A Case Against Purity

What Can We Learn at the Intersection of Mental Health and Substance Use Disorders

Eden Evins, MD
Cox Family Professor of Psychiatry,
Harvard Medical School
Founding Director,
Mass General Hospital
Center for Addiction Medicine

LIFETIME PREVALENCE OF CO-OCCURRING DISORDERS MORE COMMON THAN NOT

Specific comorbidities in MDD:

- 36% develop TUD
- 20-30% develop AUD
- 15-20% CUD
- 10-15% cocaine use disorder
- 10-15% amphetamine use disorder
- 5-10% OUD

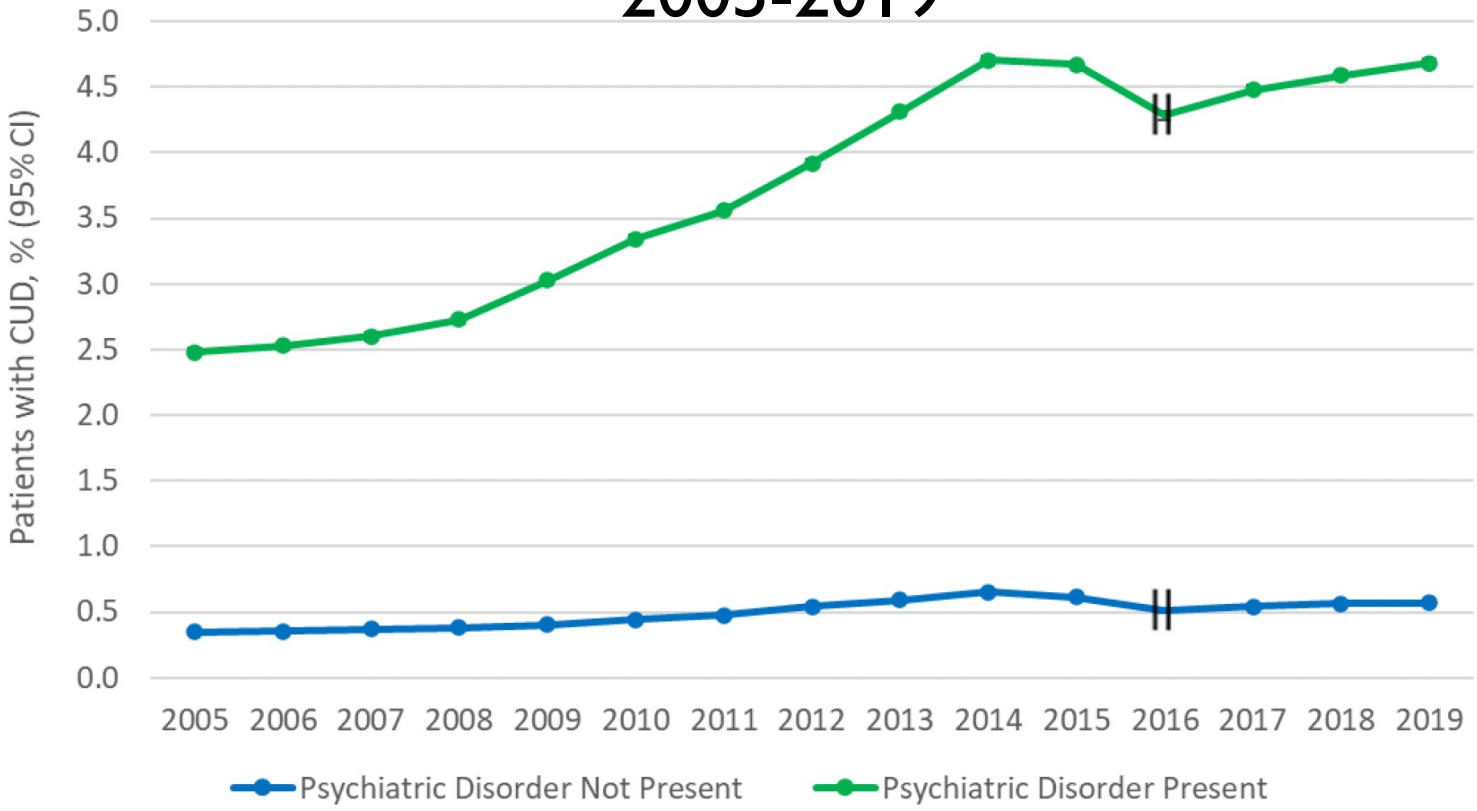
In schizophrenia:

- 50-90% develop TUD
- 24-50% develop AUD
- 27-50% CUD
- 6-24% cocaine use disorder
- 8-32% amphetamine use disorder
- 4-11% OUD

Schiz Bull, others

Should a SUD literally be part of the syndrome?

Trends of Prevalence of CUD by Psychiatric Disorders in VA Patients, 2005-2019

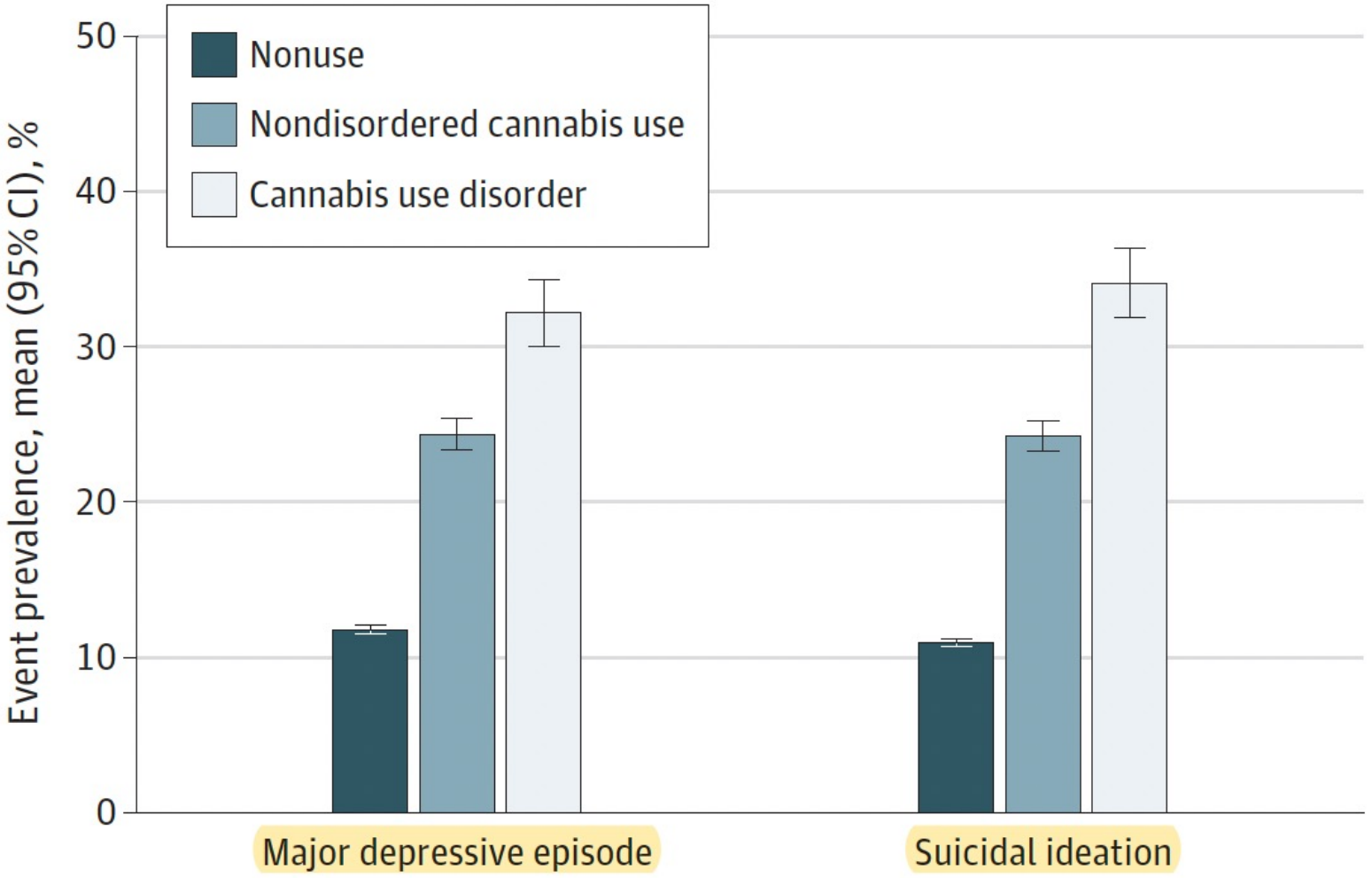


[a] Dichotomous psychiatric summary variable indicating if patients were positive for any disorder from ≥1 of the 5 categories (depressive disorders, anxiety disorders, PTSD, bipolar disorders, psychotic-spectrum disorders) each year, 2005-2014 and 2016-2019.

Hash marks at 2015 indicate that this year was not included in models due to a change in ICD coding.

