Transdiagnostic Psychopharmacology: Managing Multiple Comorbidities

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Disclosures

Supernus: Expert Witness

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Objectives

- Identify common patterns of psychiatric comorbidity in children and adolescents that complicate medication selection and sequencing.
- Prioritize treatment targets when managing co-occurring ADHD, mood, anxiety, and behavioral disorders.
- Apply transdiagnostic principles to medication selection and sequencing in complex clinical presentations.
  - Mood lability vs. Depression/Anxiety
  - The SSRI dilemma
- Evaluate the risks and benefits of polypharmacy when managing youth with multiple psychiatric diagnoses.
  - Deprescribing: beyond the buzzword

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Before we start, what to look for in 26-27

- Centanafadine (a triple NE, DA 5-HT reuptake inhibitor, Otsuka) has had successful Phase III trial for ADHD in children, adolescents and adults). Effect size (0.3 to 0.4) similar to other non stimulants for ADHD (JAACAP June 2026).FDA approval expected.
- Xanomeline-trospium
  - A Phase III study of Xanomeline-trospium for treatment of irritability in children and adolescents With Autism(NCT07284745).
  - BALSAM study in adults with bipolar disorder (NCT06951711)
  - Phase III in adolescents 13-17 years old with schizophrenia (NCT07288567)
- Brexpiprazole
  - Adolescent schizophrenia successful trial (2 mg/day v Placebo) Lancet Psychiatry May 2025 12:245
  - Negative study in autism (age 5-17 years) (NCT04174365)
- Cariprazine- One Phase III study complete, positive effect on Aberrant Behavior Checklist Irritability Scale vs placebo, 2nd study needed for FDA approval.

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Before We Start: Meta-analyses of Youth Bipolar Disorder Pharmacology

Study	Population	Key Findings
Tural Hesapcioglu et al. 2024 J Affect Disr 349:438	15 RCTs, n=2,372, acute mania	Risperidone 0.5–2.5 mg/day, aripiprazole30 mg/day, olanzapine, quetiapine 400/600 mg/day, asenapine 5/10 mg, and ziprasidone were effective versus placebo. Oxcarbazepine had highest discontinuation due to adverse events, high placebo response rate
Vita et al. 2025 JAACAP 64:143	18 studies, n=2,844, acute mania	All 6 SGAs (aripiprazole, asenapine, olanzapine, quetiapine, risperidone, ziprasidone) outperformed placebo and mood stabilizers for mania symptom reduction. Risperidone showed largest effect size (SMD −1.18). **Mood stabilizers as a class did not outperform placebo. SGA more SE's ☹**
DelBello et al. 2022 JAACAP 61:243	4 RCTs, bipolar depression	Lurasidone and olanzapine-fluoxetine combination demonstrated significant CDRS-R improvement; quetiapine did not (placebo response). Lurasidone had favorable metabolic profile.

Case Presentation- Alexis

- Alexis is 14-year-old girl. Her parents divorced when she was six and she lives with mother, her father visits intermittently. She has frequent arguments with mother, periods of constant mood lability since age 10. Two past psych hospitalization since age 13 for cutting herself. Verbal aggression at school with teachers, frequent tiffs with girls at school. Has been on multiple SSRIs, unclear effect. Depressed all the time as per mother. Has had 4 therapists, all dismissed her and her mother for missed appointments/lack of progress.

- Alexis does not want to be at appointment, says doctors are stupid. Rates herself a "0" on the PHQ-9. Mother says she was in GT in 4th grade but could not keep up with projects. Mediocre grades since then. Many boyfriends, with break ups & crying for several days. No hx of euphoria. Stays up all night but sleeps in the day.

- Witnessed father hitting mother before divorce, but enjoys time with father but enraged and blames mom when he cancels her weekend. Failing three classes, does not turn in homework.

Case Presentation – Alexis

- Past psychotropic medication:
  - Fluoxetine up to 60 mg a day. Was hospitalized for cutting after breakup with boyfriend after dose was maxmimized
  - Duloxetine 60 mg a day in past, no clear effect
  - On Abilify after hospitalization, dc'd since she felt sedated.
  - Currently on Zoloft 75 mg a day.
  - Took Seroquel q hs for sleep in past, which worked well
- Intermittent THC use (smokes weed) mainly with friends on weekends, it relaxes here)
- No history of sexual or physical abuse
- Carries bipolar II diagnosis from hospital stay

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Case Presentation – Alexis

- Alexis feels she has ADHD. She took a friend's Adderall and felt she could focus better.
- Parent and Youth ADHD Rating scale in the clinical range for Inattentive symptoms, just missed clinical range for Impulsive-Hyperactive due to no hyperactive items being checked.
- Alexis says she is meeting her friends later, mother says she is grounded, Alexis bursts into tears and says, "this is why I want to kill myself"
- How to proceed?

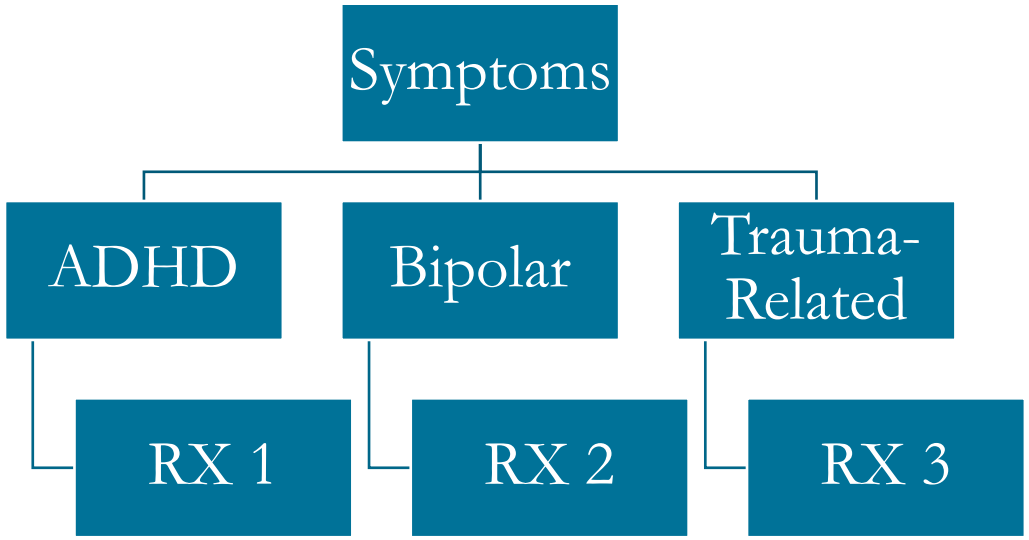
Case Study- Mac

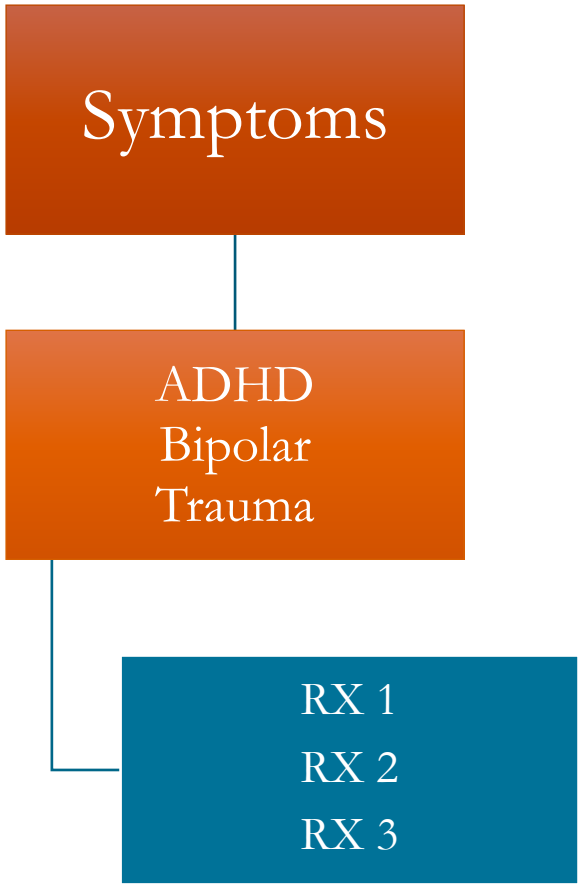
- “Mac” is a 14-year-old teen with long history of severe mental illness, admitted to new RTC. Exposed to meth as fetus, adopted by family member. Has had **>10** psychiatric hospitalizations in last three years for disorganized, irrational and aggressive behavior. Removed from lower level RTC due to unmanageable behavior. Has failed multiple mood stabilizers and antipsychotics.
- In **five days** since admission has had eight restraints, time outs and staff have trouble redirecting him, seems not to understand social cues, is often looking off.
- School is a bright spot, is doing work!
- On mental status, Mac denies AVH or any emotions at all. No eye contact with examiner, eyes dart around the room, gives minimal answers. No seeming interest in people in the room, often highly illogical. Verbal skills so bad examiner first suspects ID but chart shows full scale IQ to be 100.

Case Study- Mac

- Due to multiple failures of prior antipsychotics and mood stabilizers, during last hospitalization he was placed on 50 mg tid of clozapine at last hospital, level of clozapine is 150, ANC 2500 cells/µL.
- Other Medications on admission:
  - Jornay 100 mg q hs
  - Valproate 1000 mg q hs (Level 51)
  - Sertraline 100 mg q am
  - Clonidine 0.1 mg tid (BP 129/81)
  - Hydroxyzine 25 mg bid
- How to proceed?

Diagnoses: are you a lumper or a splitter?





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Do splitters end up as lumpers anyway?

- Bianchi et al Eur Child Adolesc Psych 26:549, 2017
- Child Behavior Checklist (CBCL) obtained on both a referred (N = 1225) and a general population (N = 3418)
- Latent Class Analysis (LCA) used to look at grouping
- Machine learning techniques will help us look at complex data- 4 major groups emerged.

