use disorders and suicide or suicide attempts in people with mental illness: a Danish nation-wide, prospective, register-based study of patients diagnosed with schizophrenia, bipolar disorder, unipolar depression or personality disorder. *Addiction*. 2017;112(7):1250-1259.

Disparities in treatment for MDD and SUDs



Lu W, Muñoz-Laboy M, Sohler N, Goodwin RD. Trends and Disparities in Treatment for Co-occurring Major Depression and Substance Use Disorders Among US Adolescents From 2011 to 2019. JAMA Netw Open. 2021 Oct 1;4(10):e2130280.

Psychosocial interventions for subjects with alcohol misuse and depressive symptoms

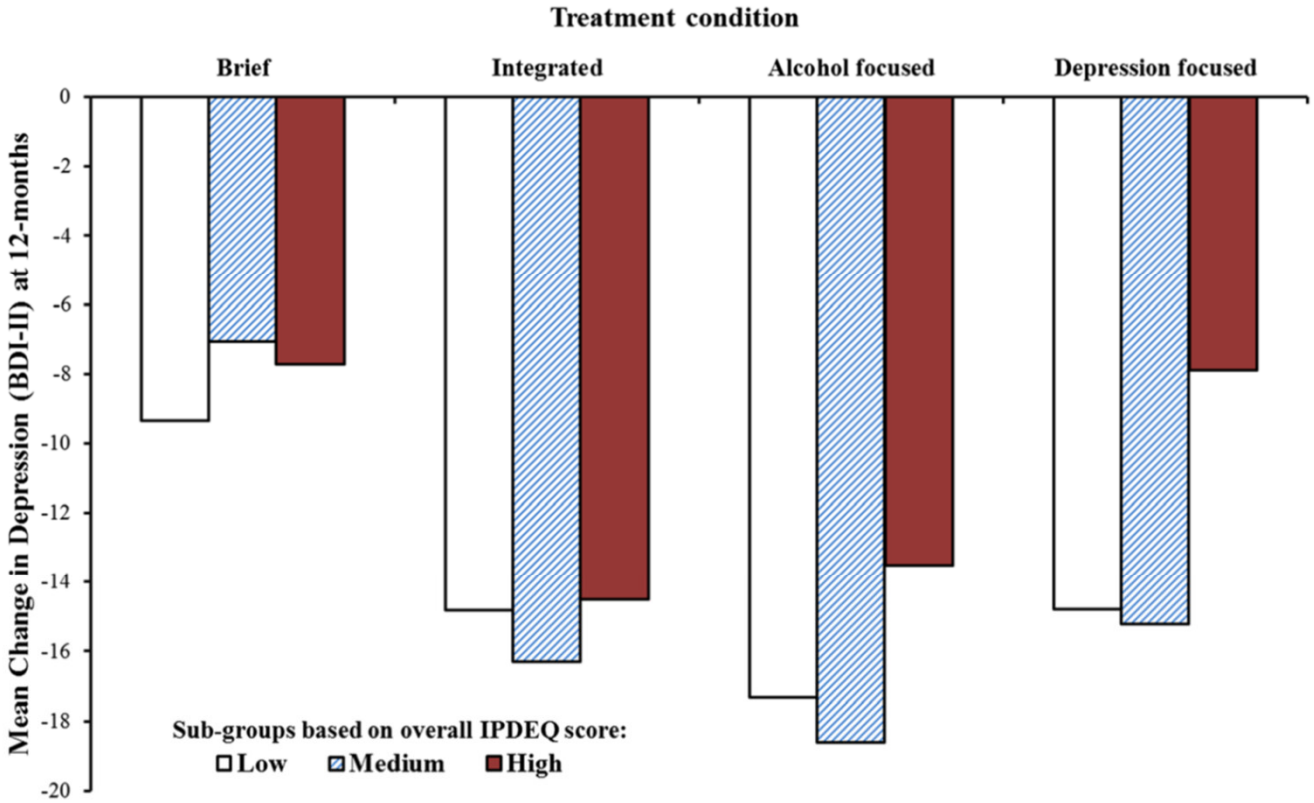
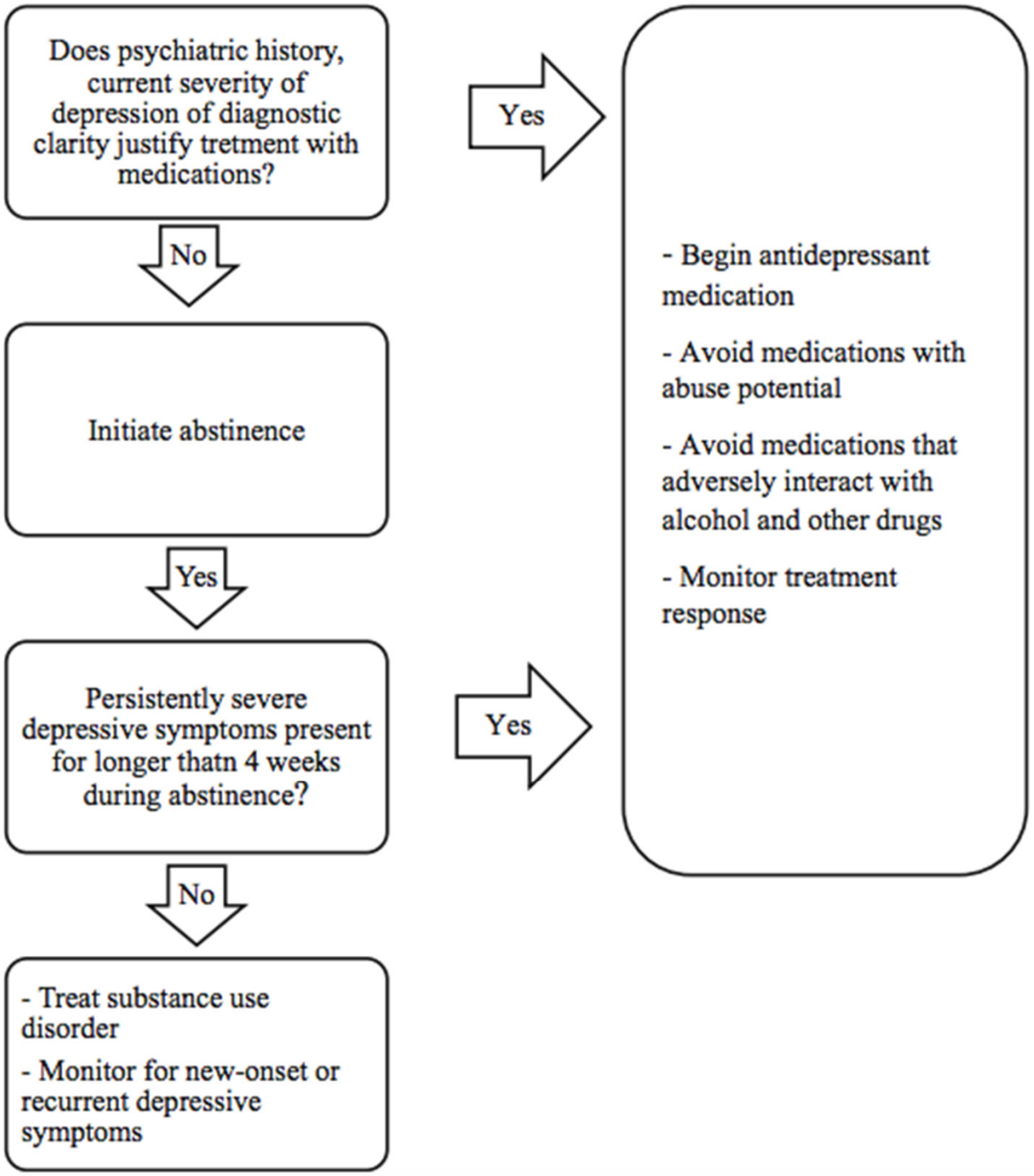


Fig. 2 Change in depression (BDI-II) at 12-months by treatment condition and IPDEQ sub-group ($N = 231$)

McCarter KL, et al. Associations between personality disorder characteristics and treatment outcomes in people with co-occurring alcohol misuse and depression. *BMC Psychiatry*. 2016


Does psychiatric history, current severity of depression of diagnostic clarity justify tretment with medications?
Yes
No
- Begin antidepressant medication
- Avoid medications with abuse potential
- Avoid medications that adversely interact with alcohol and other drugs
- Monitor treatment response
Initiate abstinence
Yes
Persistently severe depressive symptoms present for longer thatn 4 weeks during abstinence?
Yes
No
- Treat substance use disorder
- Monitor for new-onset or recurrent depressive symptoms