Livne, et al., *medRxiv*. 2023

Adverse Psychosocial Events in Adolescents with No Use, Nondisordered Cannabis Use and CUD

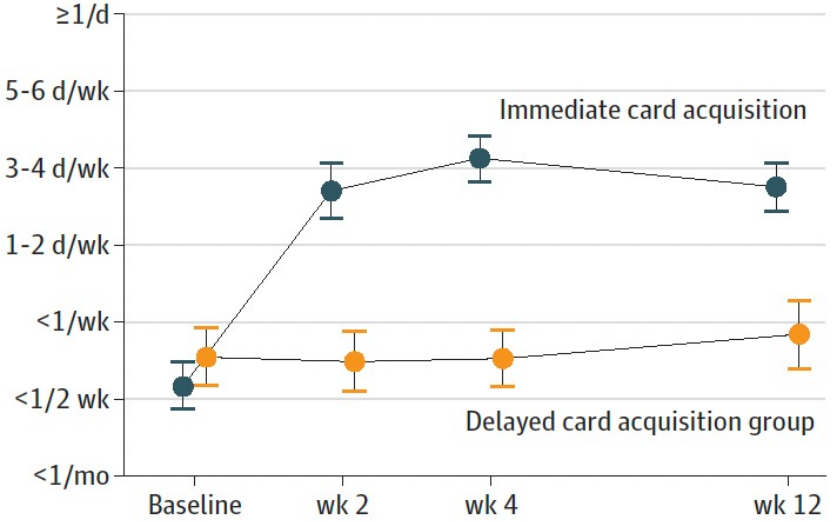


NSDUH 2015 - 2019

Sultan, et al., *JAMA Network Open* 2023

Incidence of Cannabis Use Disorder (CUD) Greater in Those Trying Cannabis to Treat Anxiety and/or Depression vs Pain or Insomnia

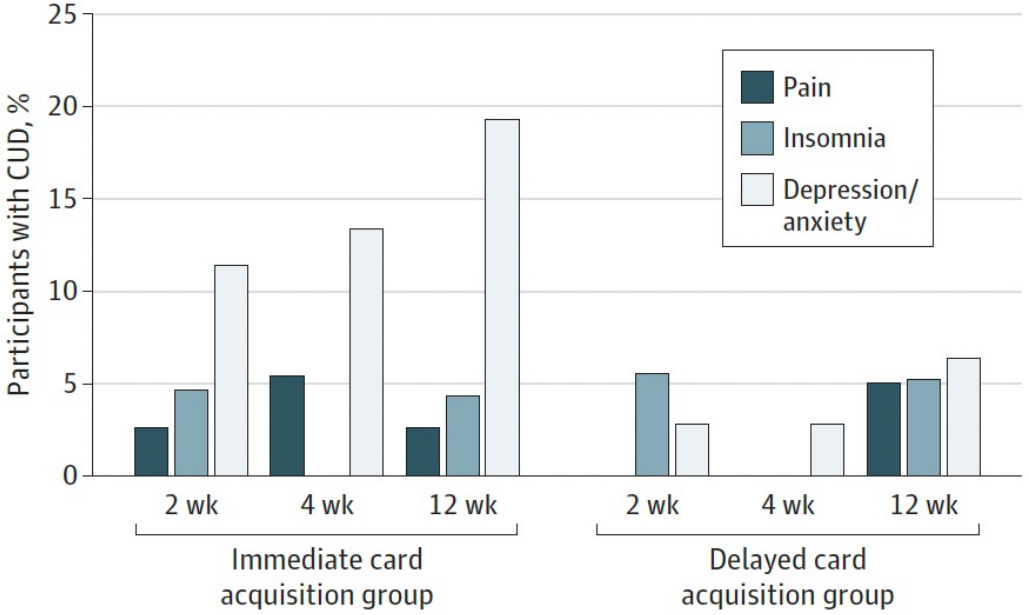
A Frequency of cannabis use in immediate card acquisition group vs delayed card acquisition group



No. at risk

	Baseline	wk 2	wk 4	wk 12
Immediate card acquisition group	105	101	102	100
Delayed card acquisition group	81	80	78	74

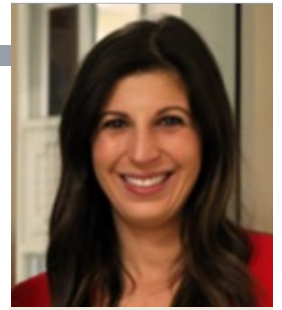
B Incidence of CUD by randomization group and primary complaint