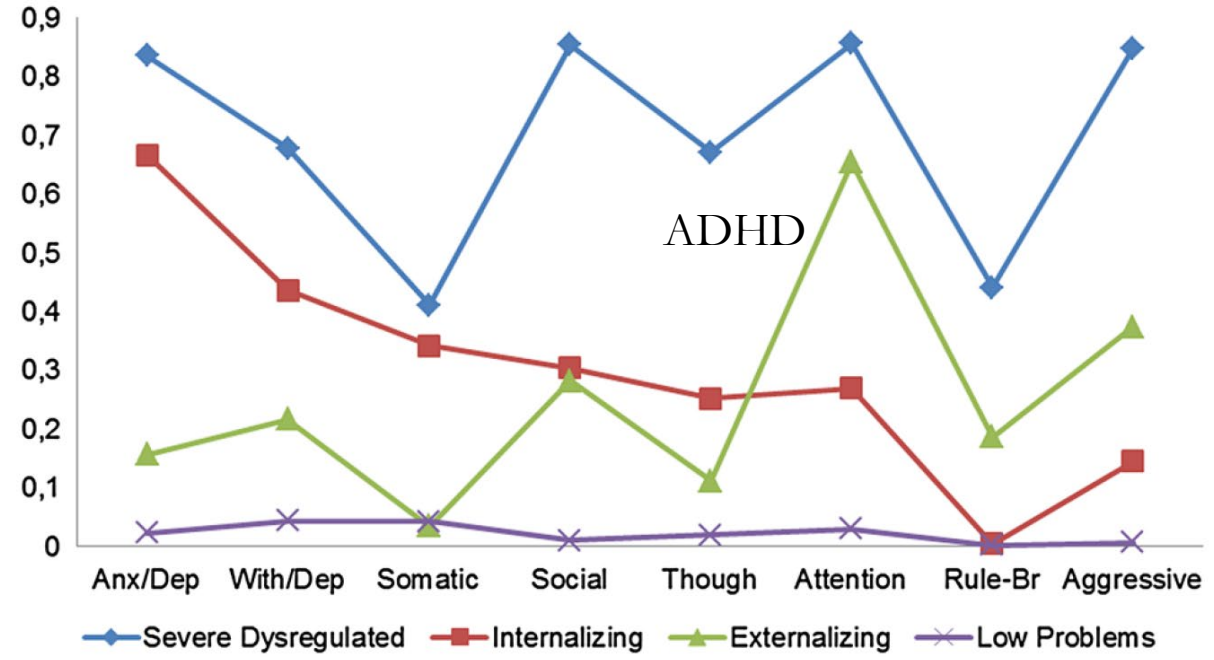

Fig. 1 CBCL/6–18 profiles according to the 4-class solution in the total sample

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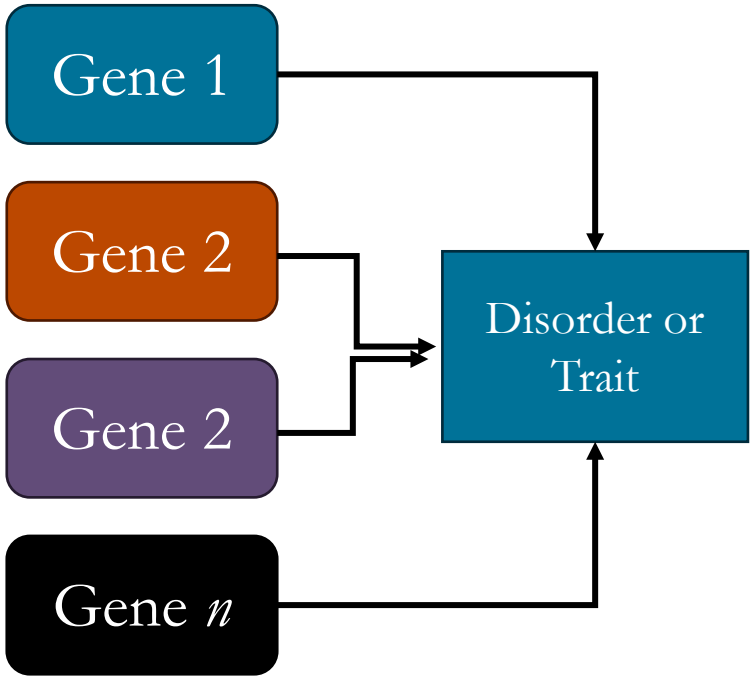
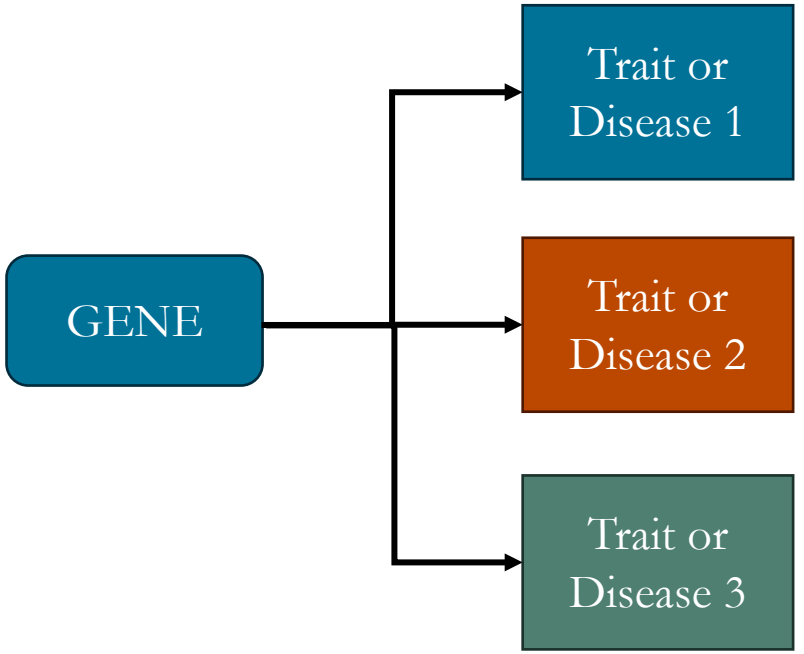
What are new genetic studies telling us about psychopathology?

Polygenicity



Thousands of variants/genes can be involved in a single disorder

Pleiotropy



Each of these genes can influence many traits or disorders

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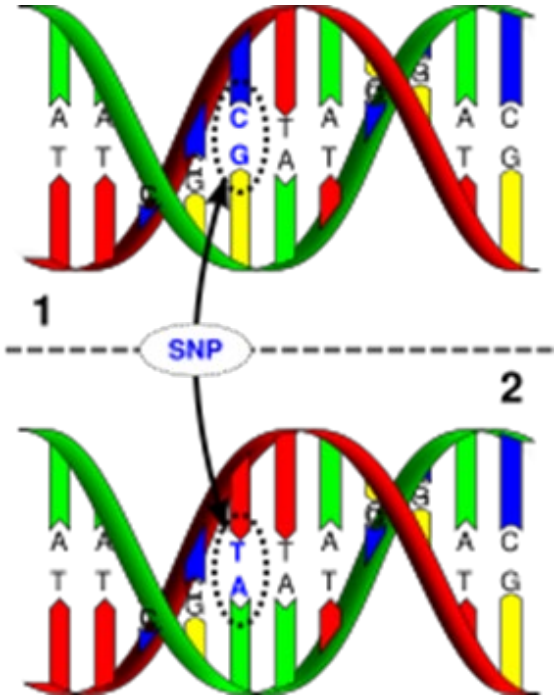
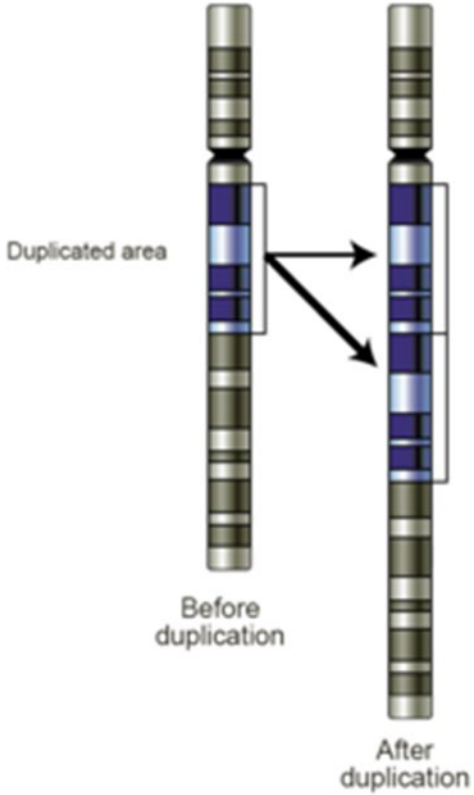
Single Nucleotide Polymorphism vs Copy Number Variant

Single Nucleotide Polymorphism (SNP)
Sequence Variation



Related to typical variation (height, IQ ADHD, hypertension)

Copy Number Variant(CNV)
Structural Variation



Can be a deletion as well as a duplication

Related to ID, cognitive deficits, physical anomalies, epilepsy

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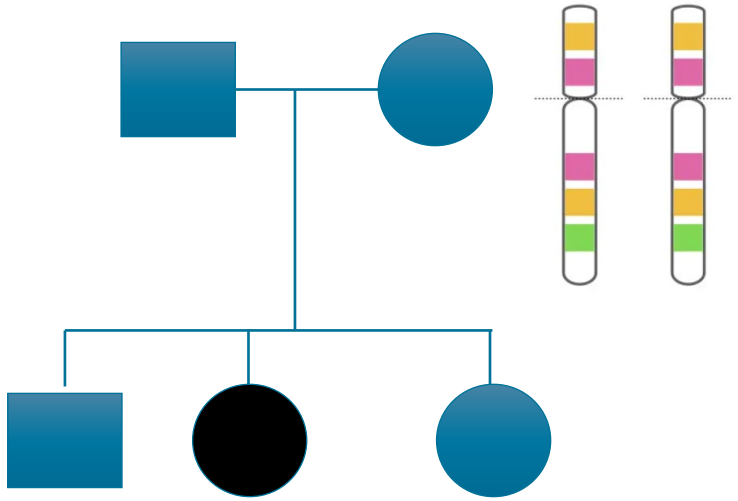
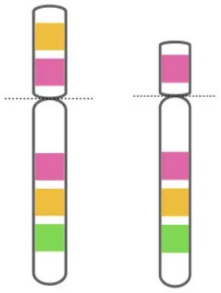
De Novo vs Inherited Copy Number Variant

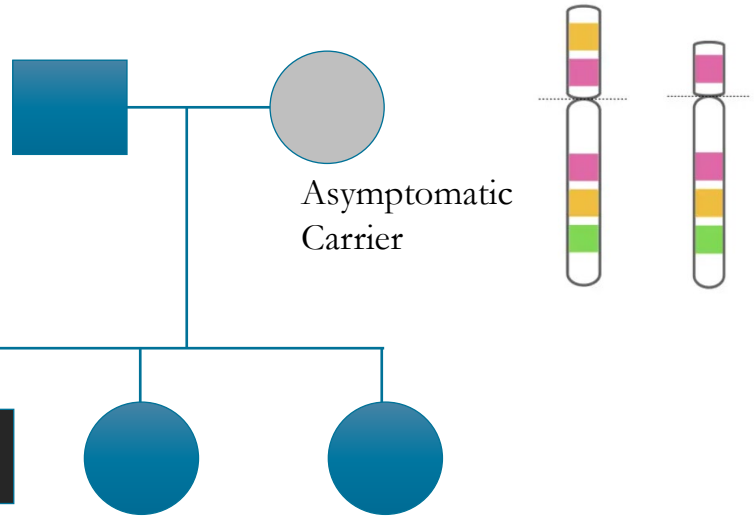
DE NOVO



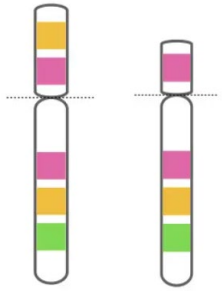
Affected
Proband



INHERITED



Affected
Proband



The larger the deletion or duplication, the greater the effect of the variation and more likely it is to cause disease.