A new therapeutic target in dual diagnosis

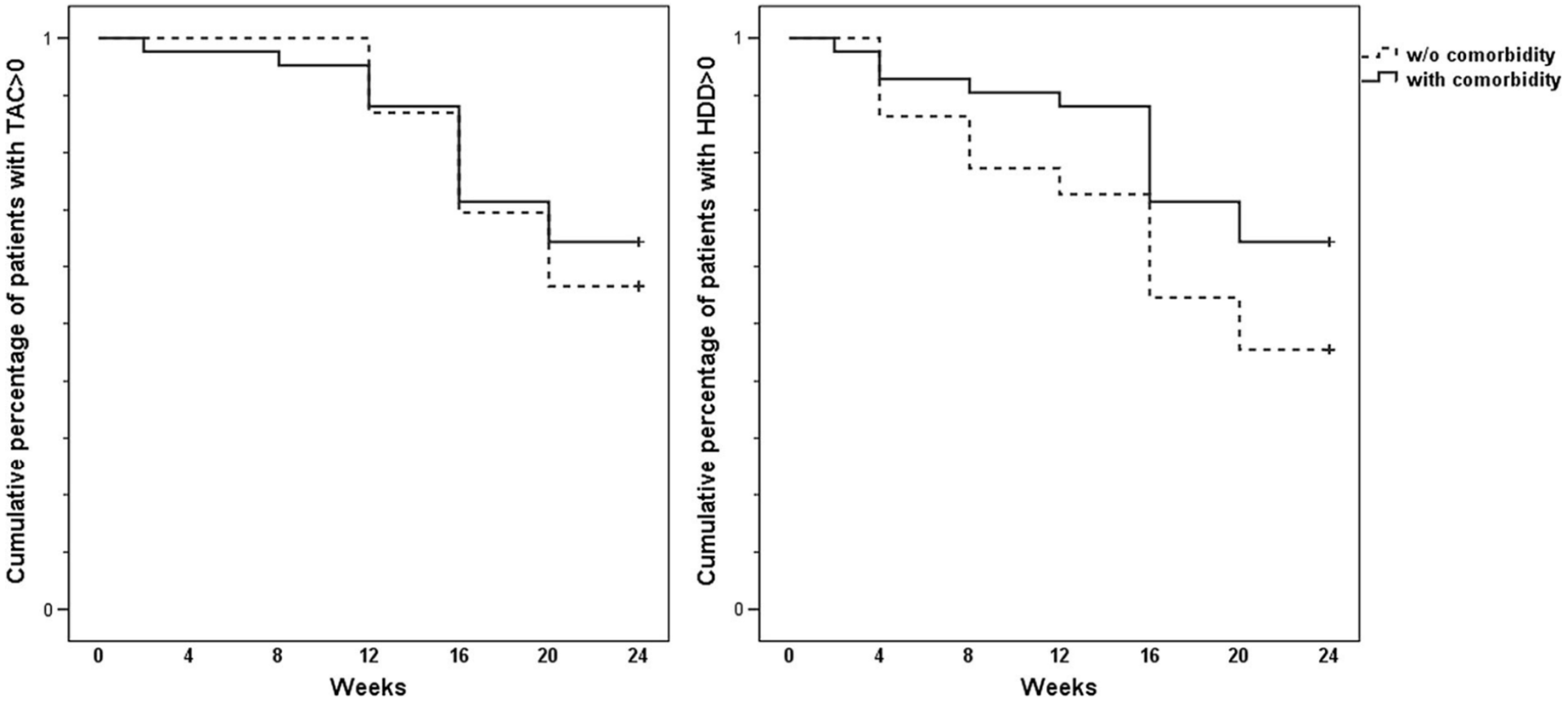
Clinical Guidance: Co-Occurring Mood and Substance Use Disorders

An emerging approach to treating comorbid mood and substance use disorders is simultaneous pharmacologic treatment of each. Patients with both types of disorders often have severe illness that is more difficult to manage than either one alone. Treatment for the mood disorder often improves mood symptoms but not alcohol or drug use. Pettinati et al. point to FDA-approved medications specifically for alcohol and opiate dependence. Their previous study of sertraline plus naltrexone, in addition to cognitive-behavioral therapy, showed greater effects on both depression and alcohol use from the combined medications than from either alone (Am J Psychiatry 2010; 167:668). Co-occurring bipolar and substance use disorders are difficult to treat; adding a medication for the substance disorder to a bipolar disorder treatment does not consistently decrease use. However, treating the substance use disorder is especially indicated for patients with an early onset of bipolar disorder.

- An emerging approach to treating DD is simultaneous pharmacological treatment of each
- Utility of prescribing a combination of medication to reduce both mood symptoms and substance use

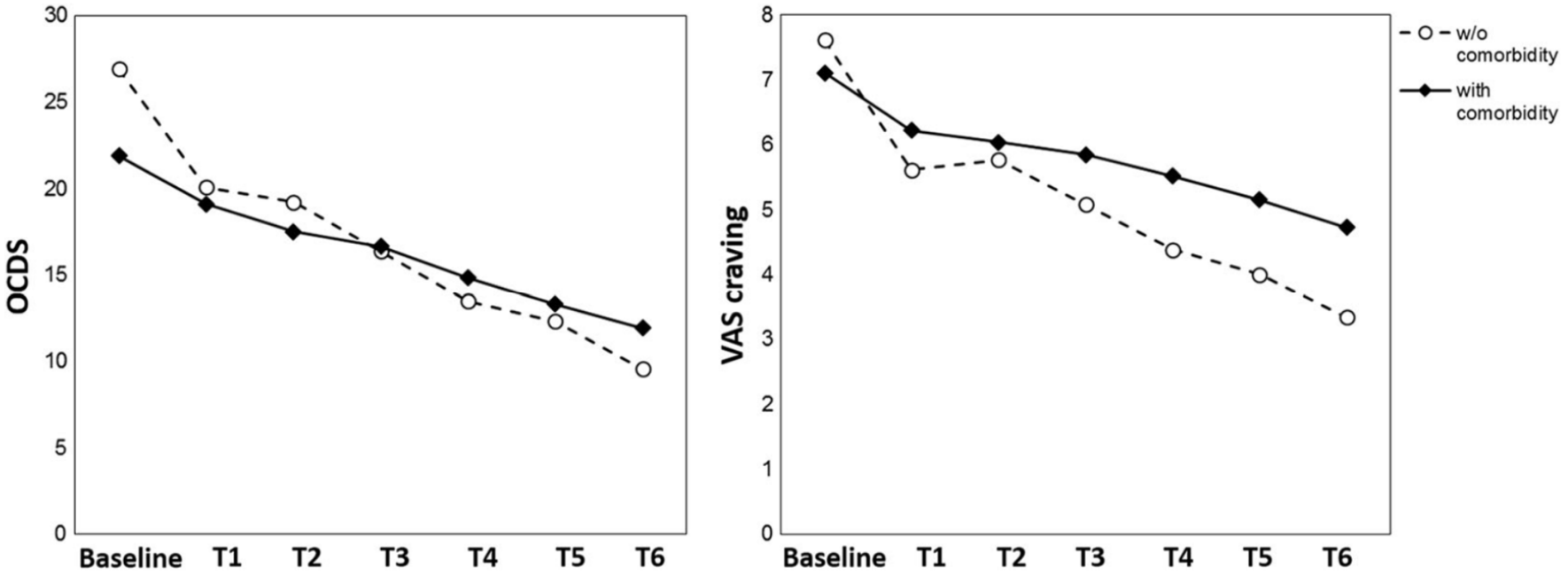
Pettinati HM, et al. Current status of co-occurring mood and substance use disorders: a new therapeutic target. *Am J Psychiatry*. 2013

Nalmefene reduced TAC and HDDs in AUD subjects with psychiatric comorbidity



Di Nicola M, et al. Nalmefene in Alcohol Use Disorder Subjects with Psychiatric Comorbidity: A Naturalistic Study. *Adv Ther*. 2017

Nalmefene reduced alcohol craving in AUD subjects with psychiatric comorbidity

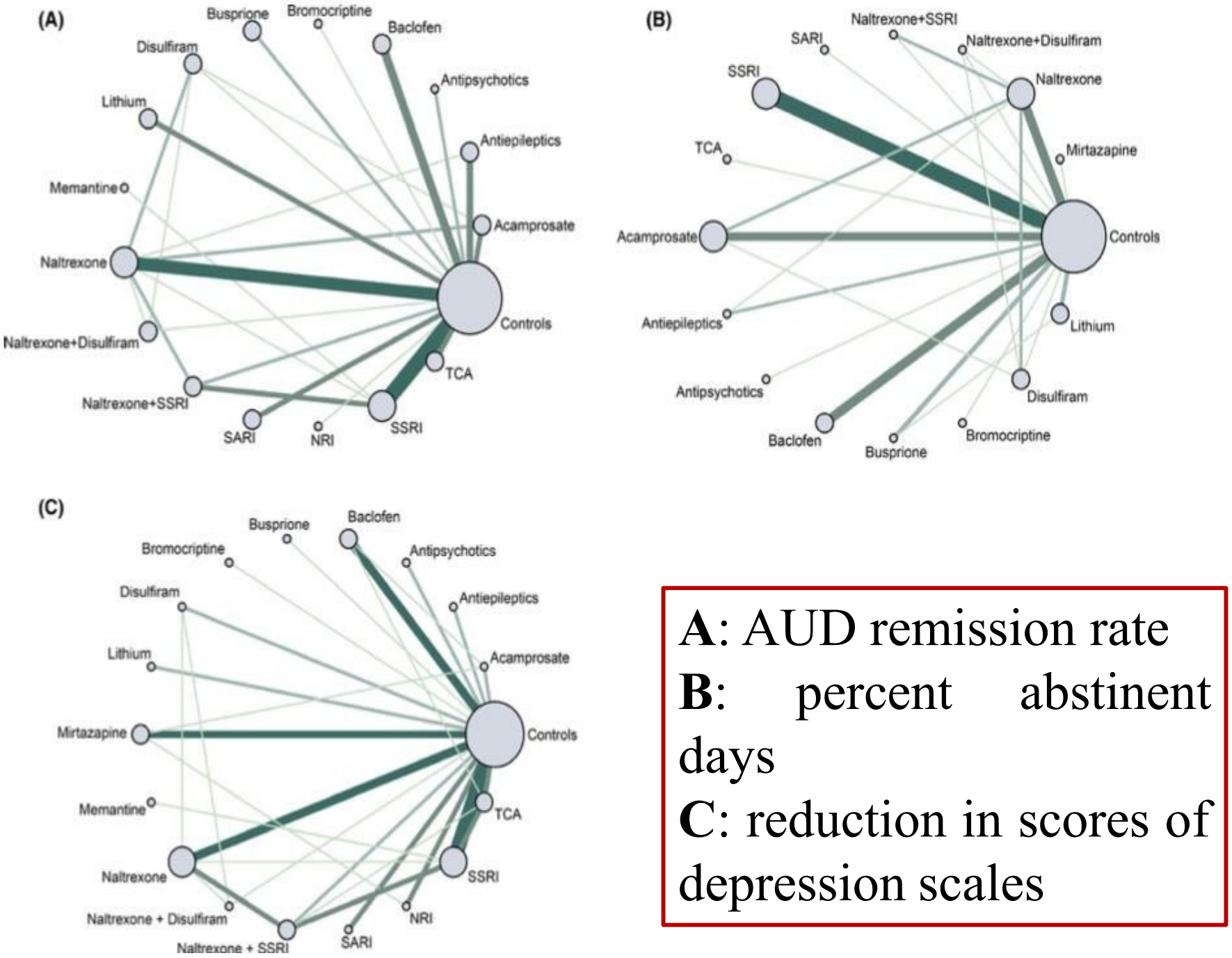


Di Nicola M, et al. Nalmefene in Alcohol Use Disorder Subjects with Psychiatric Comorbidity: A Naturalistic Study. *Adv Ther*. 2017