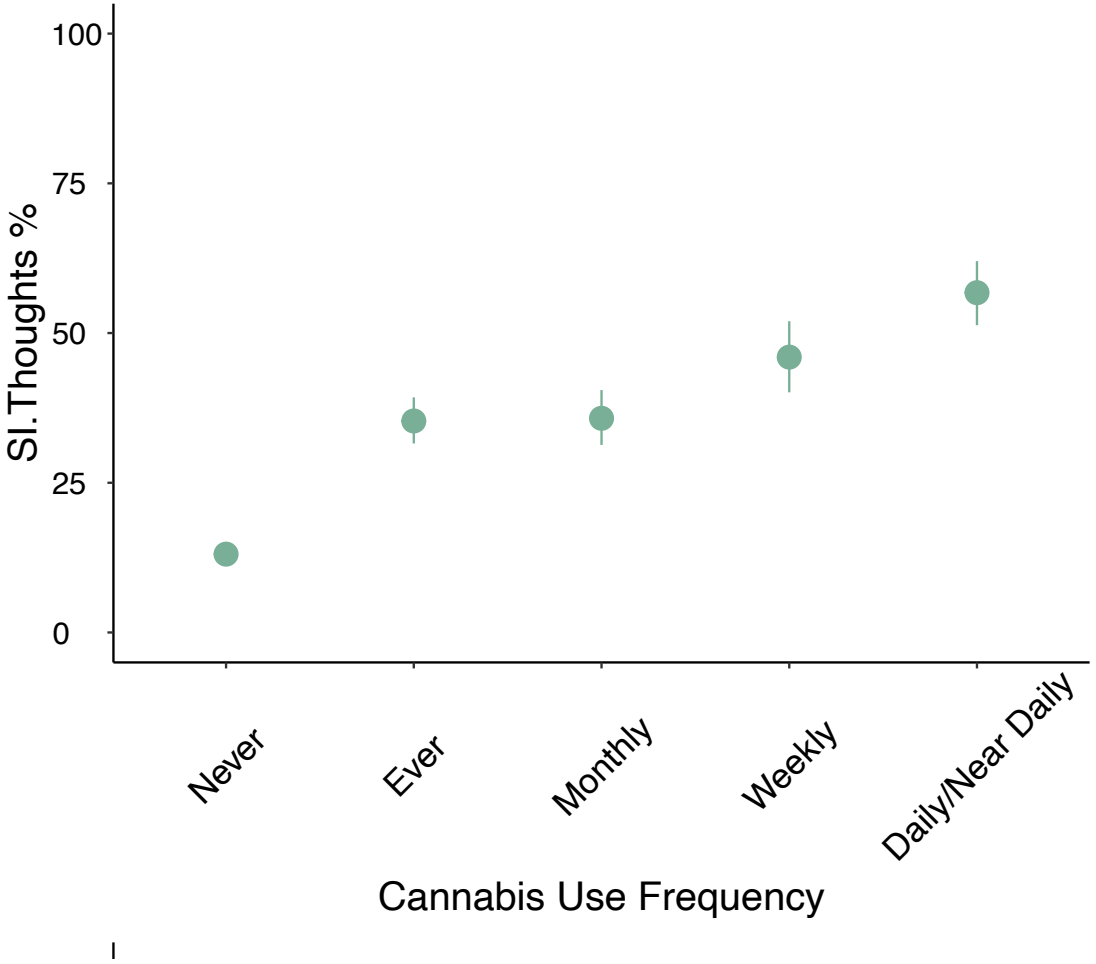


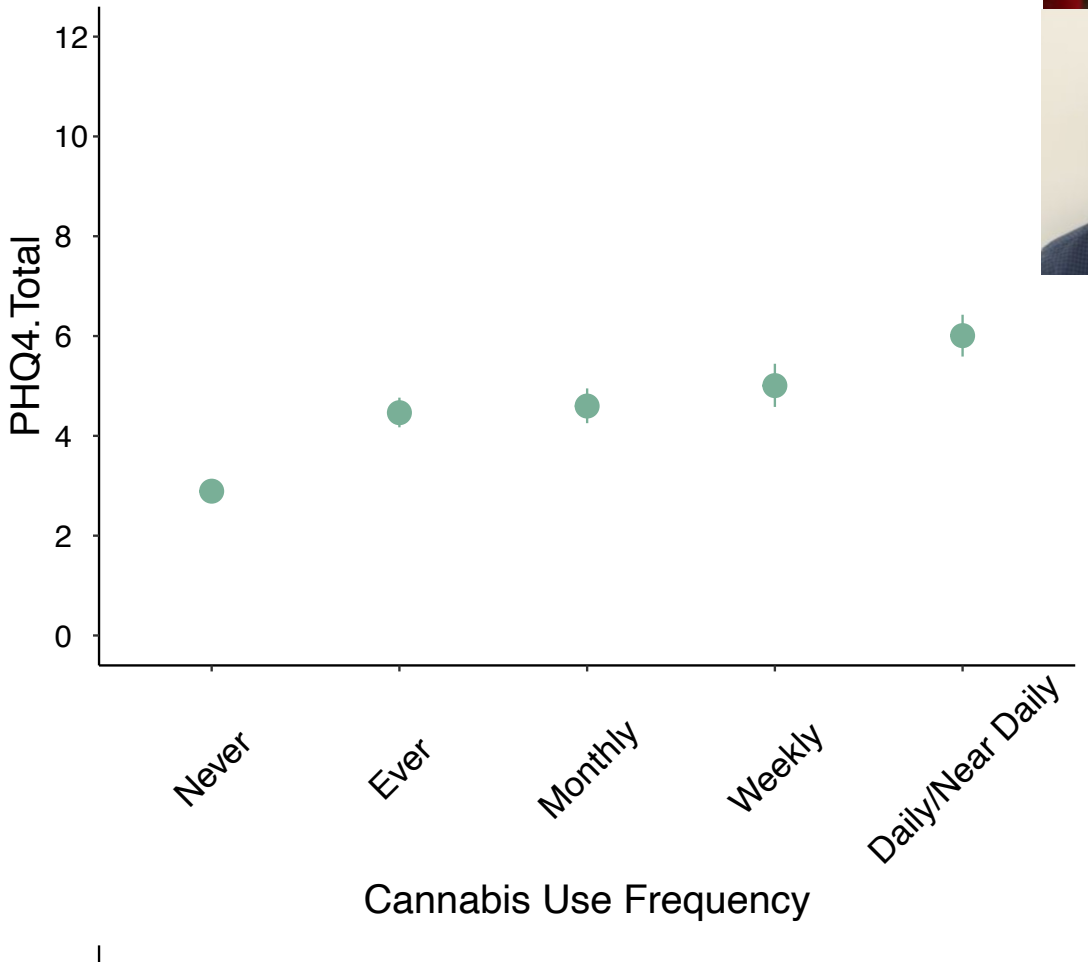
A, Cannabis use was assessed via a self-reported scale, which asked for frequency of cannabis use at each visit. There was a significant increase in use in the immediate card acquisition group vs the delayed card acquisition group (2.44; 95% CI, 2.08-2.81; $P < .001$). B, Cannabis use disorder was defined as 2 or more CUD symptoms on an 11-point scale. The odds of developing CUD were 2.9-fold higher in the immediate card acquisition group vs the delayed card acquisition group (adjusted odds ratio, 2.88; 95% CI, 1.17-7.07; $P = .02$).

Gilman, et al., *JAMA Network Open* 2022

Cannabis Use Frequency Associated with Psychiatric Symptom Severity: Mass School-wide Survey

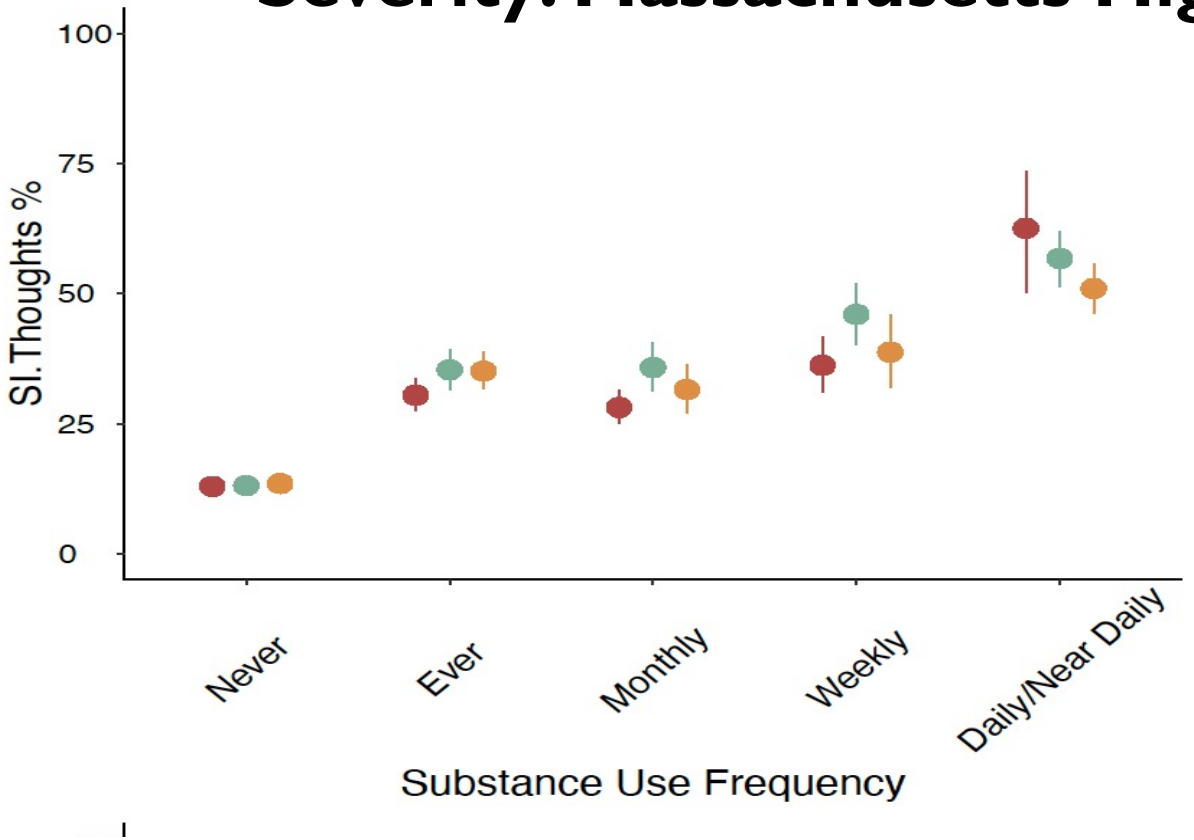


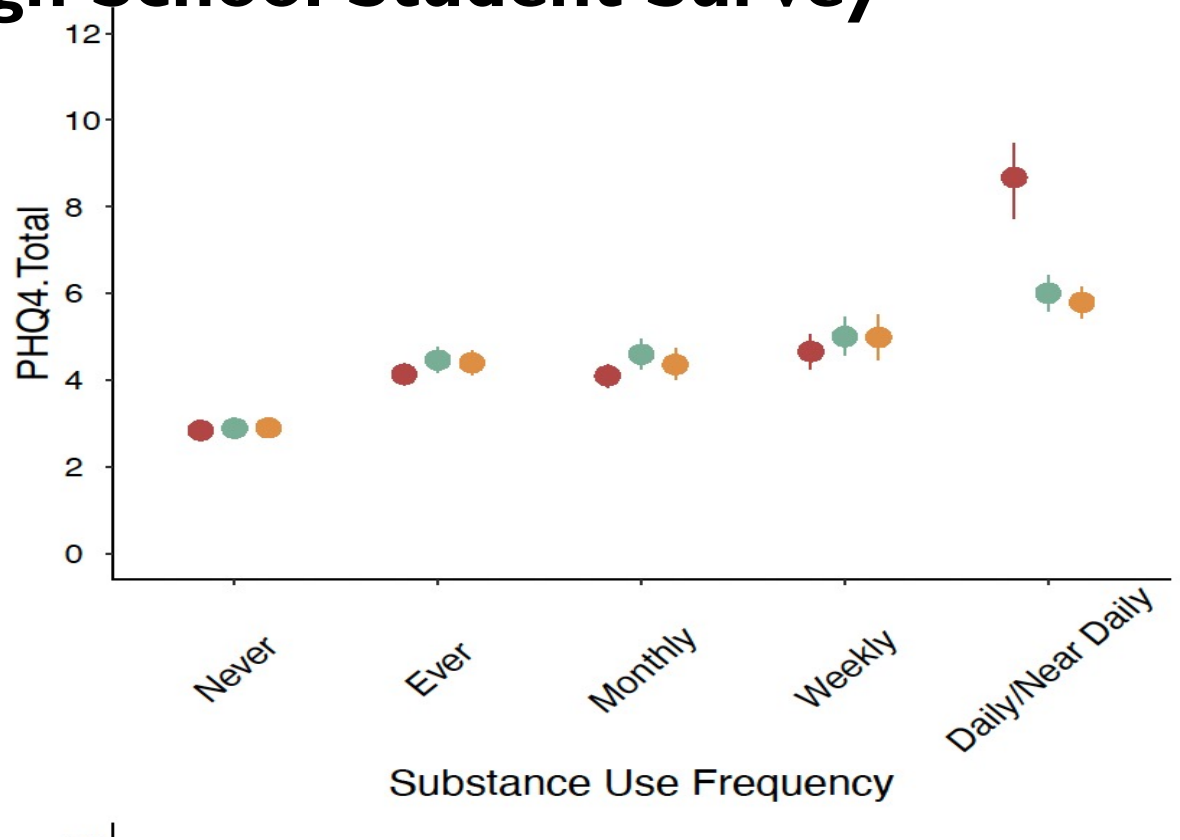




Tervo-Clemmens, et al., *JAMA Peds* 2024.