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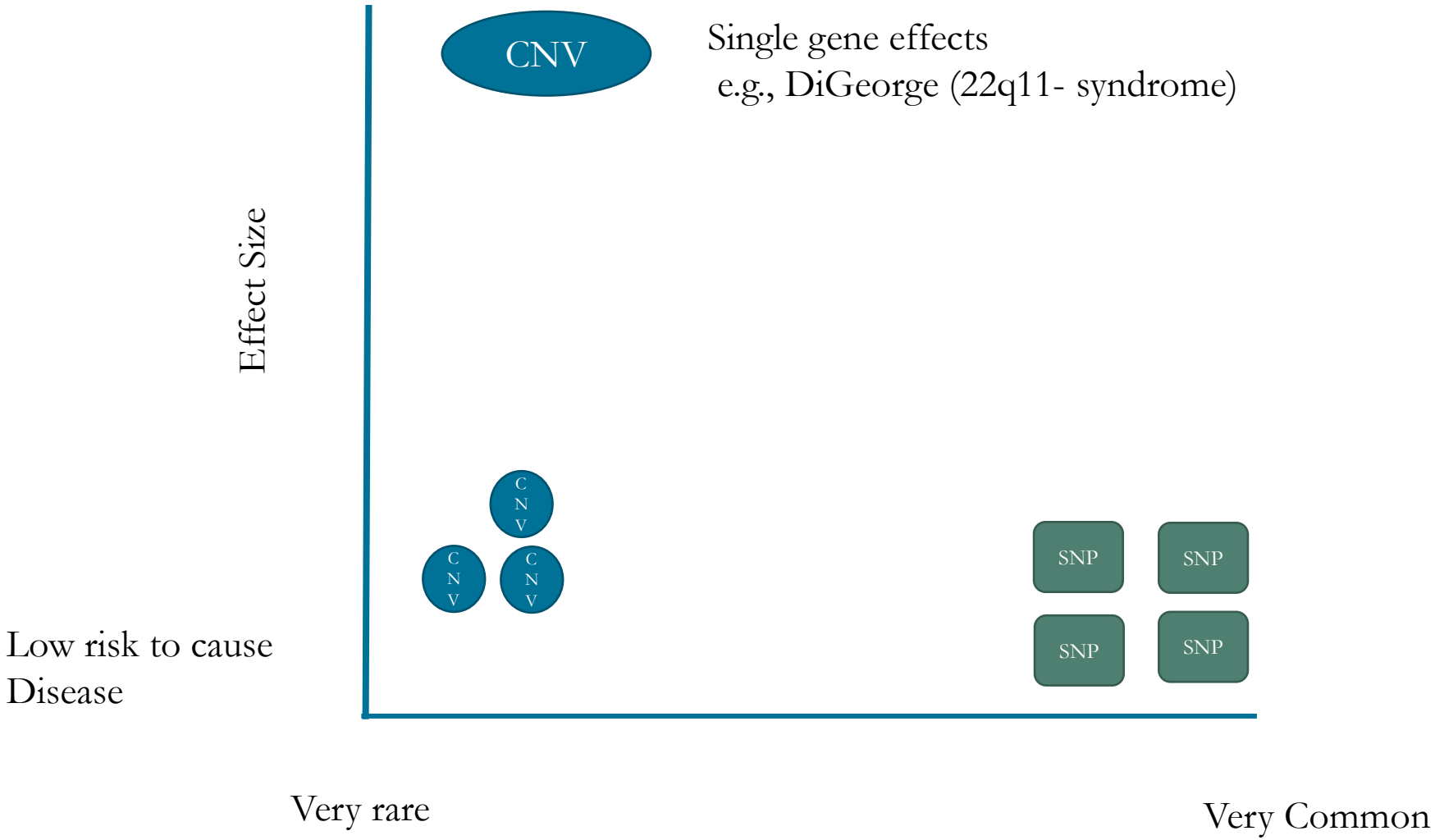

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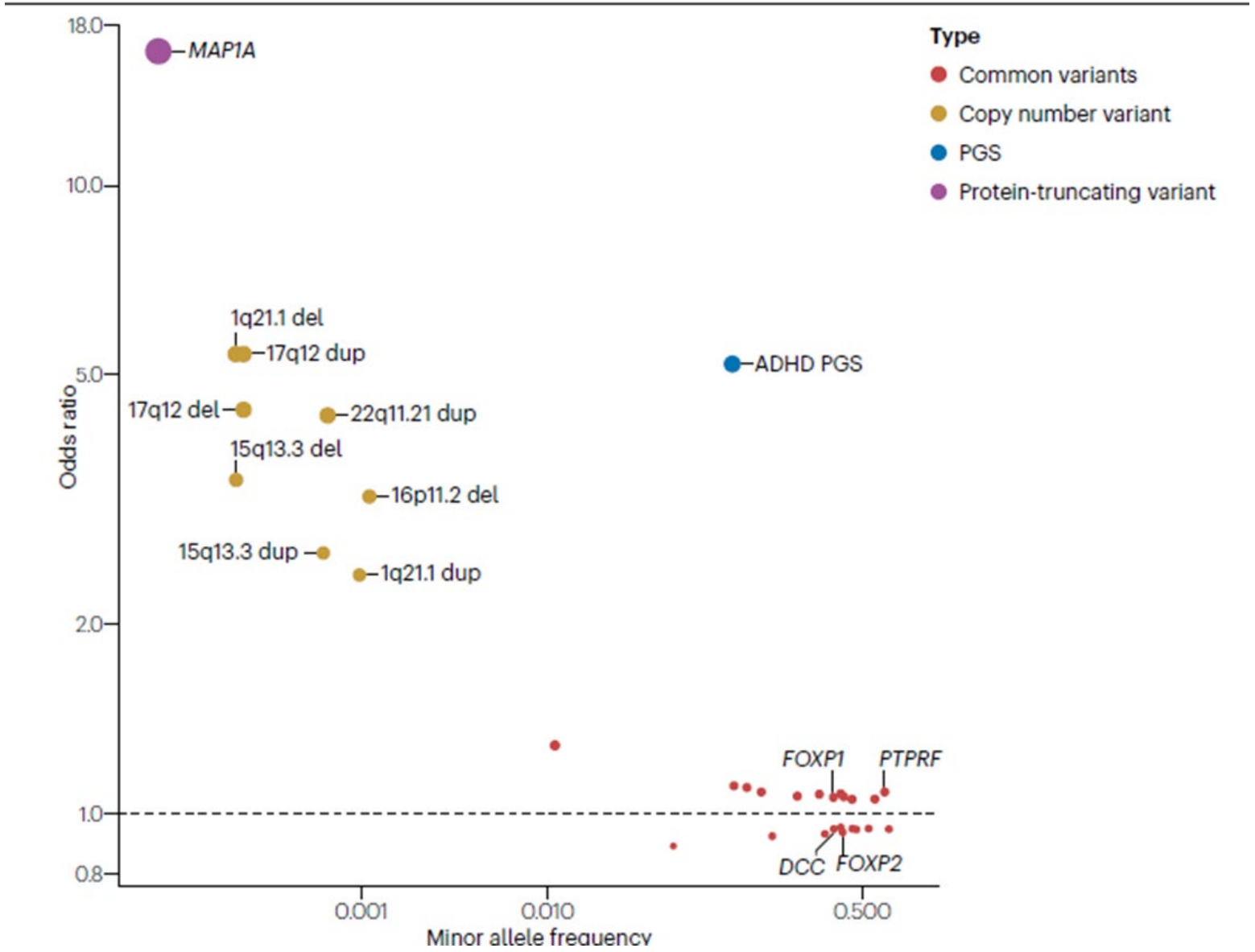