Antidepressants for subjects with co-occurring depression and alcohol-dependence

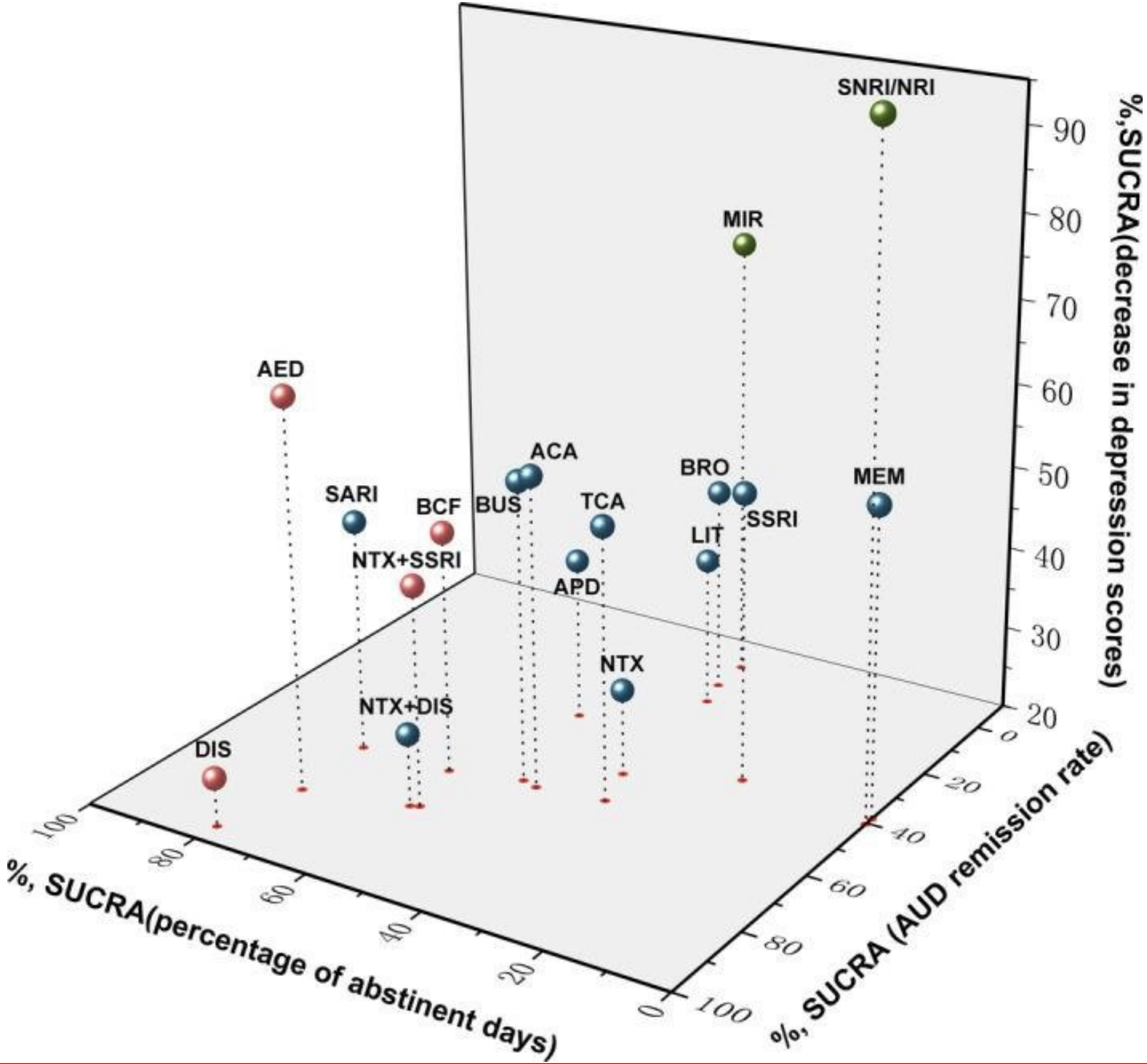
- 33 studies (2242 participants; 68% males; mean age: 42 years)
- Treatment mean duration: 10 weeks (3 to 26 weeks)
- Moderate-quality evidence found that ADs increased the number of participants abstinent from alcohol during the trial and reduced the number of drinks per drinking days compared to placebo
- Minimal risk of developing adverse effects

Agabio R, et al. Antidepressants for the treatment of people with co-occurring depression and alcohol dependence. *Cochrane Database Syst Rev*. 2018.



A: AUD remission rate
B: percent abstinent days
C: reduction in scores of depression scales

Li J, et al. Efficacy of pharmacotherapeutics for patients comorbid with alcohol use disorders and depressive symptoms-A bayesian network meta-analysis. *CNS Neurosci Ther*. 2020



Li J, et al. Efficacy of pharmacotherapeutics for patients comorbid with alcohol use disorders and depressive symptoms-A bayesian network meta-analysis. *CNS Neurosci Ther*. 2020

Emerging evidence for treatment of co-occurring MDD and SUDs

64 RCTs, N=6128 participants

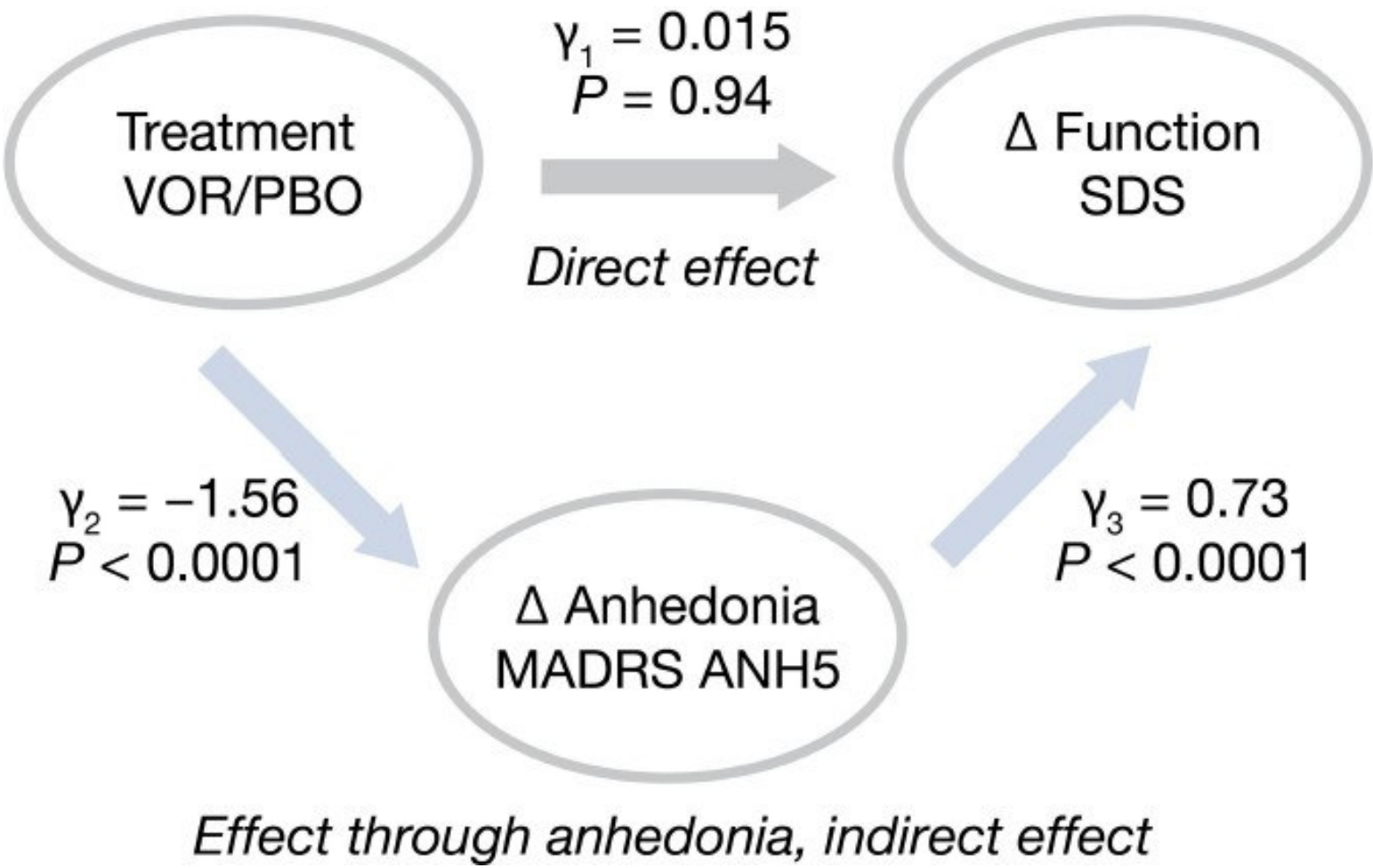
SSRIs:

- reduced depressive symptoms in opioid, alcohol, cocaine, cannabis, and nicotine use disorders;
- facilitated abstinence for opioid, alcohol, cocaine, cannabis, and nicotine use;
- reduced craving for alcohol, cocaine, and nicotine use;
- reduced alcohol use and cocaine use.