Drug Use Frequency Associated with Psychiatric Symptom Severity: Massachusetts High School Student Survey

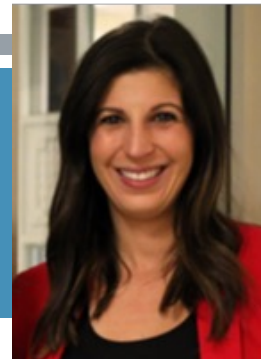




Alcohol Cannabis Nicotine

Tervo-Clemmens, et al., *JAMA Peds* 2024.

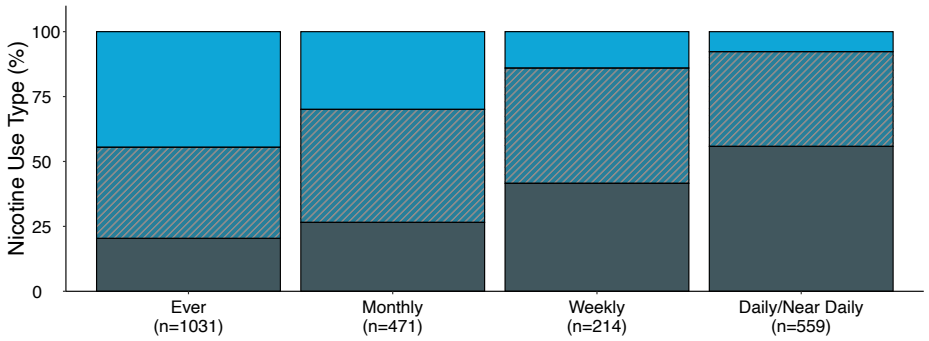
Poly-use Across Substances

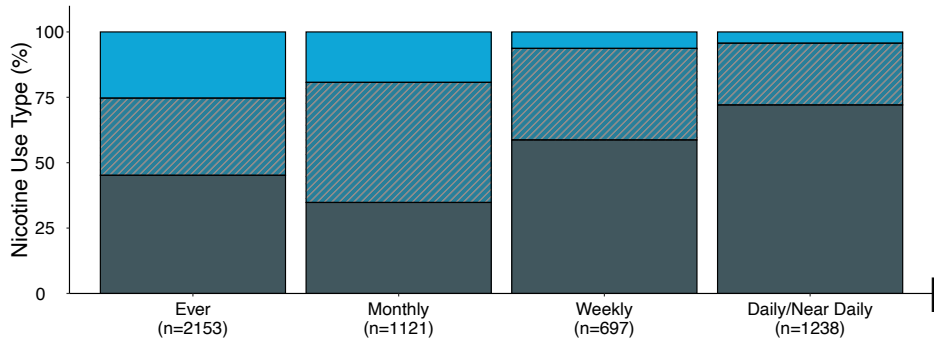


MA High School Survey

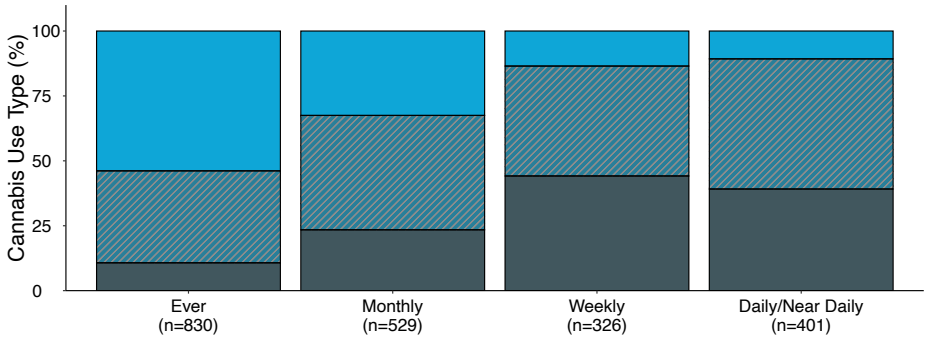
YRBS

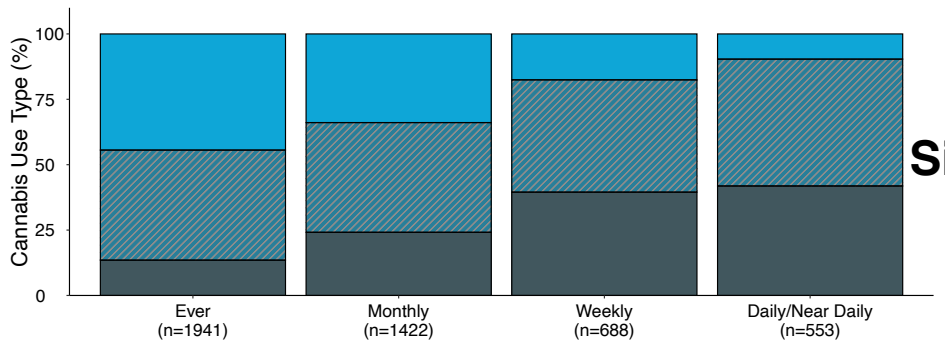
TOB



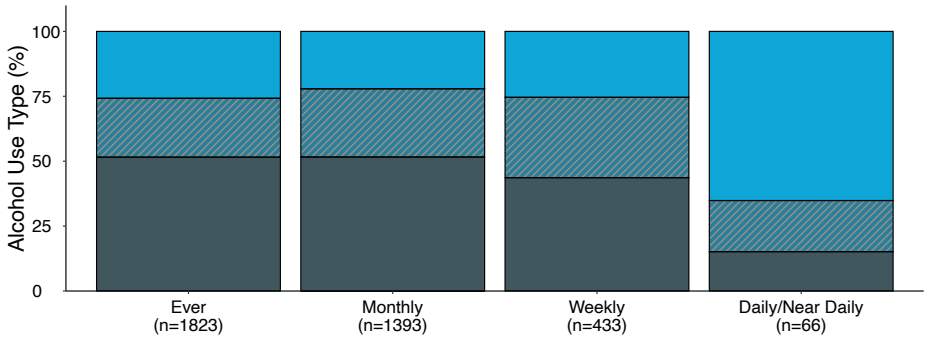


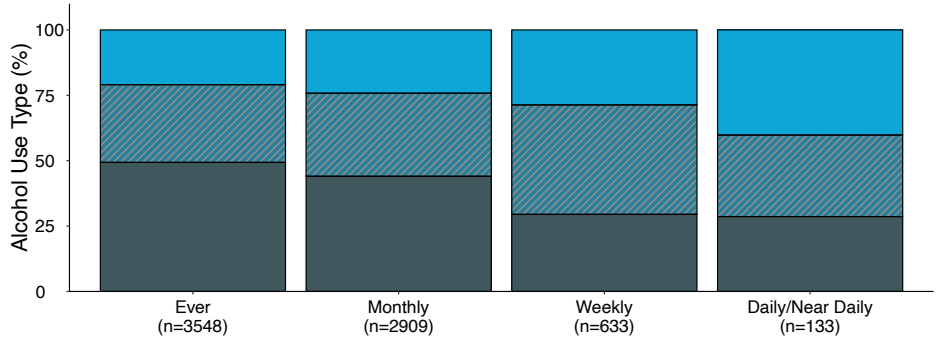
THC





ETOH





Poly-Use

Co-Use

Single Use

Tervo-Clemmens, et al., *JAMA Peds* 2024.

A Public Health Crisis

64%
of individuals with
Schizophrenia
smoke

44%
of individuals with
Bipolar Disorder
smoke

15%
of the
General Population
smoke

Mortality for patients with SMI is

3.7x higher

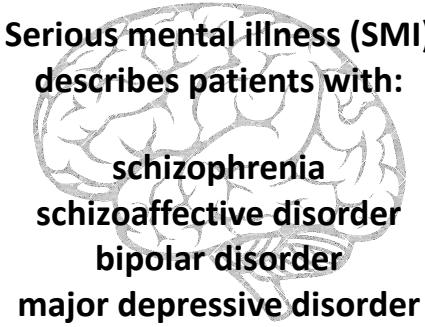
than for the general population[2]

Patients with SMI have a

25-year mortality gap

compared to the general population[3]

What is SMI?

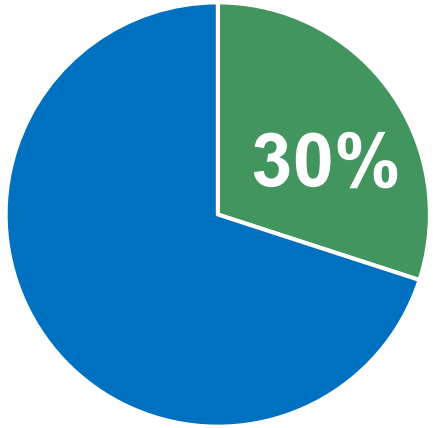


Serious mental illness (SMI) describes patients with:

schizophrenia
schizoaffective disorder
bipolar disorder
major depressive disorder

Opportunities to save lives

Long-term smoking quit rates across strategies for smokers with SMI are roughly 30%, similar to the general population.[4]



Every quit attempt helps people move towards permanent abstinence.