Faraone et al. Nature Review disease primers 10:11, 2024

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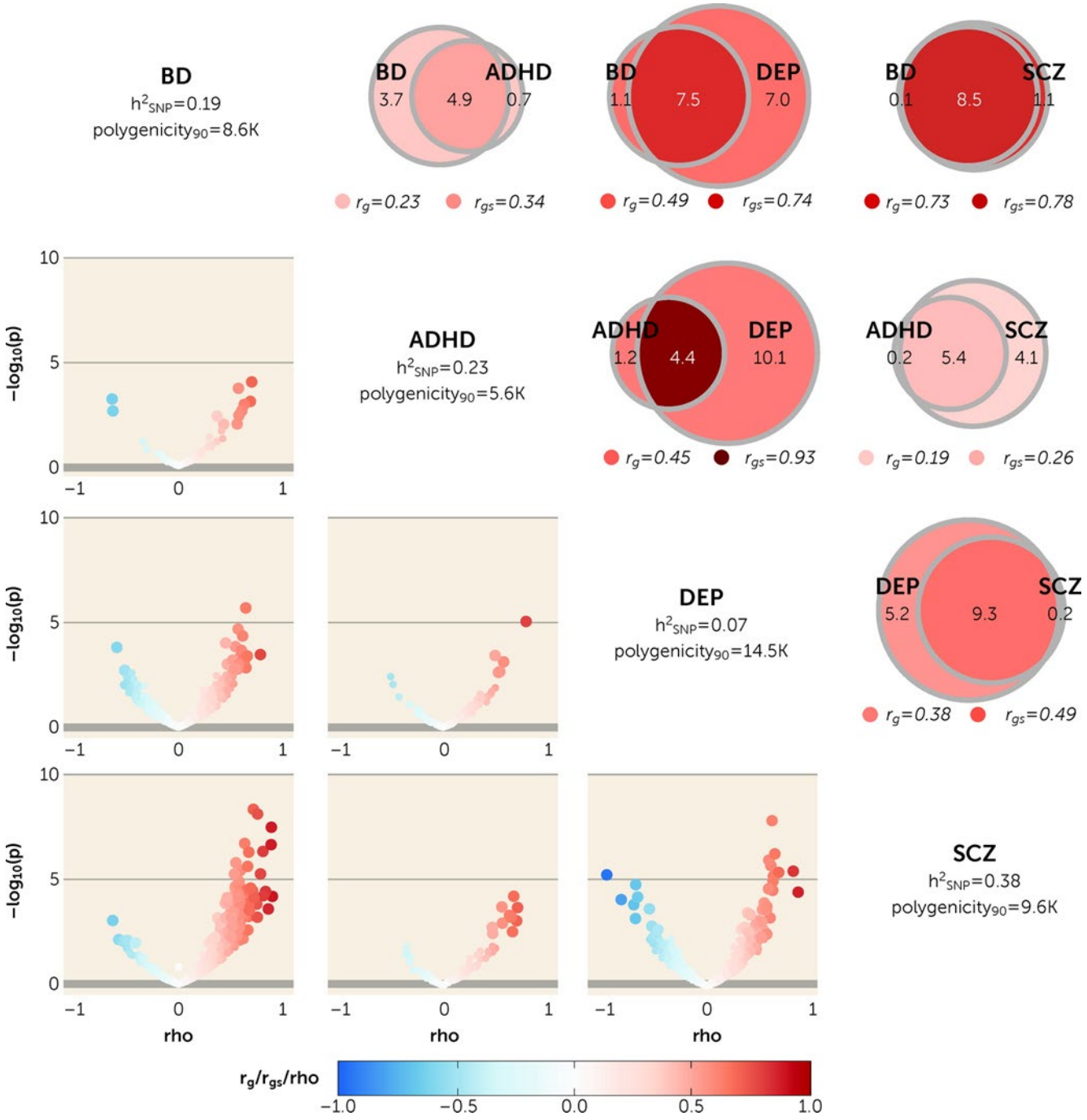

Polygenicity and Pleiotropy

- Red and Pink Circles represent overlap of SNPs (risk variants) for the major mental disorders
- Polygenicity represents number of variants in disorder

- **Volcano Maps lower left of figure**
  - Red dots- genes positively correlated with both disorders
  - Blue dots- alleles for genes in opposite direction of disorder- For gene- A- disorder 1, a- disorder 2

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Mapping the genetic landscape across 14 psychiatric disorders

- Nature 649:406, 2026, https://www.nature.com/articles/s41586-025-09820-3
- Functional genomic analyses applied to 14 childhood- and adult-onset psychiatric disorders (1,056,201 cases).
- Using genetic association data from common variants, we identified and characterized **five** underlying genomic factors that explained the majority of the genetic variance of the individual disorders (around 66% on average) and were associated with 238 pleiotropic loci.
- The shared genetic signal across the Schizophrenia-Bipolar factor was substantially enriched in genes expressed in excitatory neurons, whereas the Internalizing factor was associated with oligodendrocyte biology.

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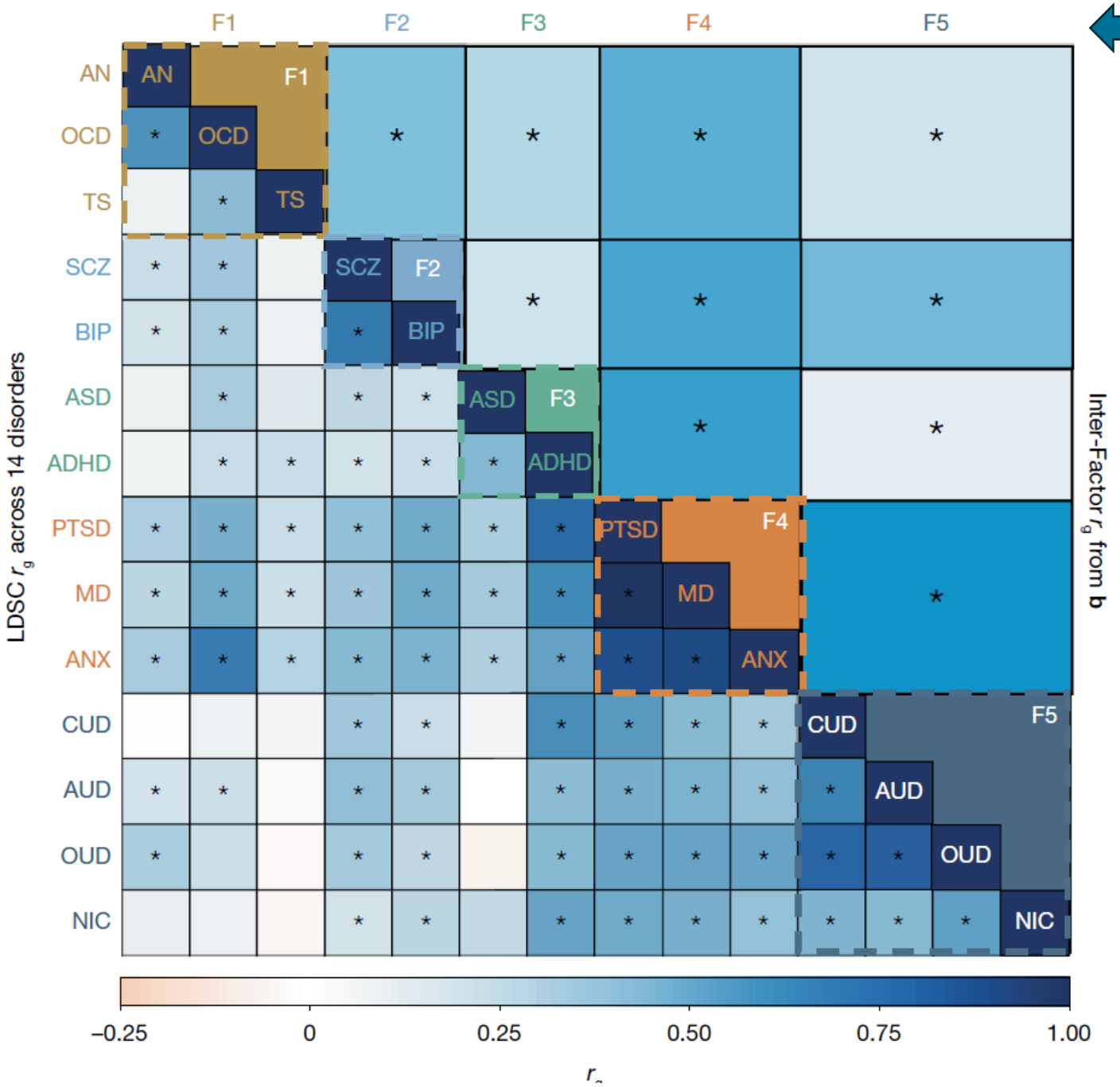

Five Genetic Groupings

- Blue Boxes represent strength of genetic correlation between disorders.
- The darker the blue, the greater the correlation.
- Disorders sort themselves into five major categories on the Heat Map

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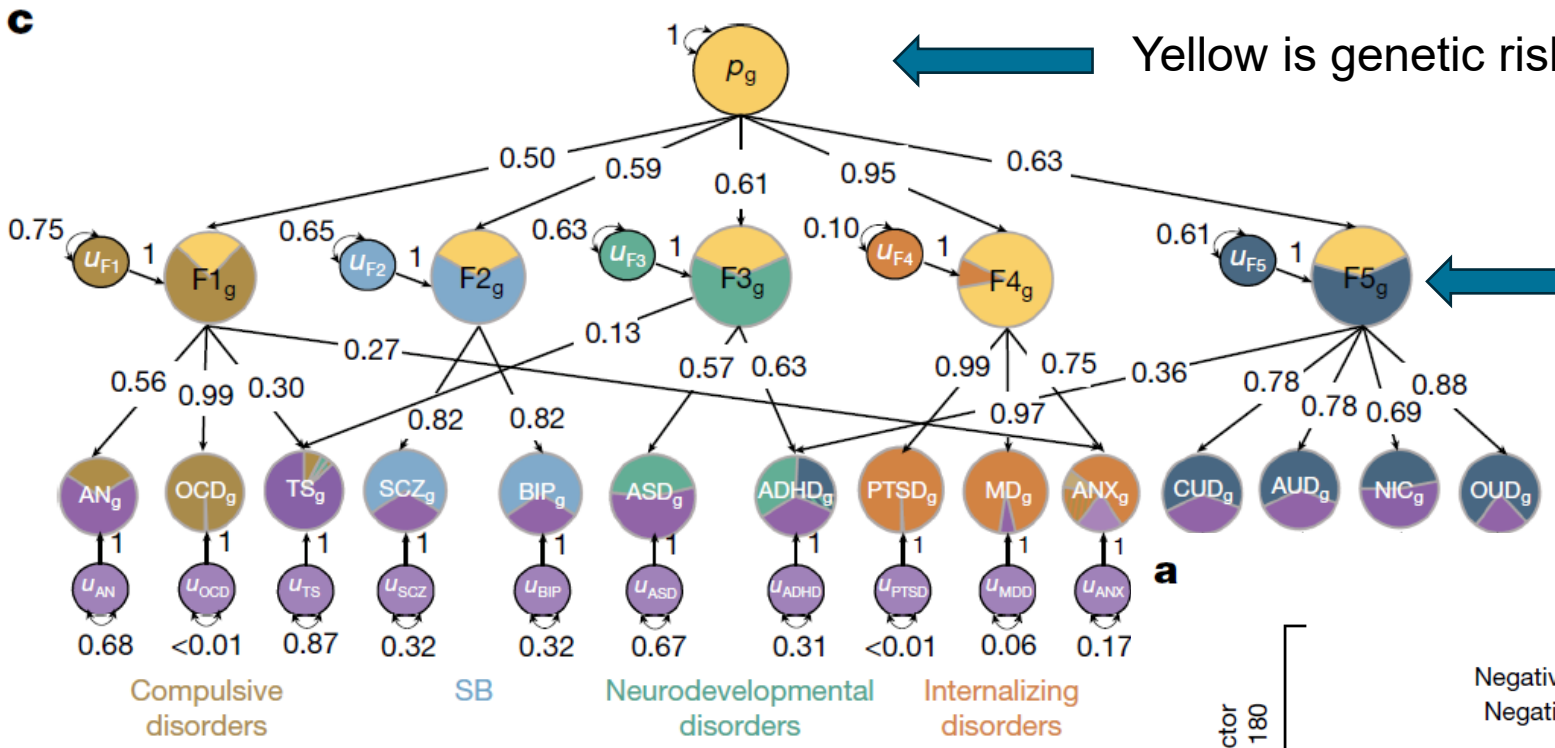
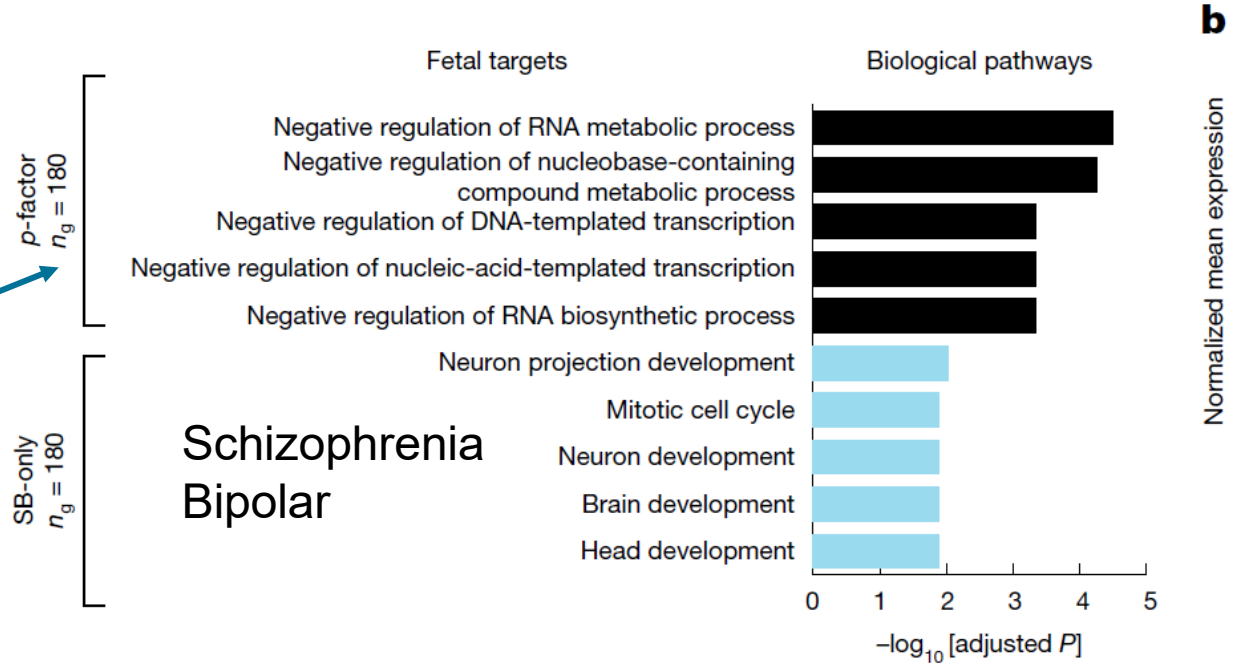