Fluoxetine showed the **highest antidepressant** effect.

Fluyau D, Mitra P, Jain A, Kailasam VK, Pierre CG. Selective serotonin reuptake inhibitors in the treatment of depression, anxiety, and post-traumatic stress disorder in substance use disorders: a Bayesian meta-analysis. Eur J Clin Pharmacol. 2022 Jun;78(6):931-942.

Efficacy of Vortioxetine on Anhedonia in patients with MDD



McIntyre RS et al. Efficacy of Vortioxetine on Anhedonia: Results from a Pooled Analysis of Short-Term Studies in Patients with Major Depressive Disorder. *Neuropsychiatric Disease and Treatment* 2021:17.

Effectiveness of Vortioxetine on Emotional Blunting in Patients with MDD

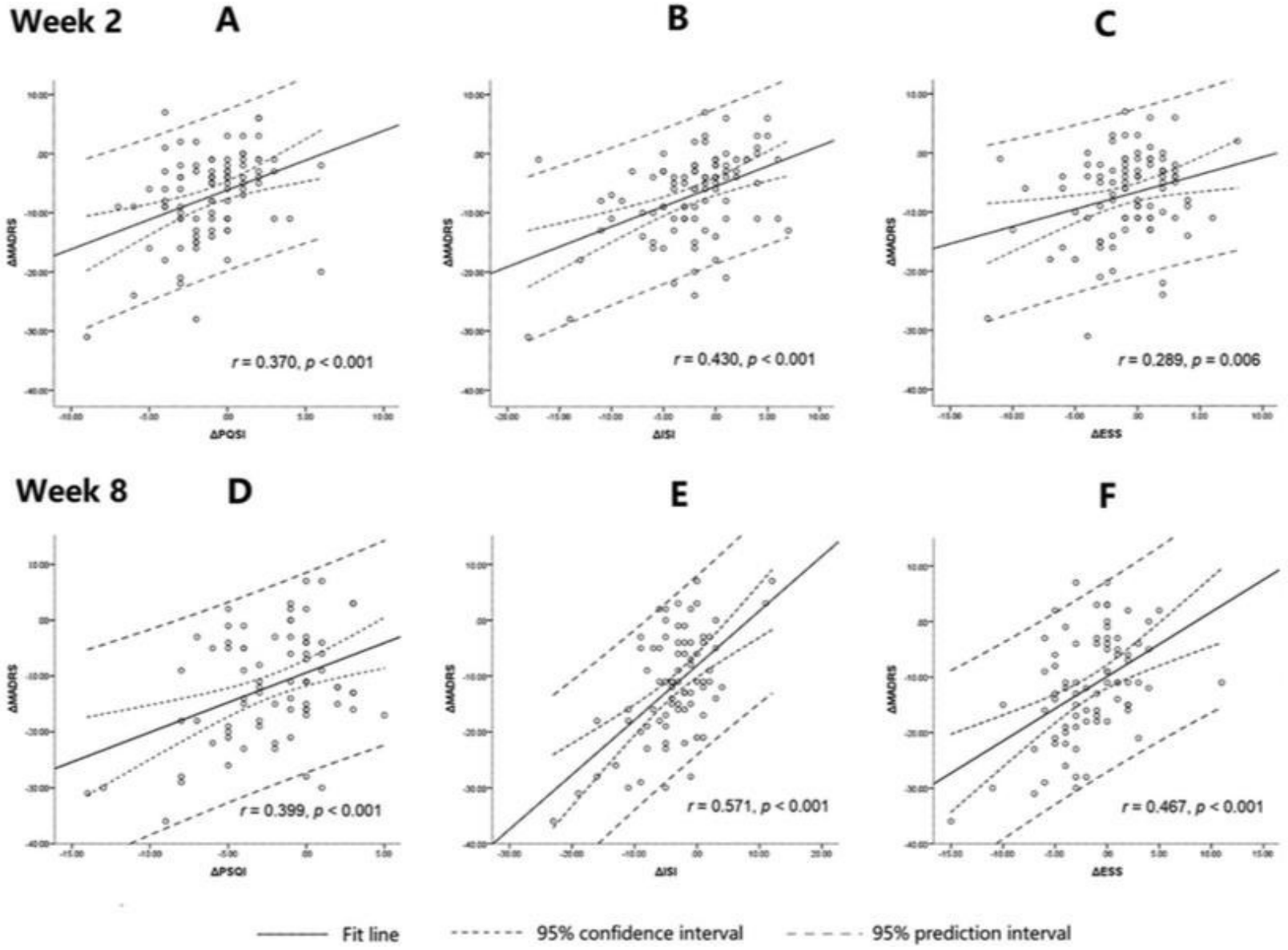
Effect of vortioxetine on emotional blunting, motivation/energy, cognitive performance, depressive symptoms, and overall functioning (FAS, MMRM).

	Mean change from baseline (SE)		
	Week 1	Week 4	Week 8
ODQ total score	-9.6 (1.6)	-21.2 (1.8)	-29.8 (1.9)
MADRS total score	-3.3 (0.5)	-9.2 (0.6)	-13.8 (0.7)
MADRS anhedonia factor score	-2.2 (0.3)	-5.9 (0.4)	-8.9 (0.4)
CGI-S	-0.3 (0.1)	-1.1 (0.1)	-1.8 (0.1)
CGI-I[a]	3.4 (0.1)	2.6 (0.1)	2.0 (0.1)
MEI total score	-	23.5 (2.4)	34.3 (2.8)
Mental or cognitive energy	-	11.0 (1.1)	15.0 (1.2)
Social motivation	-	5.8 (0.8)	9.6 (0.9)
Physical energy	-	7.2 (0.8)	10.3 (0.9)
SDS total score	-	-	-7.7 (0.9)
Work/school	-	-	-3.2 (0.4)
Social life	-	-	-2.4 (0.3)
Family/home	-	-	-2.5 (0.3)
DSST	4.3 (0.9)	-	7.8 (0.9)

$p<0.0001$ for all changes vs baseline.

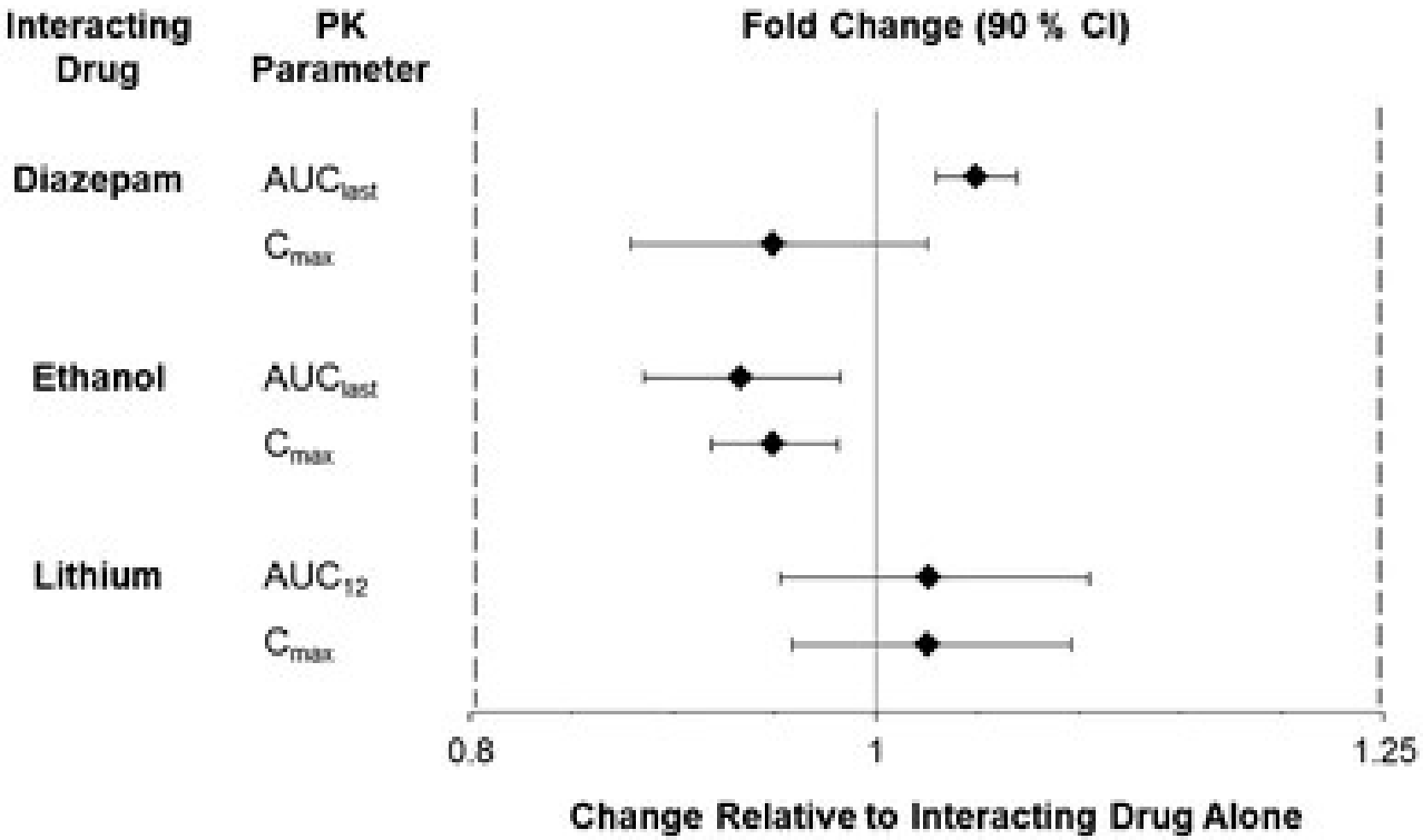
Fagiolini et al. Effectiveness of Vortioxetine on Emotional Blunting in Patients with Major Depressive Disorder with inadequate response to SSRI/SNRI treatment. *Journal of Affective Disorders.* 2021