PREMORBID CANNABIS USE: MARKEDLY POORER PROGNOSIS SCHIZOPHRENIA

From cohort of >50,000 conscripts, 400 developed schizophrenia.

Those with vs. without cannabis use before age 18-20, followed for 21 years had:

- **Higher median duration of 1st hospital stay: (59 vs. 30 days)**
- **Greater median number of hospitalizations: (10 vs. 4)**
- **Greater total hospital days: (547 vs. 184)**
- **Greater odds of having >20 hospitalizations: OR = 3.1 (1.3 – 7)**
- **Greater odds of hospital stay >2 years: OR = 2.4 (1.1 – 7)**

Adjusted for other drug use, risky alcohol use, family SES, IQ, urbanicity, personality disorder, marital status

Manrique-Garcia, et al., *Psychol Med* 2014

‘DUAL DX’ TERM PRACTICALLY SYNONYMOUS WITH POOR CLINICAL PROGNOSIS

- Prognosis over decades can be impacted.
  - Up to 30% of risk for schiz in males potentially attributable to cannabis use
- Poor prognosis is surely why we exclude them from our trials,
- Perhaps they are precisely who we need to study to make progress in therapeutics.
  - And they actually can be included in trials with good results.
  - Multidisciplinary research teams bringing experience/expertise in both psych and SUD assessment and tx needed
  - can be challenging due to clinical/cultural silos due to regulatory, training influences

Hjorthoj, Compton, et al., *Psychol Med* 2023

People with commonly co-occurring psychiatric and SUDs are enrolled into virtually all large treatment RCTs.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Muscarinic Cholinergic Receptor Agonist and Peripheral Antagonist for Schizophrenia

Stephen K. Brannan, M.D., Sharon Sawchak, R.N., Andrew C. Miller, Ph.D., Jeffrey A. Lieberman, M.D., Steven M. Paul, M.D., and Alan Breier, M.D.

JAMA: Phase III Registration Trials For Tobacco Use Disorder Treatment, Varenicline Excluded Population Who Consumed Majority of Cigarettes Consumed in US

Varenicline, an α4β2 Nicotinic Acetylcholine Receptor Partial Agonist, vs Sustained-Release Bupropion and Placebo for Smoking Cessation
A Randomized Controlled Trial

David Gonzales, PhD
Stephen I. Rennard, MD
Mitchell Nides, PhD

Context The α4β2 nicotinic acetylcholine receptors (nAChRs) are linked to the reinforcing effects of nicotine and maintaining smoking behavior. Varenicline, a novel α4β2 nAChR partial agonist, may be beneficial for smoking cessation.

Effect of Maintenance Therapy With Varenicline on Smoking Cessation
A Randomized Controlled Trial

Serena Tonstad, MD, PhD
Philip Tønnesen, MD, PhD
Peter Hajek, PhD

Context The majority of cigarette smokers who achieve abstinence relapse within the first year and require many attempts before achieving permanent abstinence. Evidence to support pharmacological treatment for relapse prevention is insufficient.

Efficacy of Varenicline, an α4β2 Nicotinic Acetylcholine Receptor Partial Agonist, vs Placebo or Sustained-Release Bupropion for Smoking Cessation
A Randomized Controlled Trial

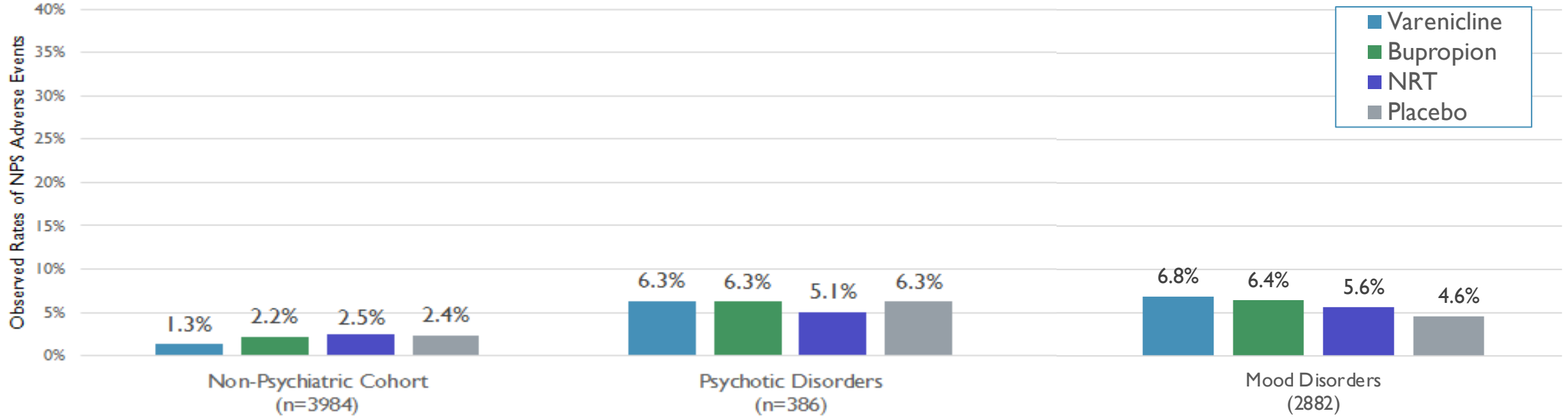
Douglas E. Jorenby, PhD
J. Taylor Hays, MD
Nancy A. Rigotti, MD

Context Varenicline, a partial agonist at the α4β2 nicotinic acetylcholine receptor, has the potential to aid smoking cessation by relieving nicotine withdrawal symptoms and reducing the rewarding properties of nicotine.

SAFETY

Effective Smoking Cessation Medications Do NOT Increase NPSAEs

Occurrence of any NPSAE during 12 weeks treatment and 4 weeks follow-up in adult smokers without or with a lifetime psychotic or mood disorder



Non-psychiatric cohort (n=3984)				Psychotic disorders (n=386)				Mood disorders (n=2882)			
Varenicline (n=990)	Bupropion (n=989)	Nicotine patch (n=1006)	Placebo (n=999)	Varenicline (n=95)	Bupropion (n=96)	Nicotine patch (n=99)	Placebo (n=96)	Varenicline (n=731)	Bupropion (n=716)	Nicotine patch (n=713)	Placebo (n=722)

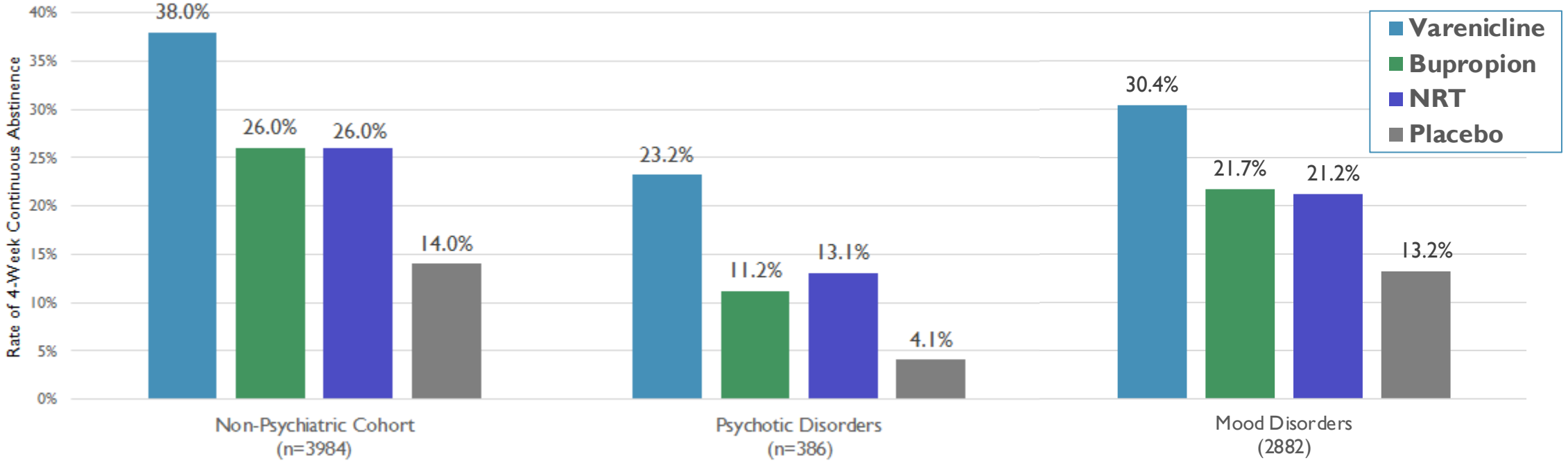
Neuropsychiatric (NPS) safety data based on EAGLES, an FDA required trial to evaluate NPS safety in over 8000 smokers with and without a psychotic, anxiety or mood disorder.