Yellow is genetic risk of all/any genetic risk for mental disorder

Colors represent risk for specific disorder in five groups



Schizophrenia
Bipolar

Processes associated with general psychopathology (P_g)

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Genetics in Psychopathology

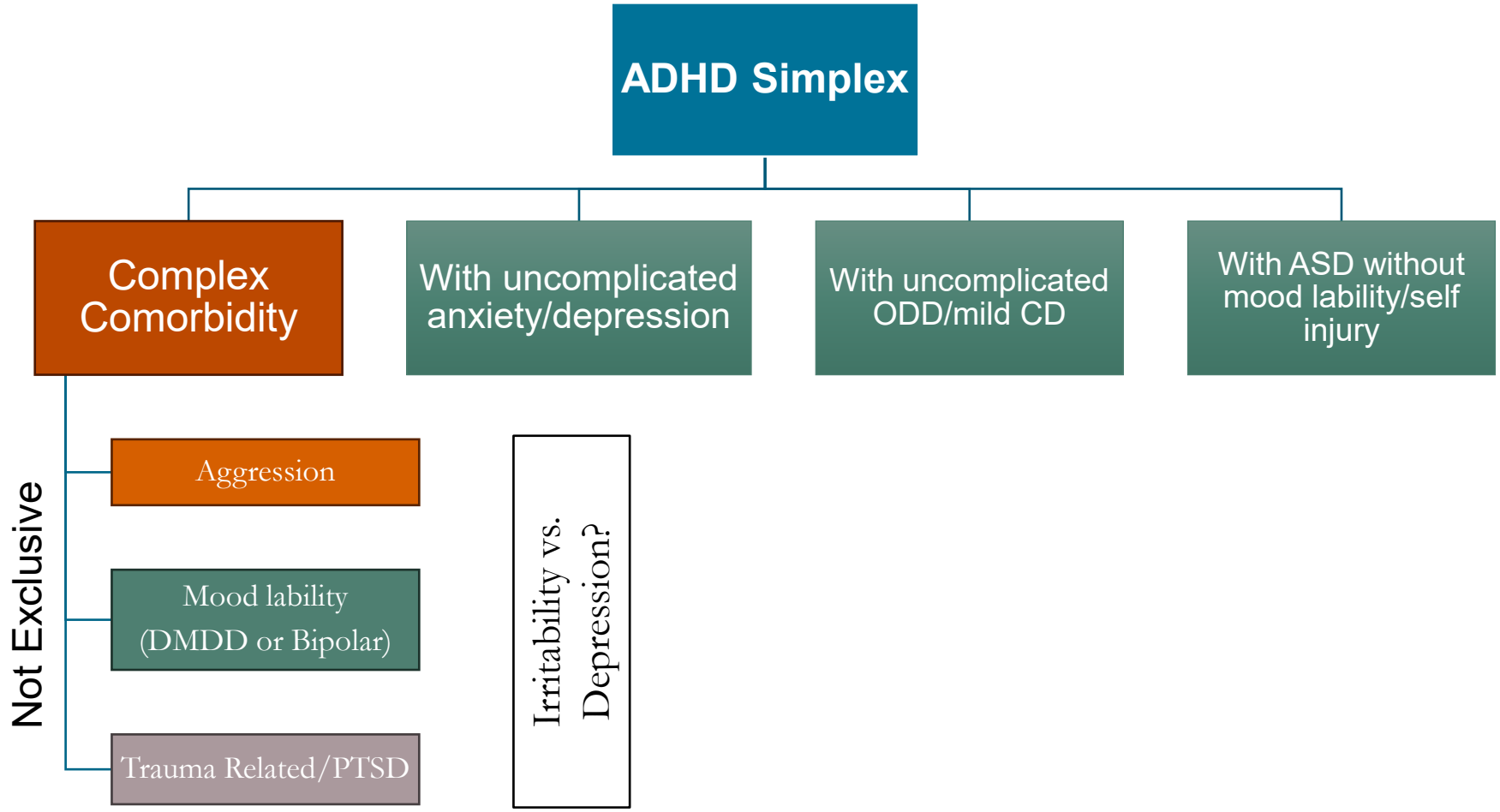
- SNPs (in the thousands) create a continuum of risk for any given individual.
- CNVs may underlay some of the risk, particularly in those with comorbid neurodevelopmental disorders.
- Genetic testing for at this point (except for ASD/ID) but watch for scientific developments.
- Disorders more alike than similar, but not the same
- **Comorbidity has a basis in biology, not simply in the vagaries of clinical interviewing**

Developing the Road Map

TIER ONE

TIER TWO

TIER THREE



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Depression and Irritability: Same or Different?

- DSM-III introduced criteria that in children and adolescents, irritability could be a proxy for depression.
- To meet DSM criteria for MDD a child should be persistently irritable (at least two weeks) and meet other DSM depression criteria.
- Always assumed the Irritable mood only, sad mood only and sad/irritable were equivalent.
- May have led to highly heterogenous groups being included in antidepressant trials- and a high placebo response rate and a small subgroup who get increased agitation and SI.
- Assumption that irritability of autism spectrum disorder is a depressive/anxiety symptoms that will respond to SSRIs- despite negative trials of SSRI in ASD (King et al. 2009).

Depression and Irritability: Same or Different?

Clinician/Researcher	Contribution
Leibenluft (2011) AJP 168:129	Led NIMH research on severe mood dysregulation (SMD), established the construct of chronic non-episodic irritability as distinct from bipolar disorder, and demonstrated its longitudinal association with unipolar depression rather than mania. Her work directly informed the creation of **disruptive mood dysregulation disorder (DMDD)** in DSM-5.
Stringaris 2013 (JAACAP 52:831)	Conducted the landmark **Great Smoky Mountains Study** analyses (2013) that empirically tested—and largely refuted—the DSM's developmental rationale for irritability as a cardinal mood criterion. Found that irritability rarely occurred without depressed mood in youth, that it was not more common in younger children, and that the DSM's developmental distinction was not supported.
Brotman (JAACAP)	Advanced translational research on the neurobiology of irritability and called for evidence-based treatments for pediatric irritability as a transdiagnostic construct
Vidal-Ribas 2016,2021 (JAACAP, Child Psych Clin NA)	Comprehensive reviews (2016, 2021) synthesizing the validity of irritability as a distinct dimension and its specific associations with depression and anxiety

DMDD criteria in DSM-5

A. Severe **recurrent temper outbursts** manifested **verbally** (e.g. verbal rages) and/or behaviorally (e.g. **physical aggression** toward people or property) that are grossly out of proportion in intensity or duration to the situation or provocation.

B. The temper outbursts are **inconsistent with developmental level**.

C. The temper outbursts occur, on average, **three or more times per week**.

D. The mood **between temper outbursts is persistently irritable or angry most of the day**, nearly every day, and is observable by others (e.g. parents, teachers, peers).

E. Criteria A-D present for 12 or more months, never more 3 months without symptoms

F. Criteria A and D are **present in at least two of the three settings** (i.e. at home, at school, with peers) and are severe in at least one of these.