Vortioxetine for insomnia and depressive symptoms: a bi-directional relationship



Cao B, et al. Changes in sleep predict changes in depressive symptoms in depressed subjects receiving vortioxetine: An open-label clinical trial. *J Psychopharmacol*. 2019

Effect of Vortioxetine on pharmacokinetics and pharmacodynamics of ethanol



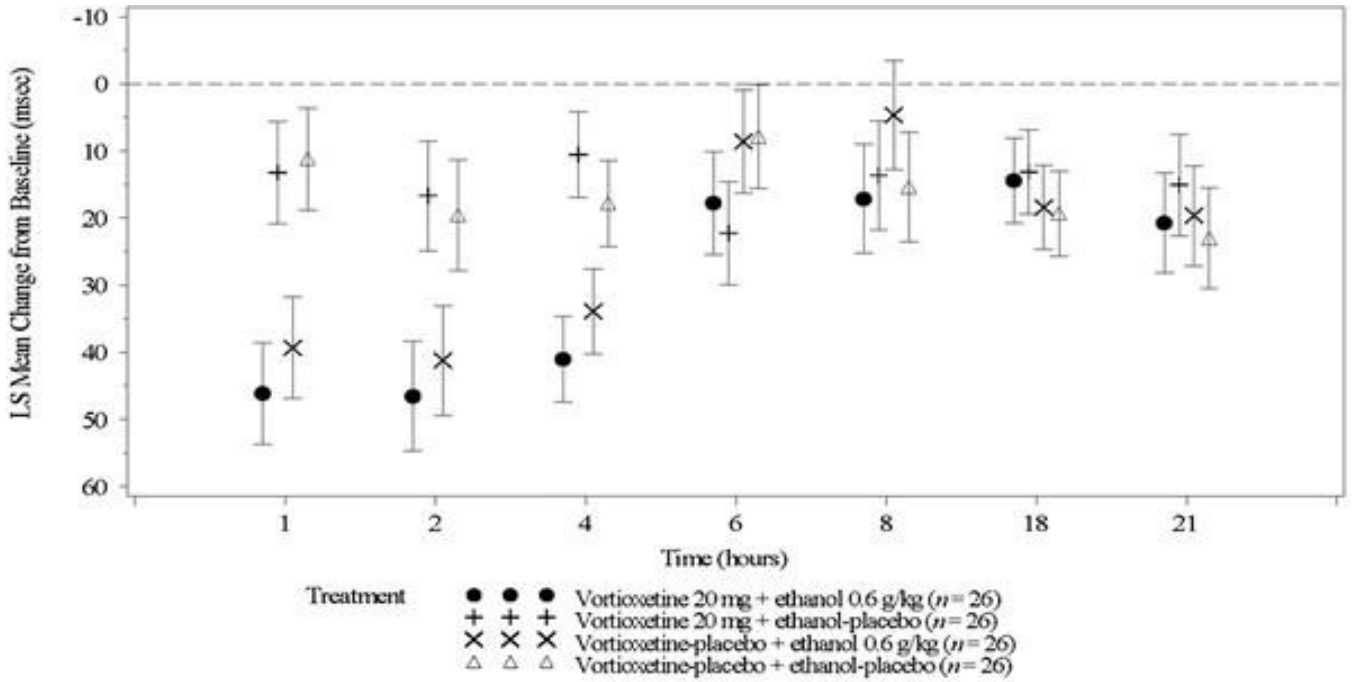
Chen G, et al. Lack of Effect of Vortioxetine on the Pharmacokinetics and Pharmacodynamics of Ethanol, Diazepam, and Lithium. *Clin Pharmacokinet*. 2016

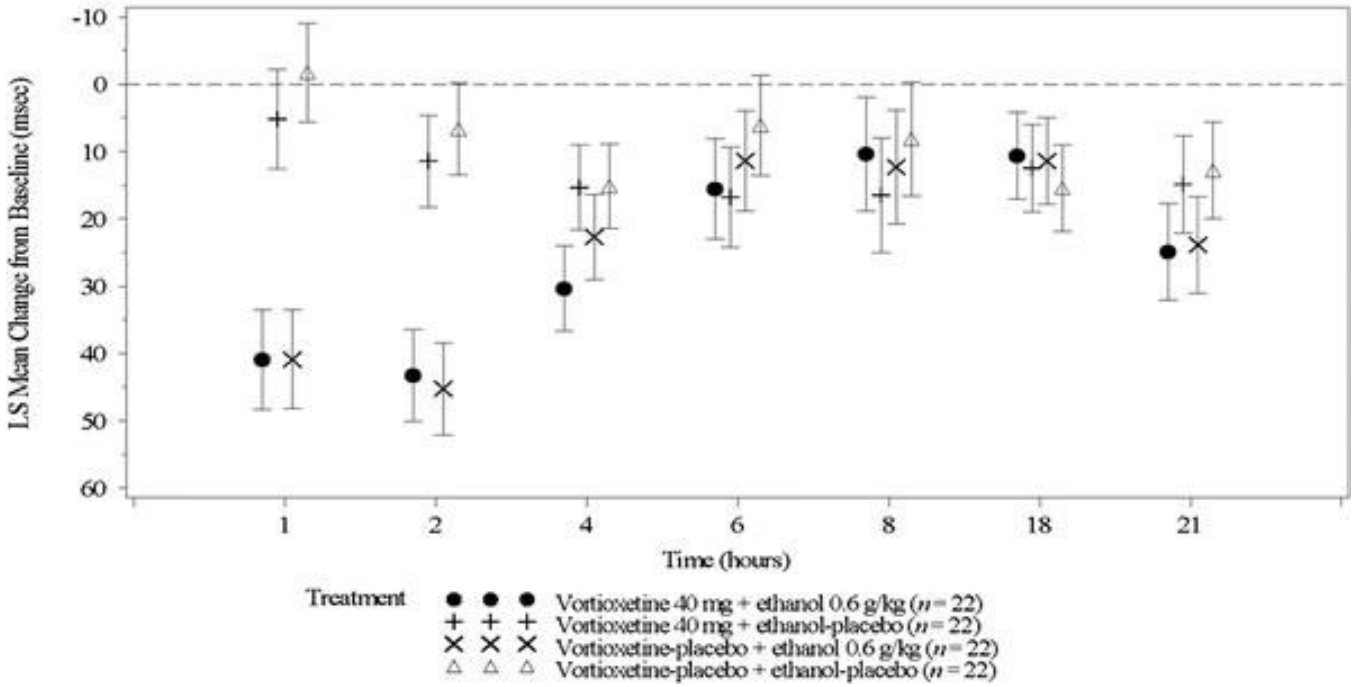
Effects of ethanol on the pharmacokinetics of Vortioxetine

	LS mean		Ratio of LS means [test/reference] (%)	90 % CI for ratio of LS means (%)
	Reference	Test		
Group 1	**Vortioxetine 20 mg + placebo (*n* = 36)**	**Vortioxetine 20 mg + ethanol (*n* = 38)**		
AUC_{last} (ng·h/mL)	476.96	474.66	99.52	94.96–104.30
C_{max} (ng/mL)	8.97	9.26	103.23	97.38–109.43
t_{max} (h)[a]	7.0	7.0		

Group 2	**Vortioxetine 40 mg + placebo (*n* = 30)**	**Vortioxetine 40 mg + ethanol (*n* = 30)**		
AUC_{last} (ng·h/mL)	880.77	939.17	106.63	103.09–110.29
C_{max} (ng/mL)	16.44	17.79	108.25	103.57–113.14
t_{max} (h)[a]	7.0	7.0		

Chen G, et al. Lack of Effect of Vortioxetine on the Pharmacokinetics and Pharmacodynamics of Ethanol, Diazepam, and Lithium. *Clin Pharmacokinet*. 2016