Anthenelli et al., Lancet 2016; Evins et al., J Clin Psychopharm 2019

EFFICACY Comparative efficacy data based on EAGLES[2]

Varenicline was superior to bupropion, NRT and placebo, while bupropion and NRT were superior to placebo for biochemically-confirmed tobacco abstinence.‡

Continuous Abstinence During Weeks 9 Through 12 in Adult Smokers Without or With a History of Psychiatric Disorder



"N" and analyses based on all-randomized populations in the EAGLES trial published in Anthenelli et al., *The Lancet* 2016; and Evins et al., *J Clin Psychopharm* 2019, West et al., *Addiction* 2018

Comparative Safety & Efficacy

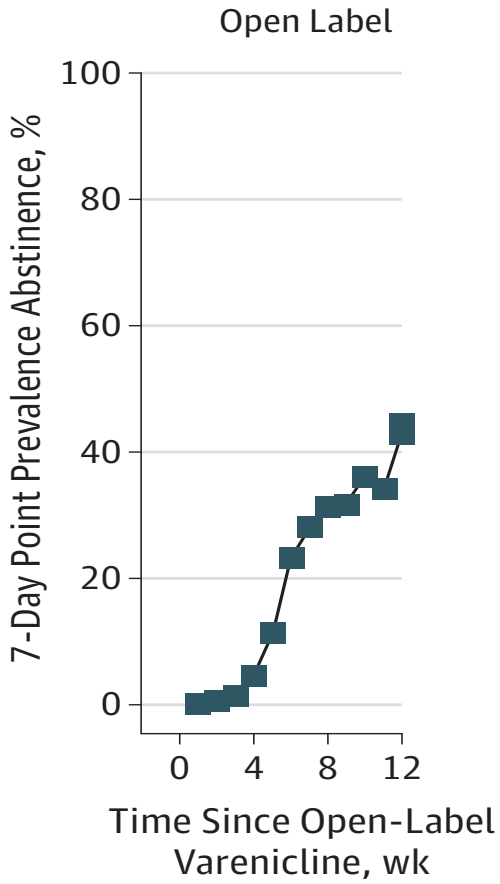
In sub-cohorts with and without psychiatric illness, varenicline was superior to bupropion, NRT and placebo, while bupropion and NRT were superior to placebo for biochemically-confirmed tobacco abstinence.

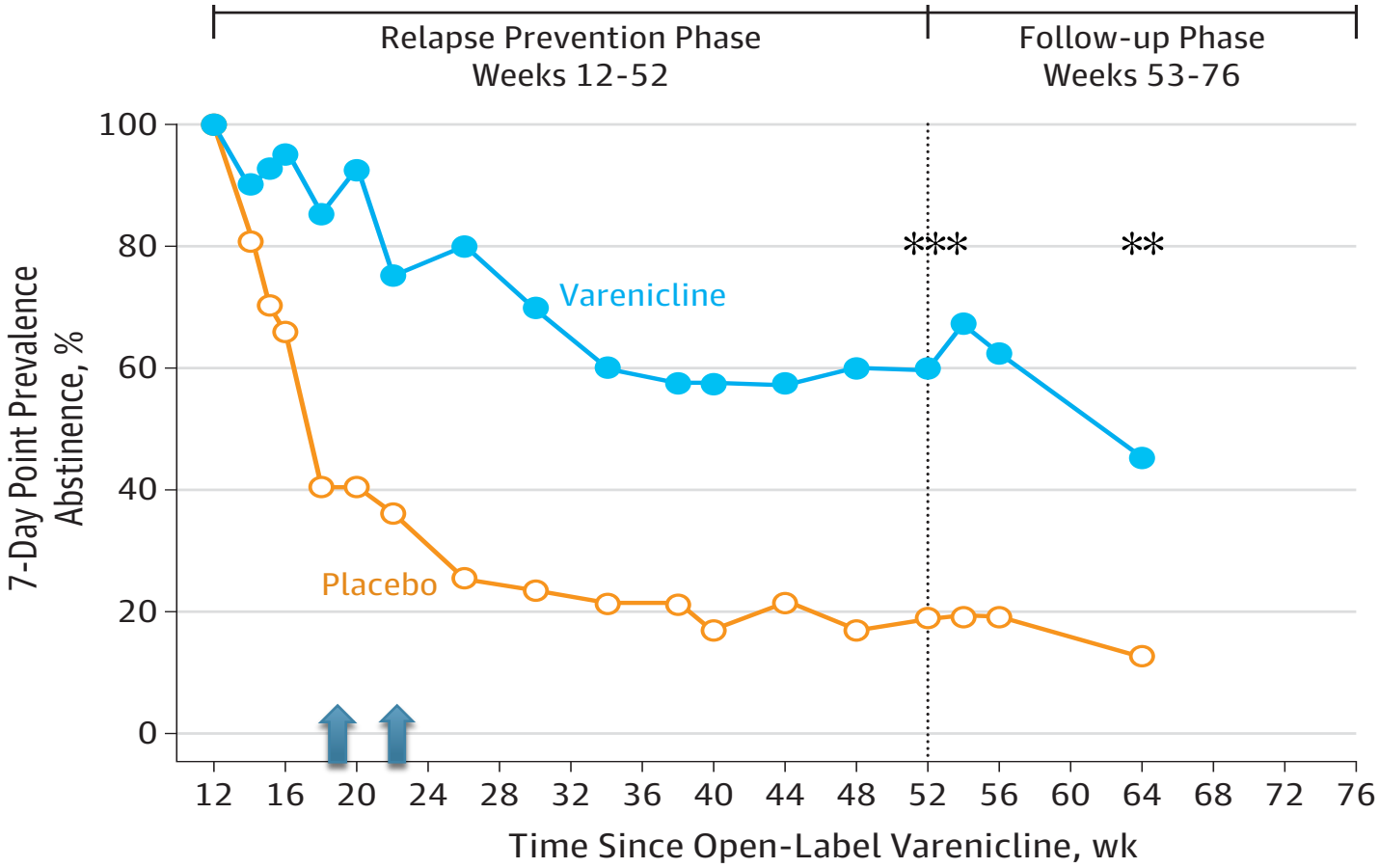
"FDA removes warnings on smoking cessation medication"

Pharmacy Times, December 16, 2016

FDA removed boxed warnings for varenicline and bupropion based on results of EAGLES, a required, randomized, double-blind, triple dummy, active-and placebo-controlled clinical trial conducted by Pfizer in collaboration with GlaxoSmithKline, designed in consultation with the FDA and the European Medicines Agency (EMA). It is the largest smoking cessation clinical trial ever conducted and the largest samples of smokers with psychotic, anxiety, and mood disorders ever conducted.

MAINTENANCE PHARMACOTX TRIPLED ABSTINENCE AT ONE YEAR IN SMOKERS WITH SMI

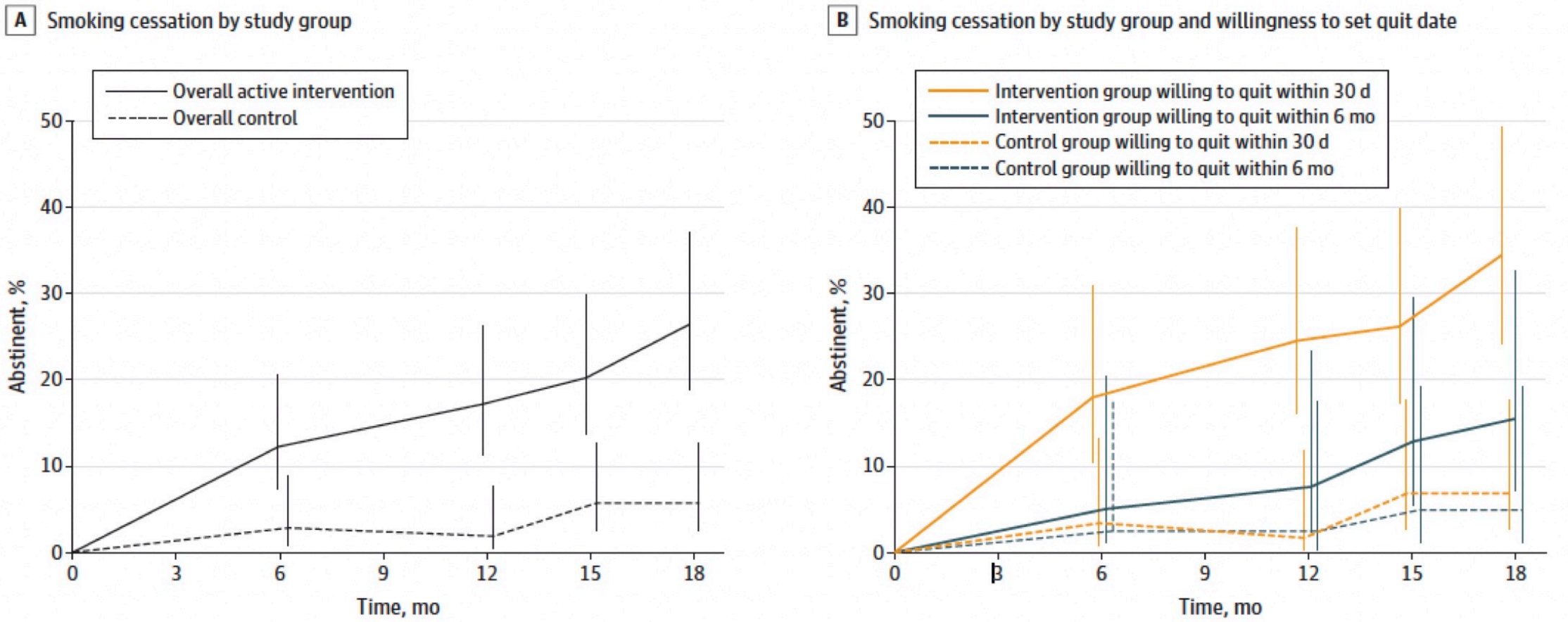




Evins, Cather, et al., *JAMA*. 2014

Sustained Offer of Pharmacotx/Behav Support Increases Abstinence in Smokers with SMI

Figure 2. Tobacco Smoking Cessation Over Time by Study Group and by Willingness to Set a Quit Date at Baseline



A, Tobacco smoking cessation over time by study group. B, Tobacco smoking cessation over time by study group and by willingness to set a quit date at baseline. Percentage abstinence estimates and 95% CIs (error bars) were derived from generalized estimating equations analysis using all available data from all randomized participants, adjusting for willingness to set a quit date and study sites.