G. The diagnosis should not be made before age 6 or after age 18

H. Age of onset by age 10.

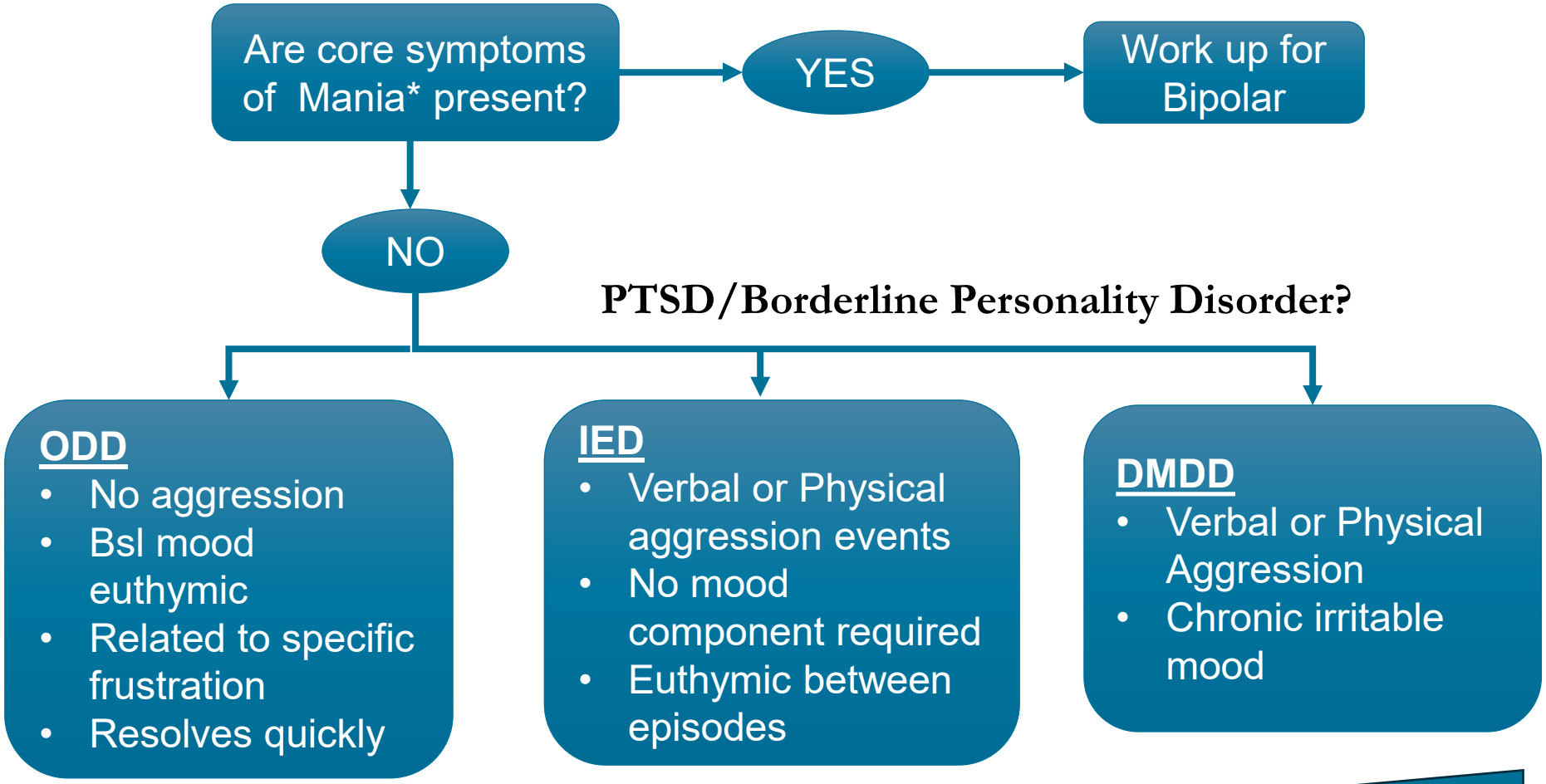
I. No history of mania

J. Not exclusively during another mental disorder. **Cannot be co-diagnosed with:**
   1. Oppositional Defiant Disorder
   2. Intermittent Explosive Disorder

K. Not due to direct effects of a substance

Differential Diagnosis of Mood Lability/Aggression

*Grandiosity, pressured speech, delusions, flight of ideas, decreased need for sleep



Comorbid Diagnoses

- Key issue is that DMDD is a descriptive diagnosis without a single presumed etiology
- Parents may need education on above point
- Other Diagnoses may contribute to it, including:
  - ADHD (most common)
  - Anxiety
  - MDD (follow up of NIH sample showed most developed MDD with time, not bipolar)
  - PTSD
    - Unwise to try to interpret aggression/mood lability as “responses to trauma” and thus only requiring trauma focused approaches for treatment
    - Note: SSRIs –have NOT been shown to be efficacious in pediatric PSTD (High placebo response rate, both controlled studies all participants receive psychotherapy)
- Irritable mood ends up being the primary state-then what do you do?

PTSD: Opportunities and Risks of Trauma Informed Care

Opportunities	Risks
• Active treatments that address specific issues of abused children • Promotes understanding of behavior of abused children in caretakers, educators and health professionals • Advocates for evidenced-based psychotherapy for abused children • Provides a framework for advocacy	• Becomes a buzzword or cliché for virtue signaling • Becomes a reason for inaction (“That’s what these kids do!) • Naiveté that a few sessions of therapy focused on the “trauma” will solve the problem • Often very antipsychiatry/ anti-psychotropic • May repeat the mistake of deinstitutionalization of the mentally ill 50 years ago- closing of RTCs over-reliance on foster care

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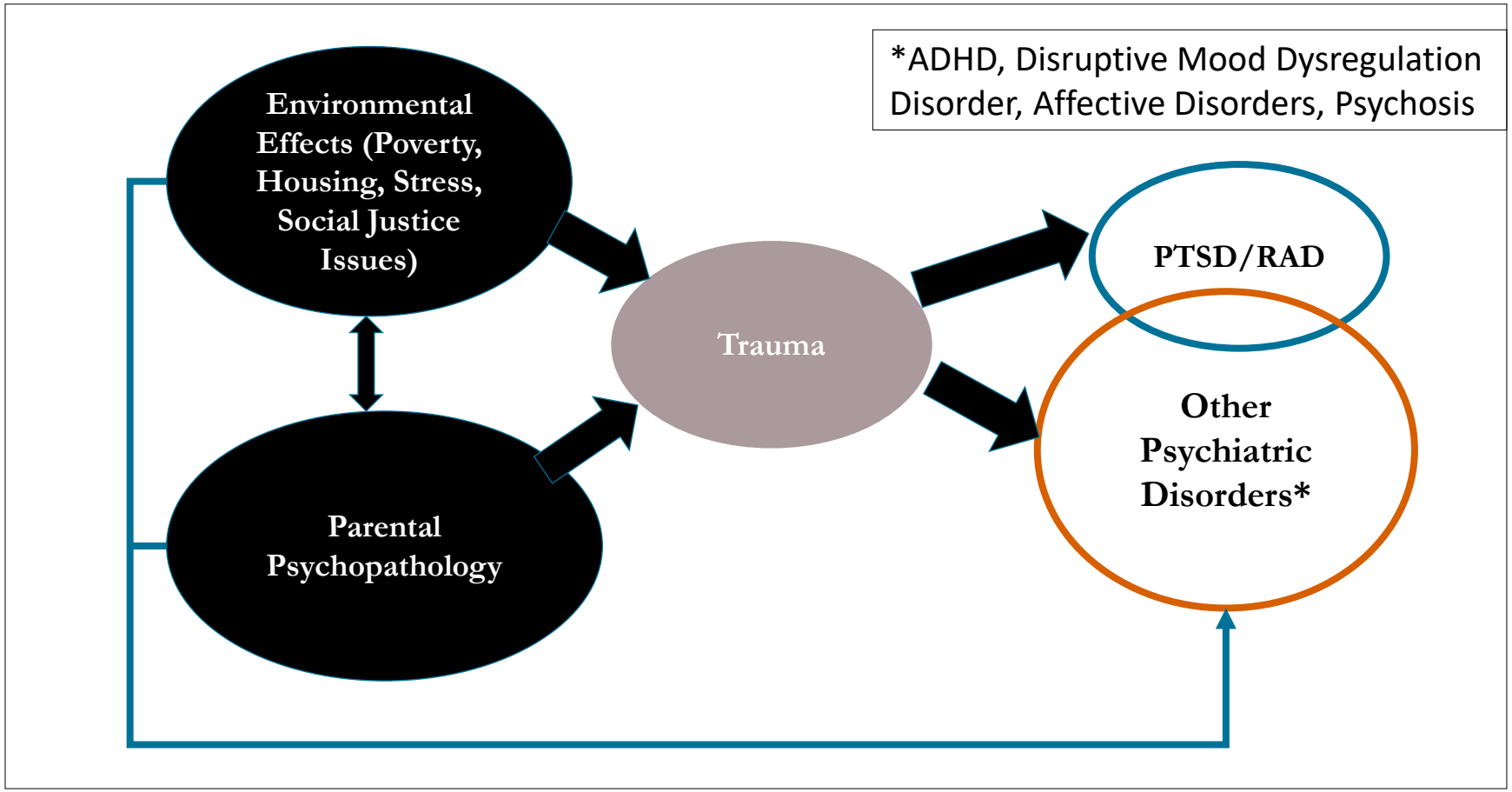
ADHD and PTSD

- ADHD is a risk factor for child abuse, treatment of the underlying ADHD reduces risk of further abuse (Lin et al. J Child Adol Psychopharm 33:59, 2023).
- ADHD almost always predates the onset of trauma
- In family history studies, PTSD is only found in the relatives of probands with PTSD or ADHD+PTSD, NOT in those with ADHD alone. (Biederman et al. Acta Psychiatrica Scandinavica 128:78, 2013). This makes it unlikely that many ADHD people in reality had PTSD.
- Danger of circular reasoning: All problems are from “Complex Trauma” or “a “Trauma related disorder”. Therefore, psychiatric symptoms means a trauma was there and it has to “uncovered”.
- In most cases, the ADHD and PTSD are comorbid, both should be treated