Vortioxetine

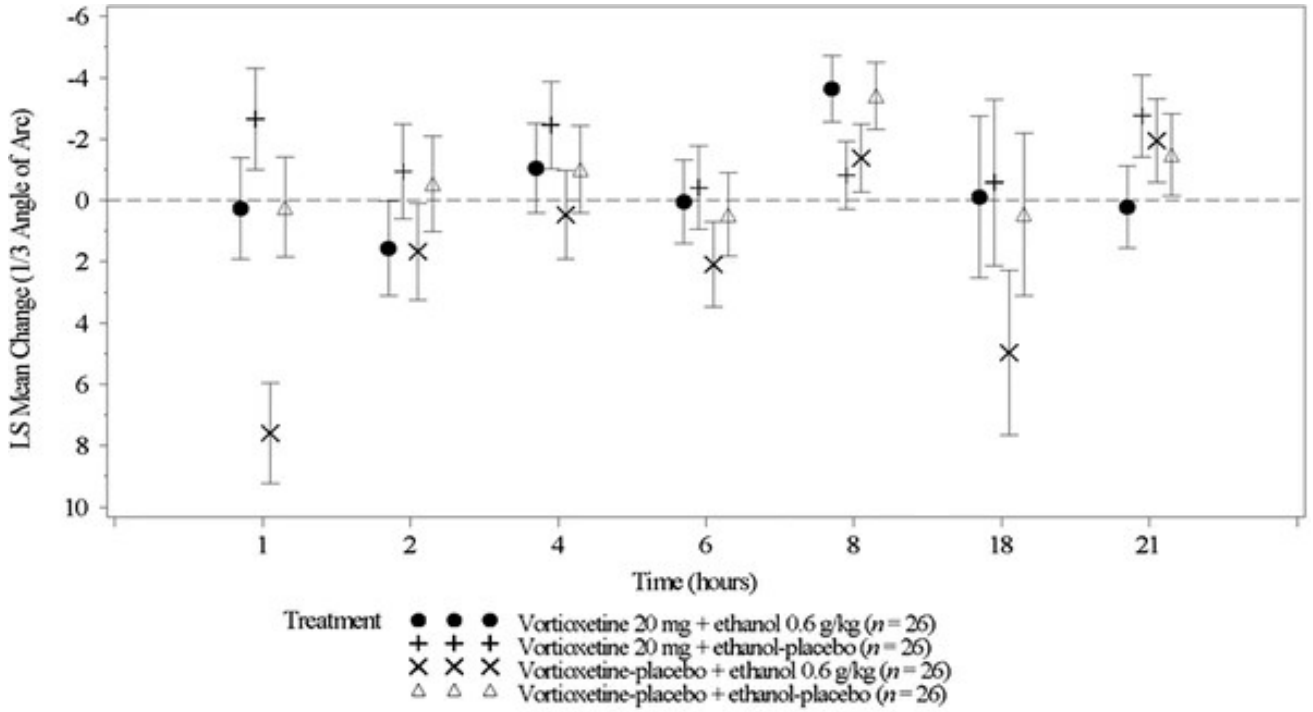
+

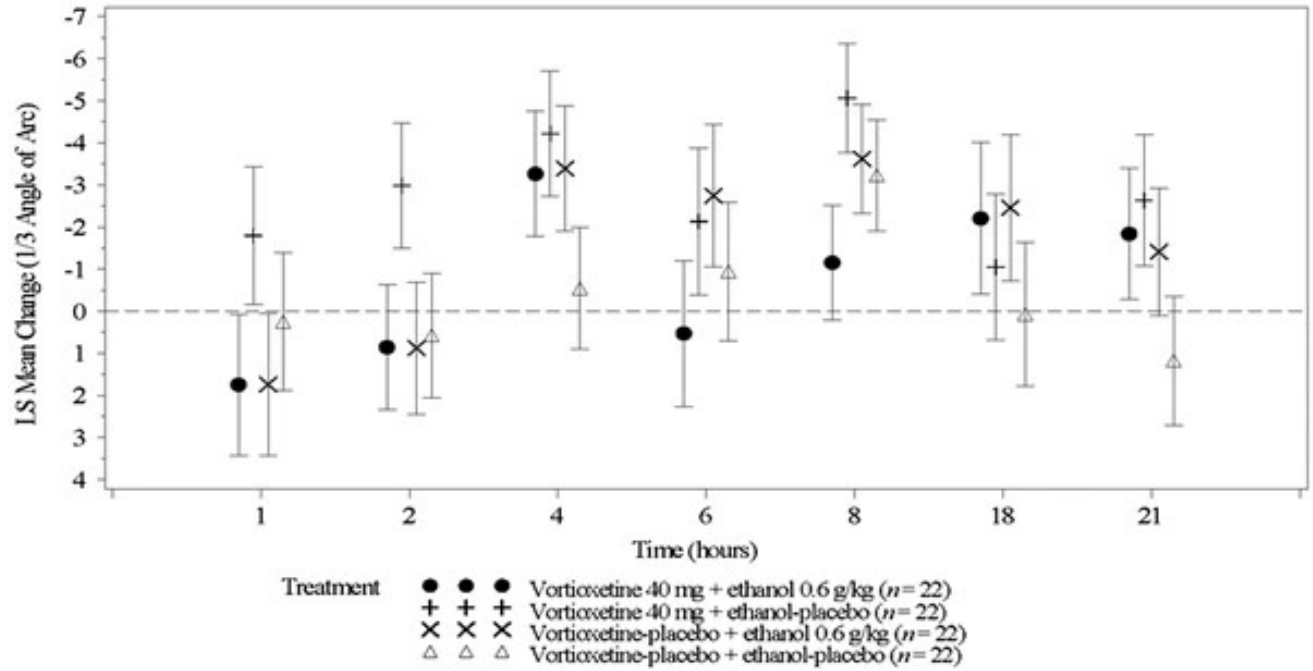
Ethanol

↓

Digit vigilance speed

Chen G, et al. Lack of Effect of Vortioxetine on the Pharmacokinetics and Pharmacodynamics of Ethanol, Diazepam, and Lithium. *Clin Pharmacokinet*. 2016





Vortioxetine

+

Ethanol

↓

Postural stability

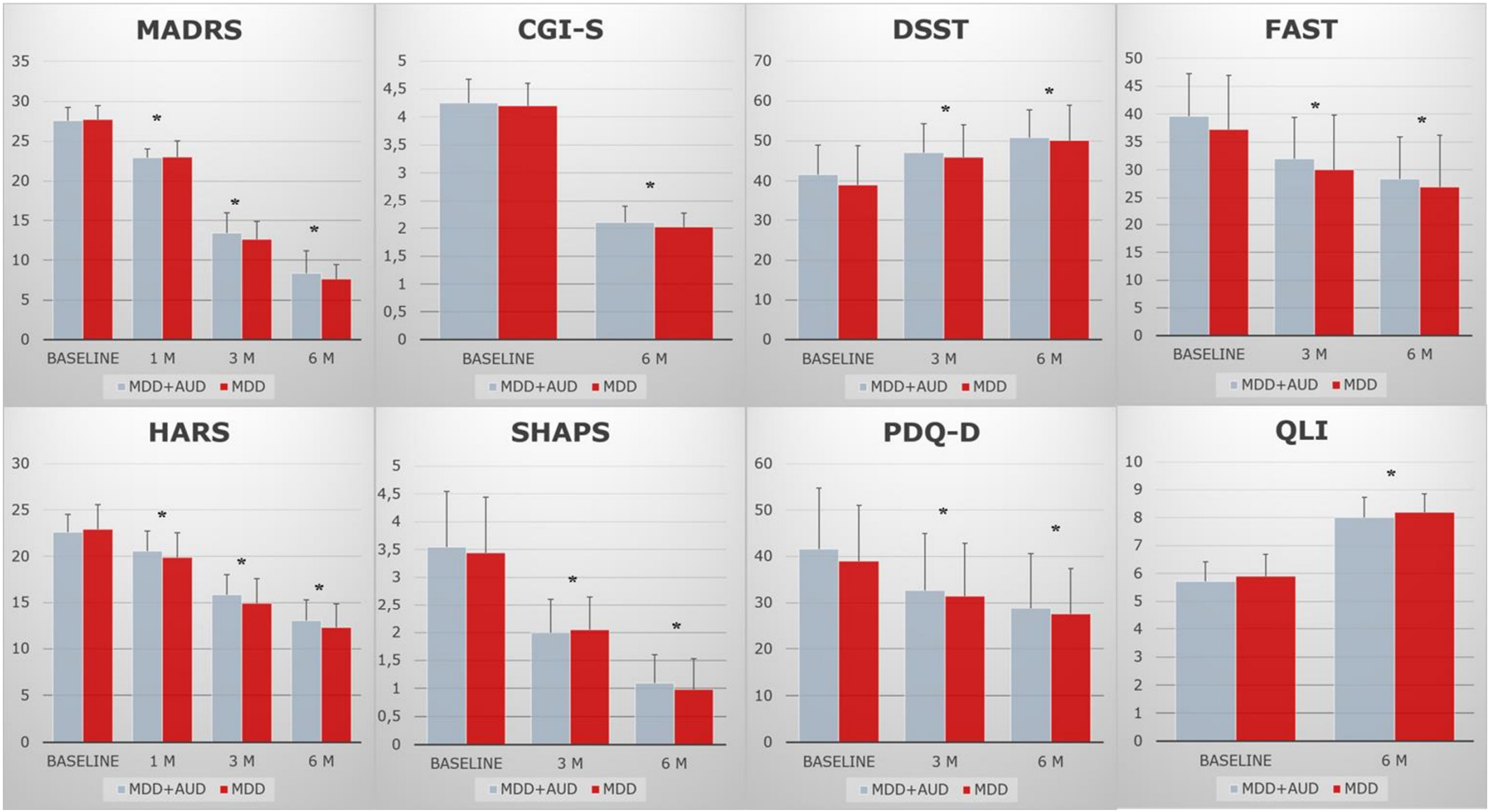
Chen G, et al. Lack of Effect of Vortioxetine on the Pharmacokinetics and Pharmacodynamics of Ethanol, Diazepam, and Lithium. *Clin Pharmacokinet*. 2016

Effect of Vortioxetine in MDD+AUD patients

- 57 MDD+AUD and 56 MDD outpatients matched for age, gender, and educational level were retrospectively evaluated.
- Eligibility: MADRS ≥26; Abstinence from alcohol ≥4 weeks.
- Timepoints: 1, 3, and 6 months.
- Vortioxetine 10-20 mg/day (mean dosage: MDD+AUD: 10.88±3.25 mg/day; MDD: 9.91±2.7 mg/day; p=.09) associated with psychosocial support.
- Measurements:
  - Depression: MADRS
  - Anxiety: HARS
  - Clinical severity: CGI-S
  - Anhedonia: SHAPS
  - Cognition: DSST, PDQ-D
  - Functioning: FAST
  - Quality of life: QLI

Di Nicola M, et al. Effect of vortioxetine in subjects with major depressive and alcohol use disorders: a 6-month retrospective analysis. *CNS Spectr*. 2020