Daumit, Evins, Cather, et al., *JAMA Psych*, 2023 *in press*

WHAT ARE THE MAJOR BARRIERS TO ADDRESSING HEAD ON THE REALITY OF COMORBIDITY IN CLINICAL AND PRECLINICAL ADDICTION RESEARCH?

---and what are some opportunities to address them…?

1. Complexity complicates interpretation

- The desire for simple, clean designs is strong
  - Researchers
  - Study section
  - FDA / Industry
  - Program
- Despite the risk that purity in enrollment criteria yields data that aren't generalizable to potentially half the population we're trying to help. And further maybe we'd get better treatments if we tested them in co-occurring populations.

COMPLEXITY AS A BARRIER TO ADDRESSING COMORBIDITY IN CLINICAL RESEARCH

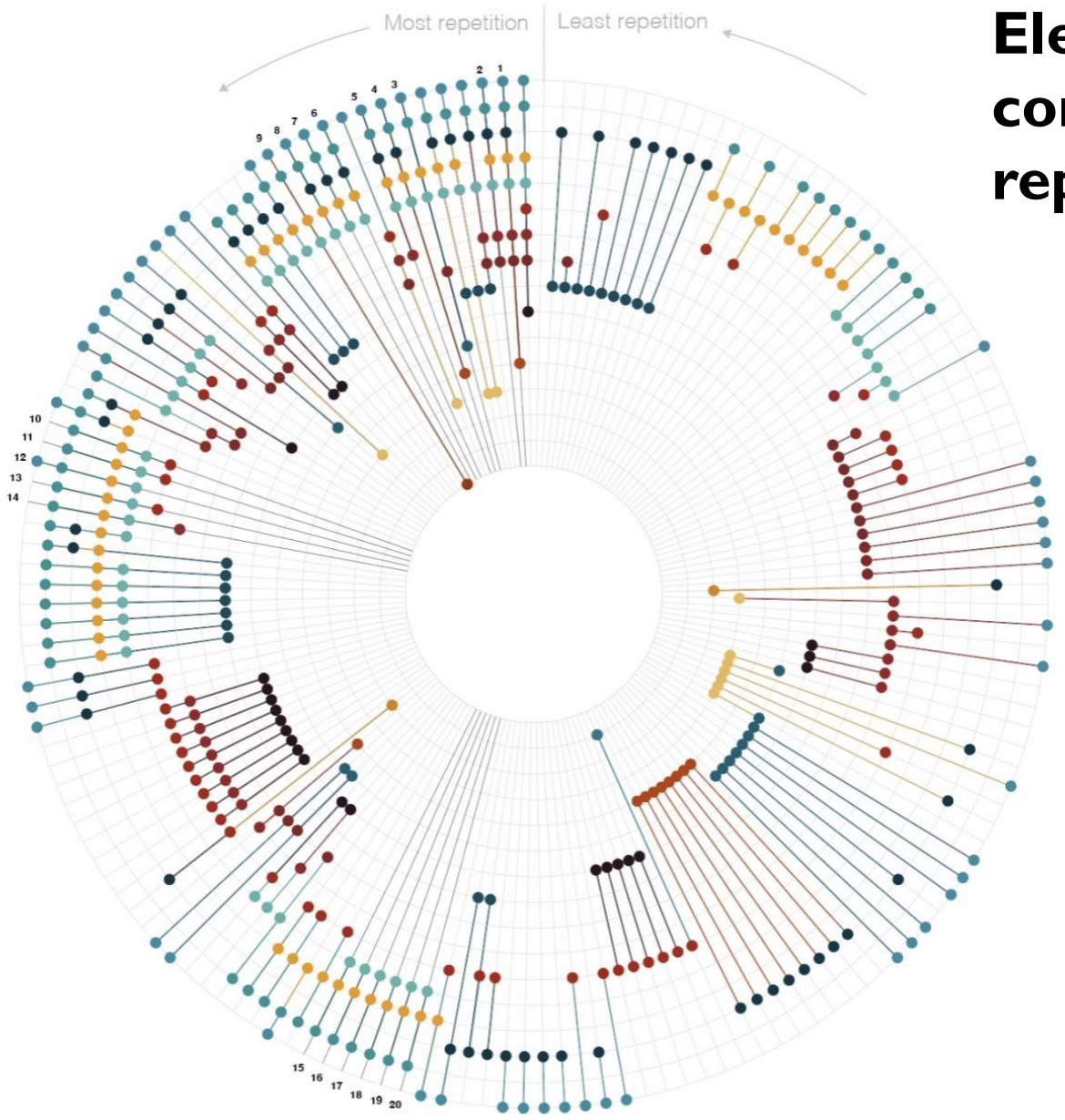
Is co-occurrence contemporaneous or lifetime?

Is contemporaneous co-occurrence pre-existing, resolved, or substance induced and largely resolved with abstinence?

Is one or the other disorder is seen as primary or more severe?

Within diagnoses, there will be variability in pathophysiology.

Many thought not to have a co-occurring disorder at enrollment will have subsyndromal, unrecognized, or not yet manifest co-occurring illness.



Elemental Psychopathology: Distilling constituent symptoms and patterns of repetition across DSM-V

Forbes, et al., PsyArXiv. 2023

Figure 3. Map of symptoms that repeat across chapters, sorted by number of chapters in which the symptom occurs. Each ring represents a chapter, and the dots on the ring are distinct symptoms in that chapter that repeat in other chapters. Joined dots falling along the same radius denote a symptom repeating between chapters. Symptoms in the diagnostic criteria for major depressive disorder are marked with numbers to highlight the considerable overlap depression symptoms show. A detailed version of this plot with symptom labels is presented in Figure S20; another version that includes all 628 symptoms—regardless of whether they repeat across chapters—is presented in Figure S21.

Nearly all of the symptoms that repeat most frequently, and that repeat across the most chapters, are symptoms of Major Depressive Disorder:

1. **Insomnia** - 22 occurrences across 8 chapters
2. **Difficulty concentrating** - 17 occurrences across 7 chapters
3. **Hypersomnia** - 17 occurrences across 6 chapters
4. **Psychomotor agitation** - 16 occurrences across 5 chapters
5. **Depressed mood** - 15 occurrences across 6 chapters
6. **Psychomotor retardation** - 14 occurrences across 5 chapters
7. **Fatigue** - 12 occurrences across 6 chapters
8. **Increased appetite** - 12 occurrences across 5 chapters
9. **Weight loss** - 10 occurrences across 5 chapters
10. **Suicide attempt** - 6 occurrences across 4 chapters
11. **Indecisiveness** - 7 occurrences across 4 chapters
12. **Decrease in appetite** - 10 occurrences across 4 chapters
13. **Diminished pleasure** - 8 occurrences across 4 chapters
14. **Diminished interest** - 7 occurrences across 4 chapters
15. ***Plan for suicide attempt** - 5 occurrences across 3 chapters
16. ***Suicidal ideation** - 5 occurrences across 3 chapters
17. ***Thoughts of death** - 5 occurrences across 3 chapters
18. **Inappropriate/excessive guilt** - 7 occurrences across 3 chapters
19. ***Feelings of worthlessness** - 5 occurrences across 3 chapters
20. **Significant weight gain** - 8 occurrences across 3 chapters

**denotes symptoms that only repeat in the context of a Major Depressive Episode*

From the inside ring out

- Ch10 – Feeding and Eating Disorders
- Ch6 – Obsessive–Compulsive and Related Disorders
- Ch13 – Sexual Dysfunctions
- Ch8 – Dissociative Disorders
- Ch12 – Sleep–Wake Disorders
- Ch9 – Somatic Symptom and Related Disorders
- Ch15 – Disruptive, Impulse–Control, and Conduct Disorders
- Ch1 – Neurodevelopmental Disorders
- Ch5 – Anxiety Disorders
- Ch7 – Trauma– and Stressor–Related Disorders
- Ch18 – Personality Disorders
- Ch4 – Depressive Disorders
- Ch2 – Schizophrenia Spectrum and Other Psychotic Disorders
- Ch17 – Neurocognitive Disorders
- Ch3 – Bipolar and Related Disorders
- Ch16 – Substance–Related and Addictive Disorders