Conceptualizing PTSD and Its Comorbid Disorders



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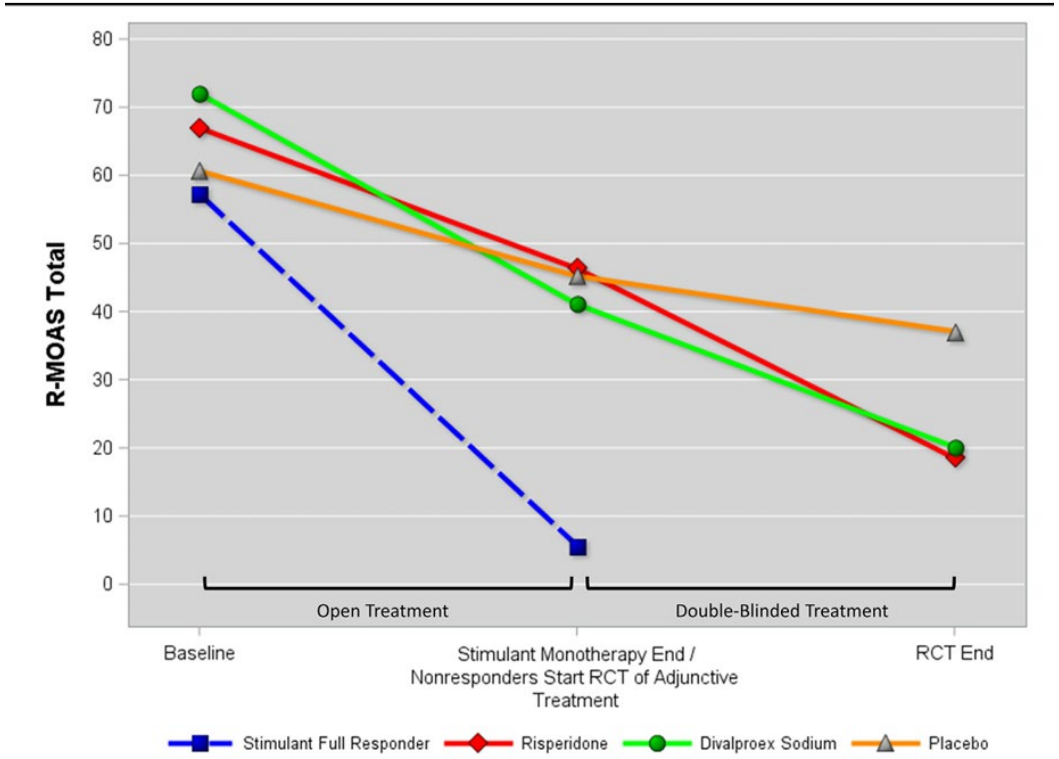
Two different pharmacological approaches to mood lability

Step 1: Fully treat ADHD first

Step 2:

Add SGA/Mood stabilizer?



Blader et al, JAAAP 60:236, 2021

Add SSRI?

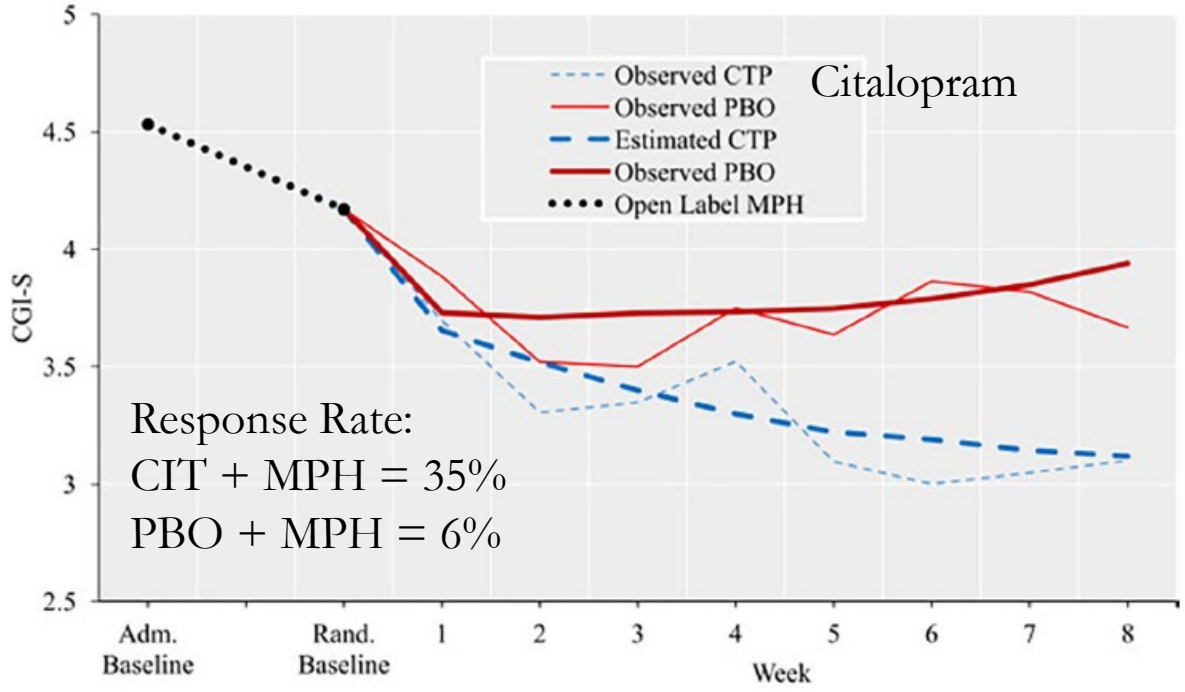


FIGURE 2. Change in Irritability Severity Before and After Randomization in the Sample Included in the Intent-to-Treat Analysis

Towbin et al, JAAAP 59:350, 2020

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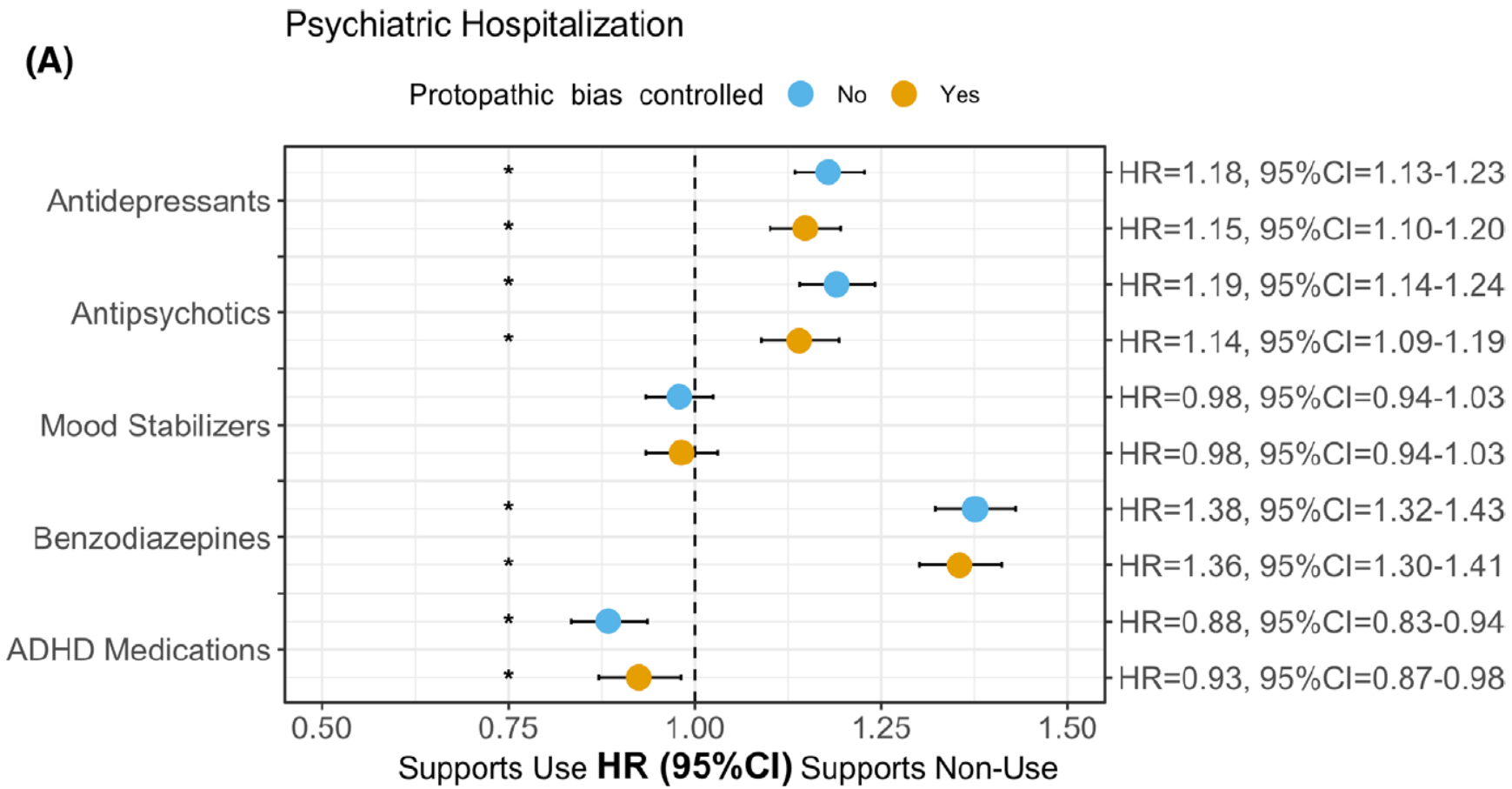
Pharmacology of BPD in real world

- Lieslehto et al. Acta Psychiatr Scand 147:603, 2023
- Look at EMR data in Sweden for 17,532 adult patients with BPD
- Hazard ratios (HR) calculated for:
  - psychiatric hospitalization and
  - Hospitalization owing to any cause or death.
- HR > 1 means mediation associated with worse outcome, <1 with better outcome

Pharmacology of BPD in real world



Among ADHD medication, stimulants had the LARGEST protective effect!