Effect of Vortioxetine in MDD+AUD patients



* p<.001 *vs.* baseline; no differences between groups

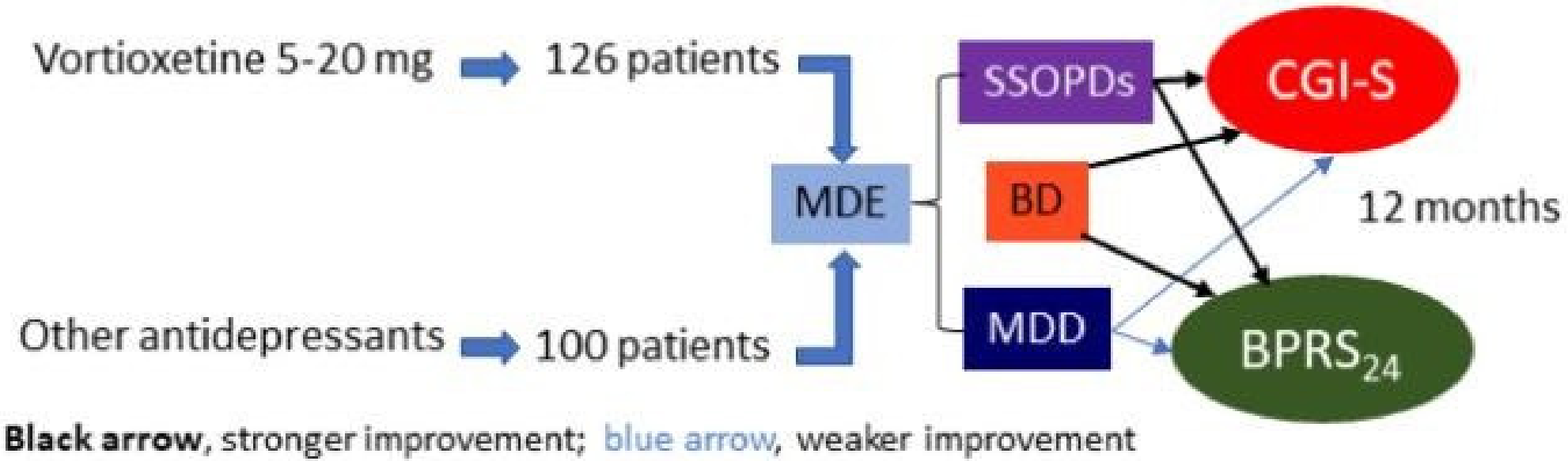
Di Nicola M, et al. Effect of vortioxetine in subjects with major depressive and alcohol use disorders: a 6-month retrospective analysis. *CNS Spectr*. 2020

Effect of Vortioxetine in MDD+AUD patients

- Two patients for each group (n=4; 3.5%) reported newly emergent adverse events; of these, only one MDD+AUD patient (0.9%) needed to discontinue VOR treatment as a result of tolerability concerns (persisting nausea with vomiting and dizziness).
- The overall drop-out rate was 26.3% (n=15, of which 6 for relapse to heavy drinking) in the MDD+AUD group and 17.9% (n=10) in the MDD group. All dropouts occurred after the third month of treatment.
- Besides, MDD+AUD patients displayed significant reductions of liver function tests at 6 months.
- In the MDD group, no changes pre- and post-treatment were observed in AST, ALT and GGT levels.

Di Nicola M, et al. Effect of vortioxetine in subjects with major depressive and alcohol use disorders: a 6-month retrospective analysis. *CNS Spectr*. 2020

Vortioxetine vs. other antidepressants for dual diagnosis treatment



Kotzalidis GD, et al. Vortioxetine vs. Other Antidepressants in Patients with Major Depressive Episode With or Without Substance Use Disorder. *Curr Neuropharmacol*. 2021.

Update on pharmacological treatment for comorbid MDD and AUD: the role of extended-release trazodone

100 MDD+AUD outpatients (2017-2019), treated with Trazodone 150-300 mg/day and psychosocial support, were retrospectively evaluated.

Inclusion criteria:

MDD diagnosis (DSM-5)

Baseline MADRS≥26 (moderate to severe depression)

Current depressive episode ≥3 months

Abstinence from alcohol ≥ 4 weeks

Di Nicola M, Pepe M, Panaccione I, Moccia L, Janiri L, Sani G. Curr Neuropharmacol. 2023;21(11):2195-2205.

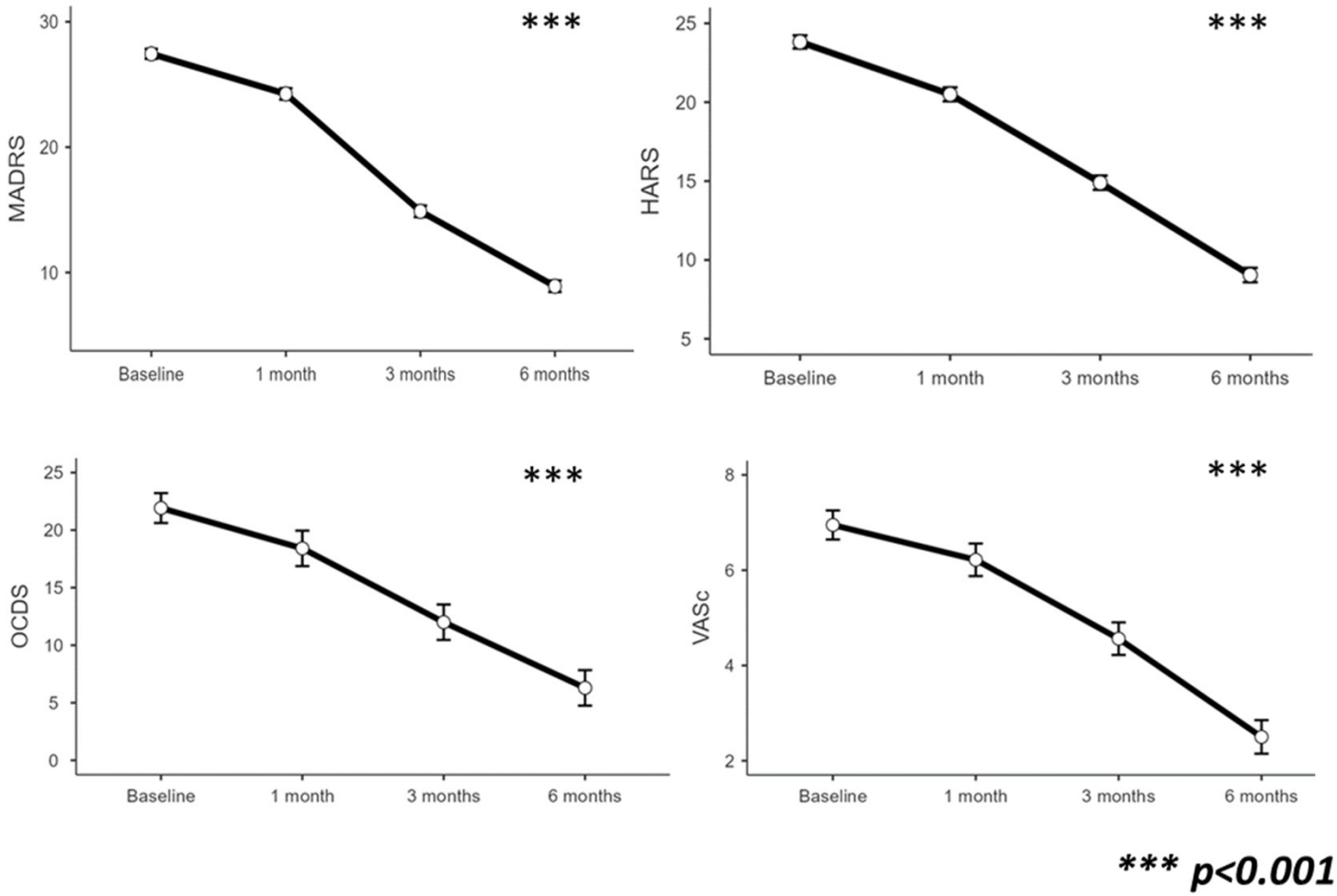
Results

Age (range: 18-65 years)	47.4 ± 12.5
Gender	
Male	57 (57)
Female	43 (43)
Anthropometric measurements	
Height (m)	1.7 ± .08
Weight (Kg)	69 ± 14
BMI (Kg/m^2)	23.6 ± 3.6
Education (years)	13.9 ± 3.7
Marital status	
Unmarried	52 (52)
Married	22 (22)
Separated/Divorced	25 (25)
Widow/er	1 (1)
Employment status	
Unemployed	35 (35)
Employed	65 (65)

Clinical history	
Age at MDD onset (years)	34.6 ± 13
Duration of illness (years)	12.7 ± 8.7
Number of lifetime episodes	3.1 ± 1.8
Duration of current episode (months)	3.7 ± .6
Family history of mental disorders	61 (61%)
Hospitalizations	.8± 1.5
Suicide attempts	10 (10)
Psychiatric comorbidity	23 (23)
Somatic comorbidity	28 (28)
Lifetime multiple substance use	48 (48)
Cocaine	13 (27.1)
Cannabis	19 (39.6)
BDZs	15 (31.2)
Opioids	1 (2.1)
Smoking	70 (70)
Dosage of Trazodone (mg/day)	192±67.8
Patients taking additional medications	66 (66)
Mood stabilizers/anticonvulsants	45(45)
Atypical Antipsychotics	7(7)
Benzodiazepines	3(2)
Anti-craving drugs	11(11)