Addressing Complexity: Dimensional Phenotypes

Facilitate Discovery of Genetic Variation Relevant to Psychopathology

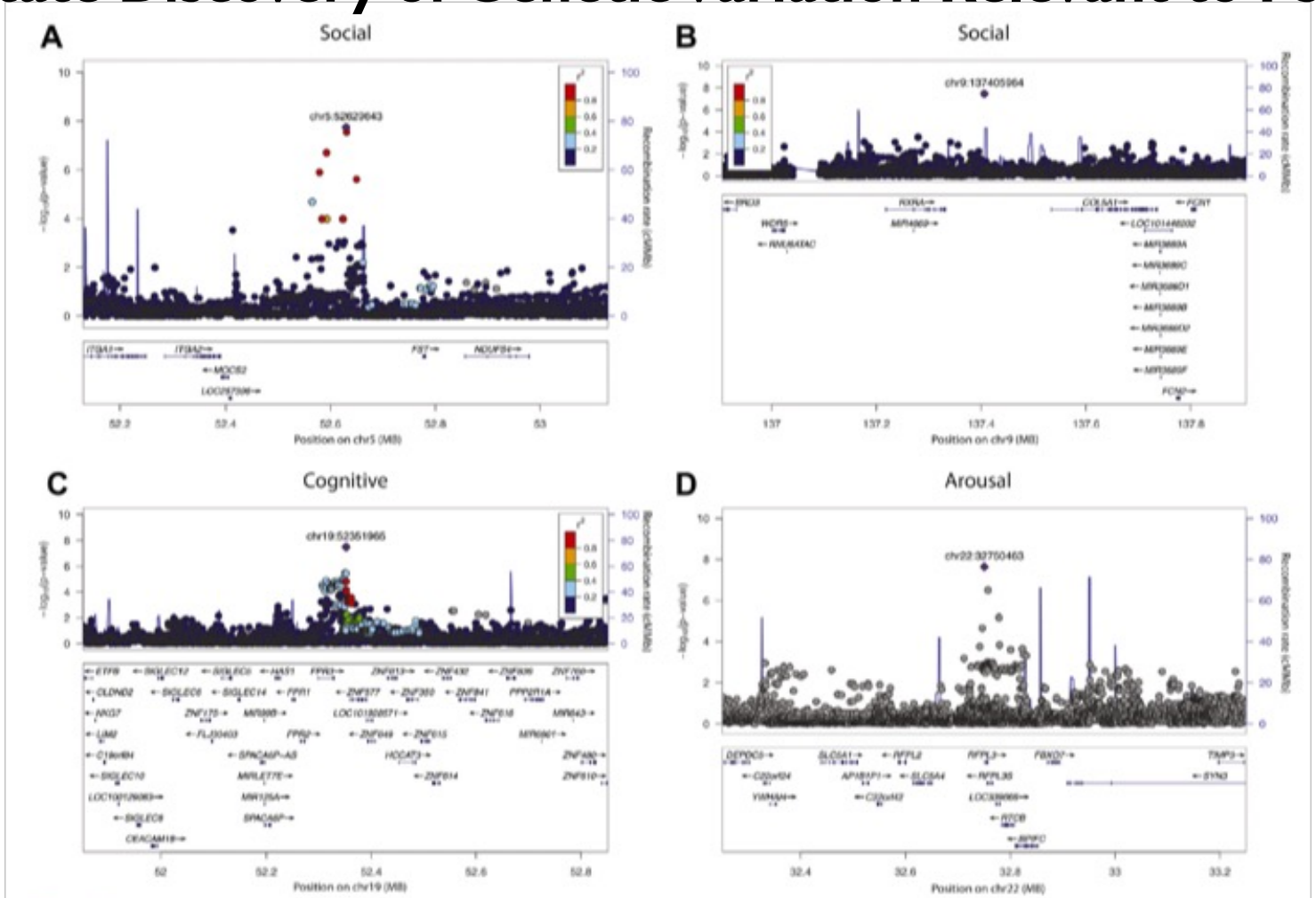
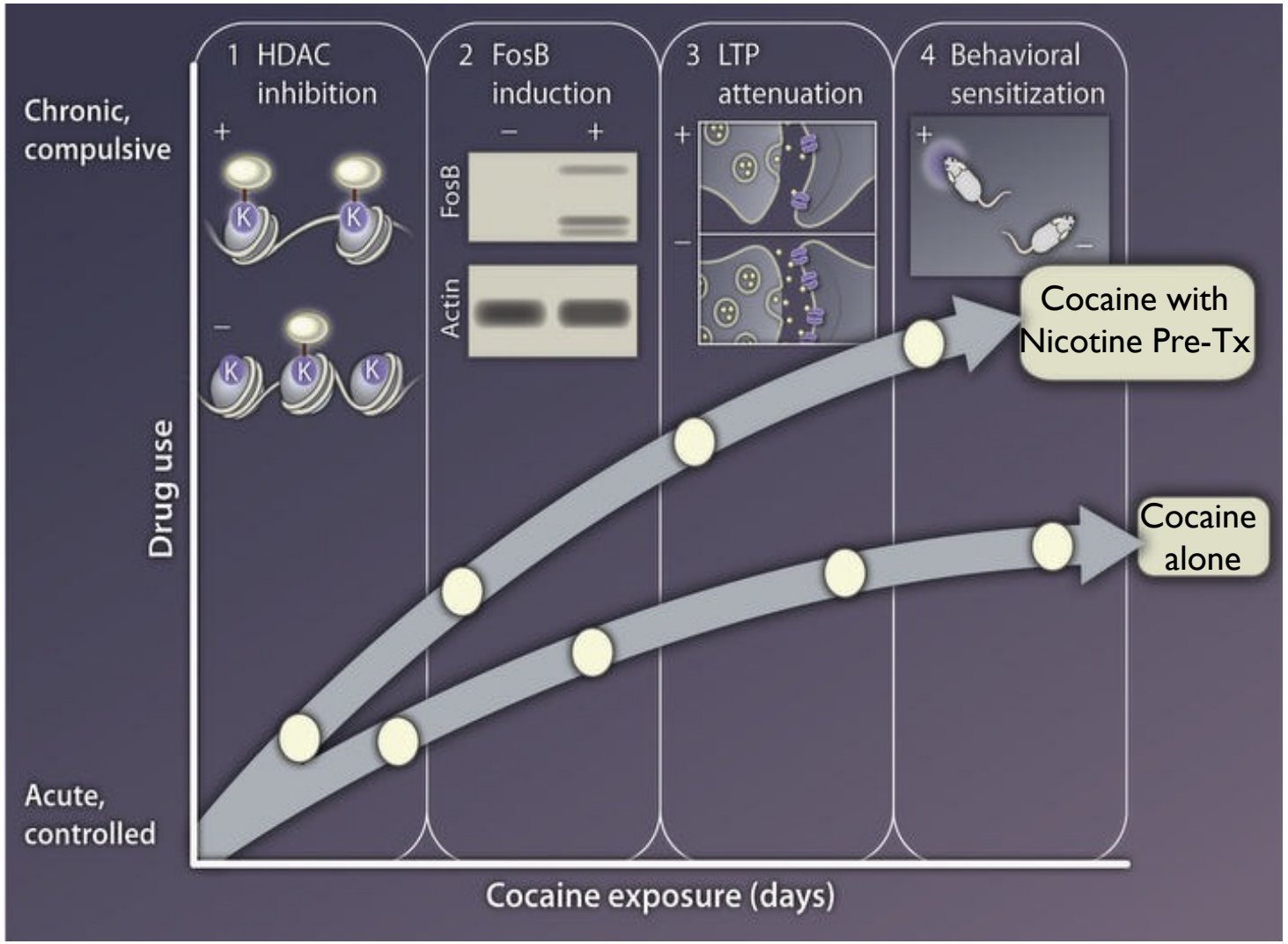


Figure 2. Region plots for four loci with genome-wide significance. chr, chromosome; cM/Mb, recombination rate.

McCoy, et al., Biol Psych. 2016

Addressing Complexity:
Animal Models Increasingly Elegantly Reflect Clinical Complexity



Volkow Commentary to Levine, et al., *Science Transl Med.* 2011

MAJOR BARRIERS TO ADDRESSING COMORBIDITY IN CLINICAL AND PRECLINICAL ADDICTION RESEARCH AND BASIC NEUROSCIENCE?

2. Stigma, The elephant in the room?

- Psych and SUDs among most potent stigmas in society, Bias and Opportunity
  - Those with comorbidity are highly marginalized populations (Less important)
  - Less likely to engage, succeed (higher dropout, lower abstinence?)
- Opportunities
  - Researchers
  - Study section
  - FDA / Industry—use Phase Ib trials to assess drugs early in affected populations
  - Program

DISCUSSION: HELP US FURTHER IDENTIFY BARRIERS YOU FACE

- Help us further identify the barriers you face to study of co-occurring disorders
- Researchers: What would help you to include study of co-occurring disorders in your work
- Reviewers: What would help you to consider inclusion of people with co-occurring disorders a strength in grant proposals
- Program: What would help to recognize and prioritize co-occurring disorders as a key to progress in SUDs treatment and prevention
- FDA / Industry: Therapeutic endpoints, Subcohort Inclusion requirements