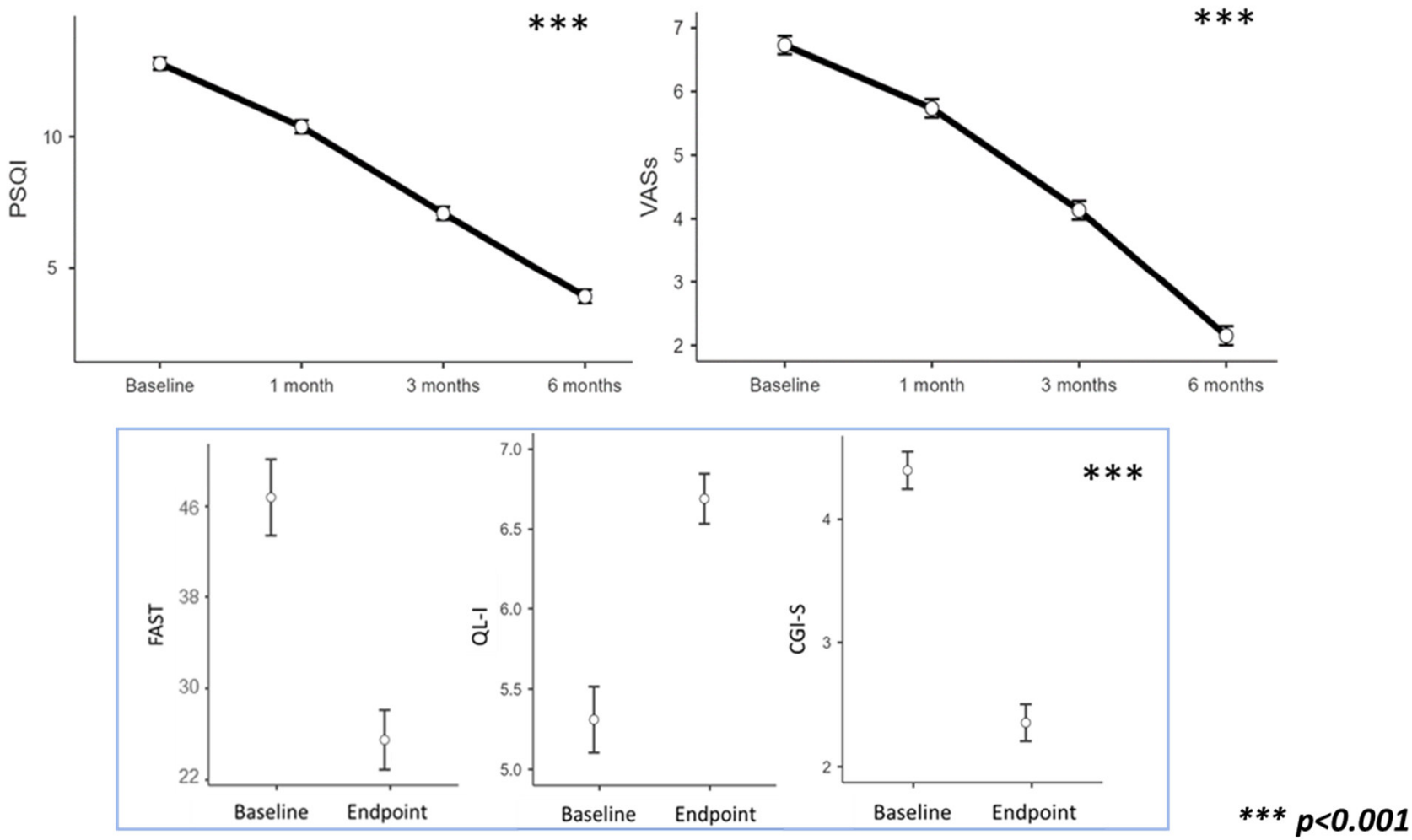
Di Nicola M, Pepe M, Panaccione I, Moccia L, Janiri L, Sani G. Curr Neuropharmacol. 2023;21(11):2195-2205.

Results: depression, anxiety and craving



Di Nicola M, Pepe M, Panaccione I, Moccia L, Janiri L, Sani G. Curr Neuropharmacol. 2023;21(11):2195-2205.

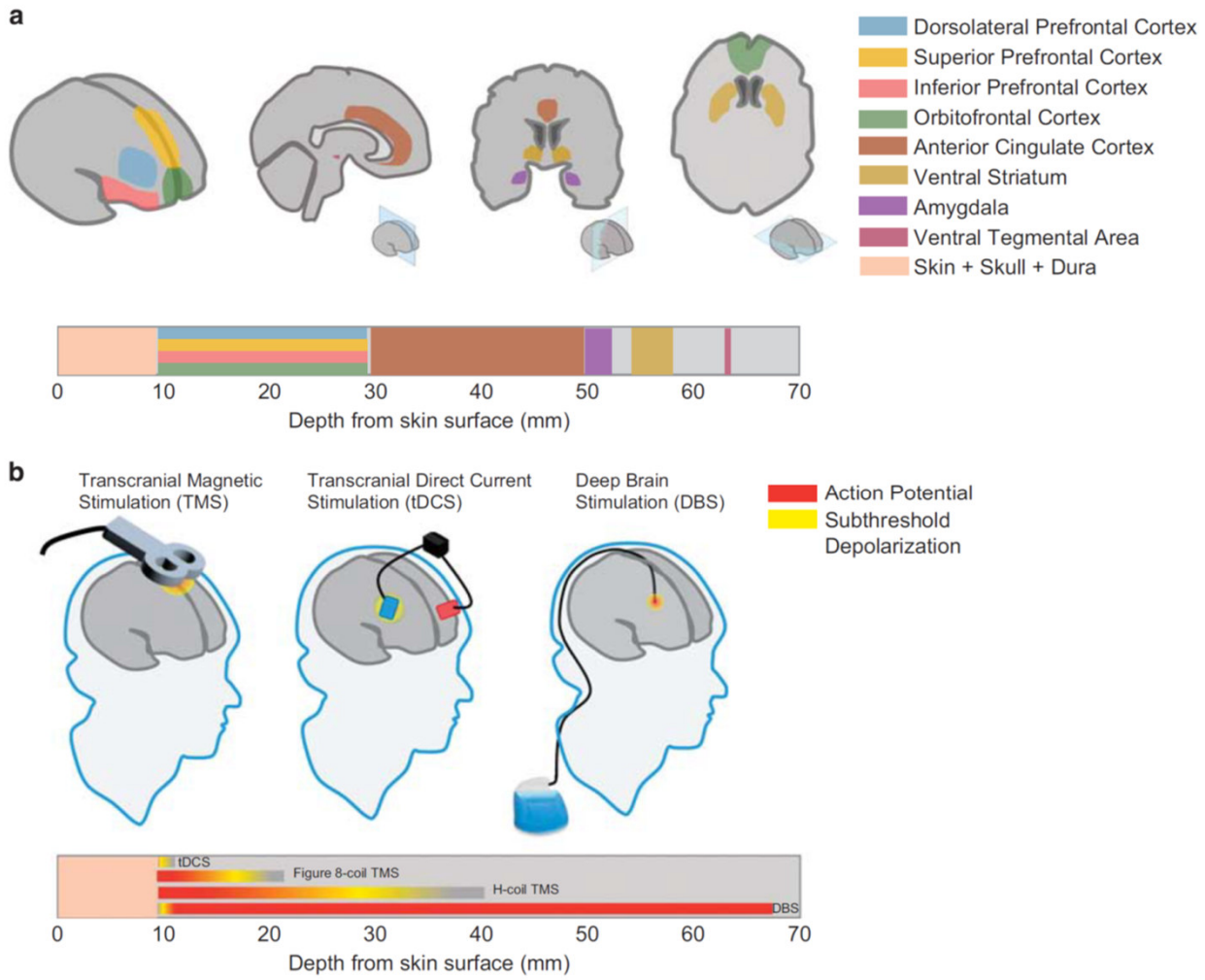
Results: sleep, functioning and quality of life



*** p<0.001

Di Nicola M, Pepe M, Panaccione I, Moccia L, Janiri L, Sani G. Curr Neuropharmacol. 2023;21(11):2195-2205.

Brain stimulation in subjects with MDD and SUD



Salling MC, Martinez D. Brain Stimulation in Addiction. *Neuropsychopharmacology*. 2016

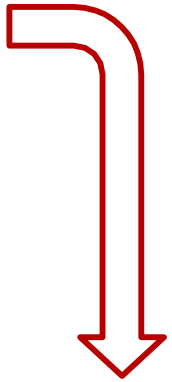
Kedzior KK, et al. Can deep transcranial magnetic stimulation (DTMS) be used to treat substance use disorders (SUD)? A systematic review. *BMC Psychiatry*. 2018

Beneficial effects of mood enhancement in preventing relapses

Specific **predictive factors** of future relapse at follow-up:

individual (age);
environmental
- employment status,
- family/marital status;

pathological
- craving,
- number of glasses consumed,
- psychiatric comorbidity, particularly **depression.**



Bio-psycho-social approach and better adapted and integrated care.

Pareaud M, et al. Factors for Maintaining Abstinence at 2 and 6 Months After Alcohol Withdrawal. J *Psychiatr Pract*. 2021

Personalization of management

The **management** of depression is becoming increasingly complex and can be **personalized** in several respects, beyond the choice of a given antidepressant medication or psychotherapy.

No biological marker is as yet ready for use in routine clinical practice, that's why a **more precise clinical characterization** of depressed patients, beyond the syndromal diagnosis, may support the development of those markers, as well as the identification of more homogeneous subtypes of depression.

Maj et al., The clinical characterization of the adult patient with depression aimed at personalization of management. *World Psychiatry*, 2020

GRAZIE PER L'ATTENZIONE!

Gemelli

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

CePID
Centro Psichiatrico Integrato di ricerca, prevenzione e cura delle Dipendenze

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