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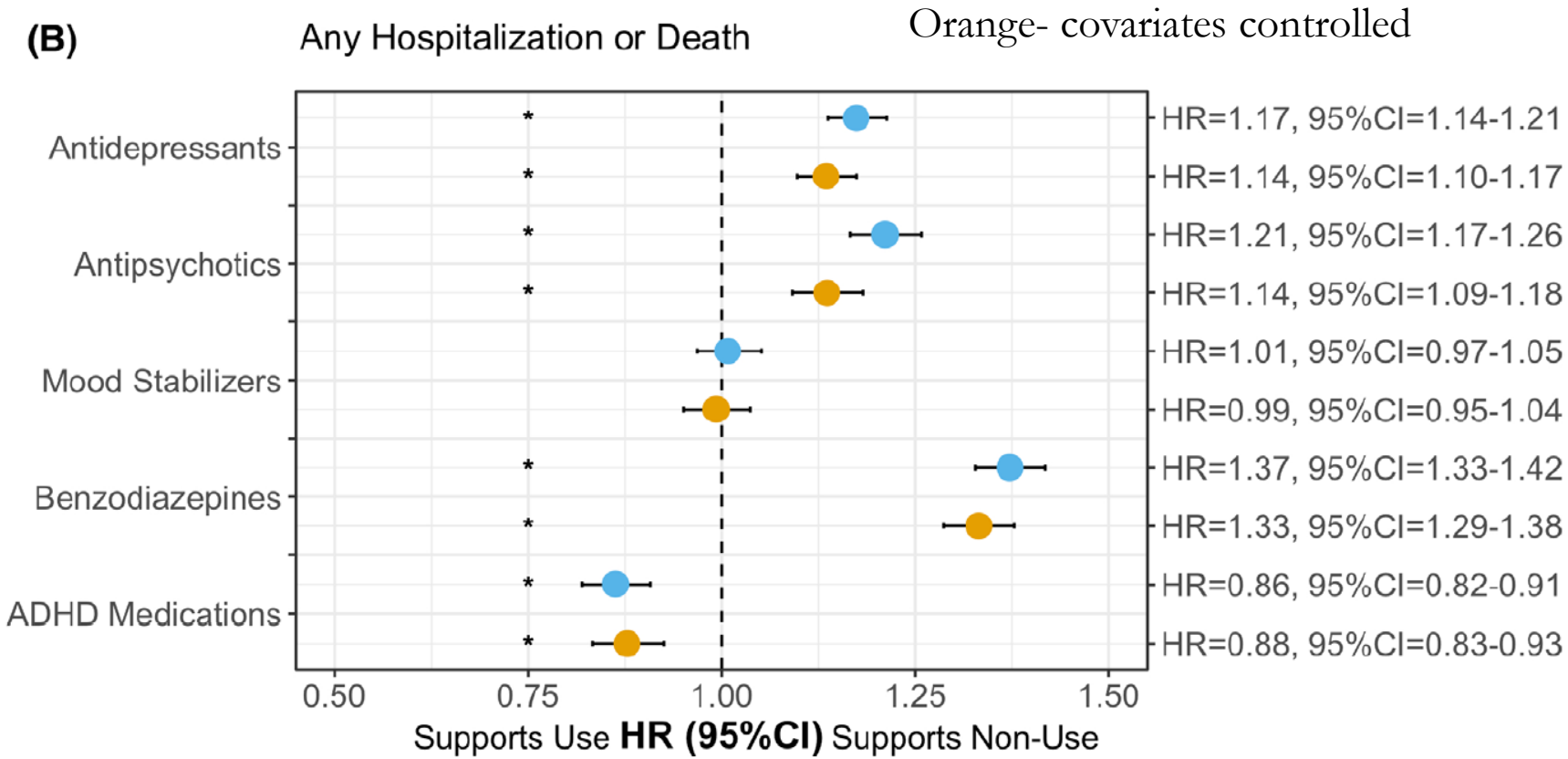
Pharmacology of BPD in real world



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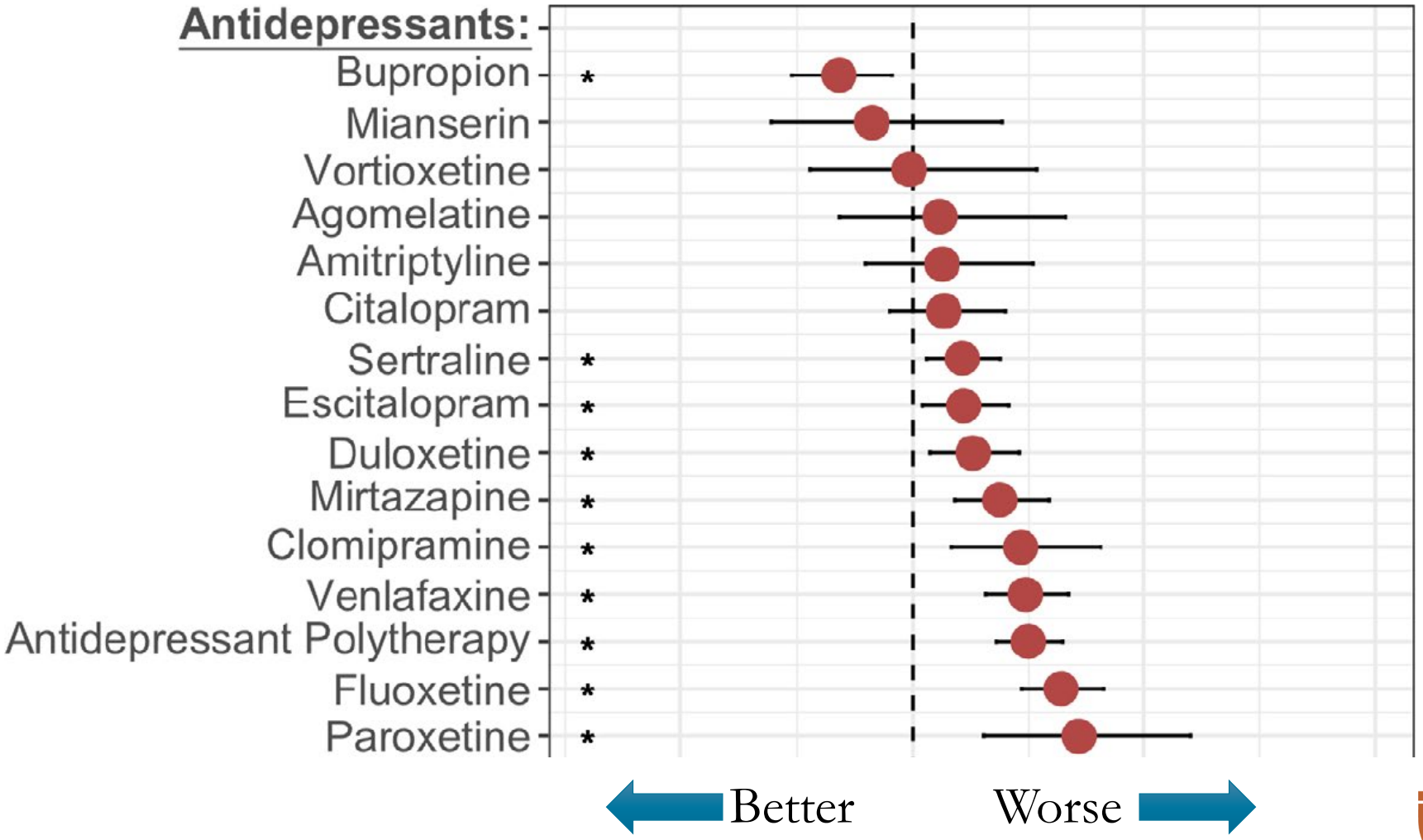
Pharmacology of BPD in real world



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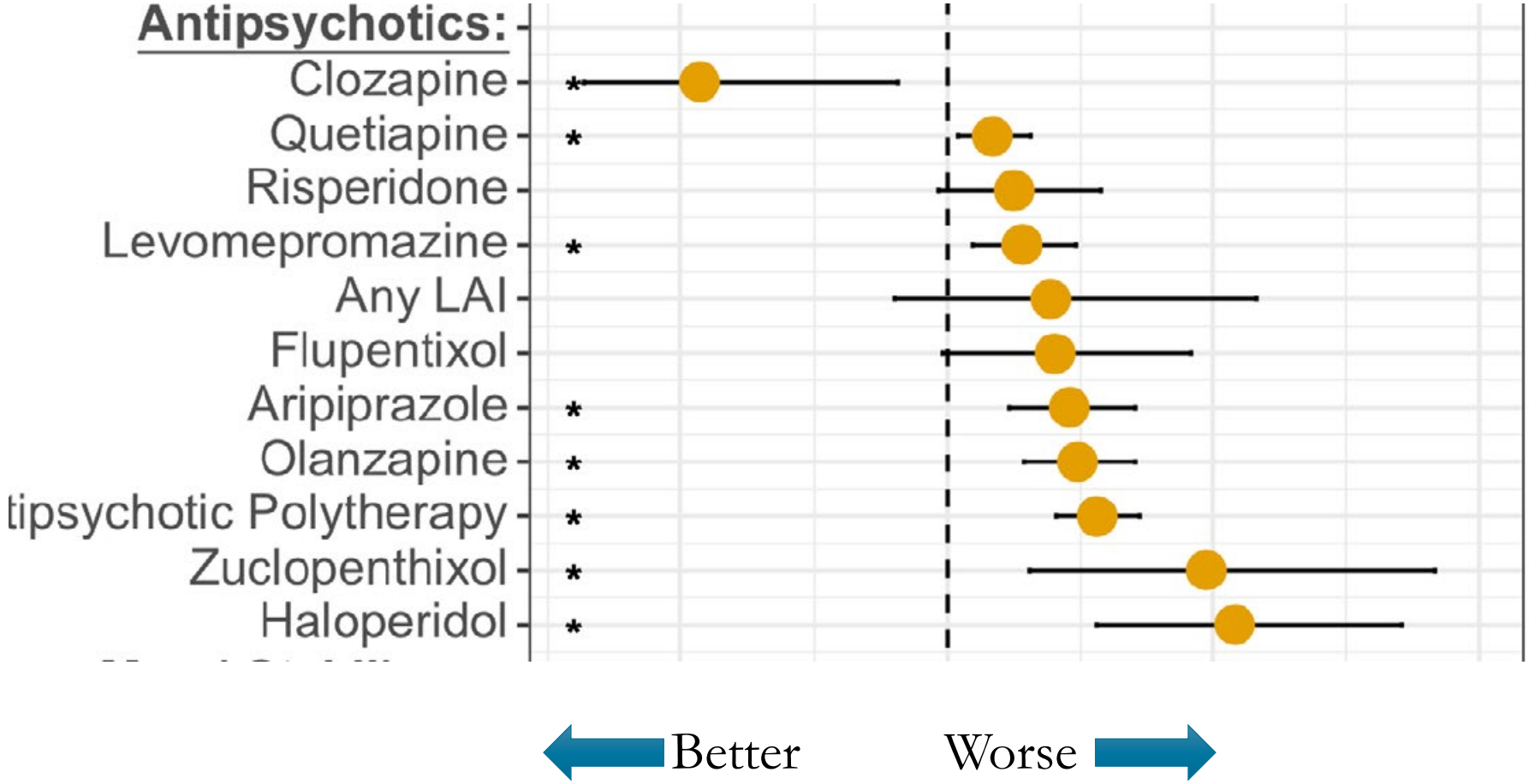
Pharmacology of BPD in real world



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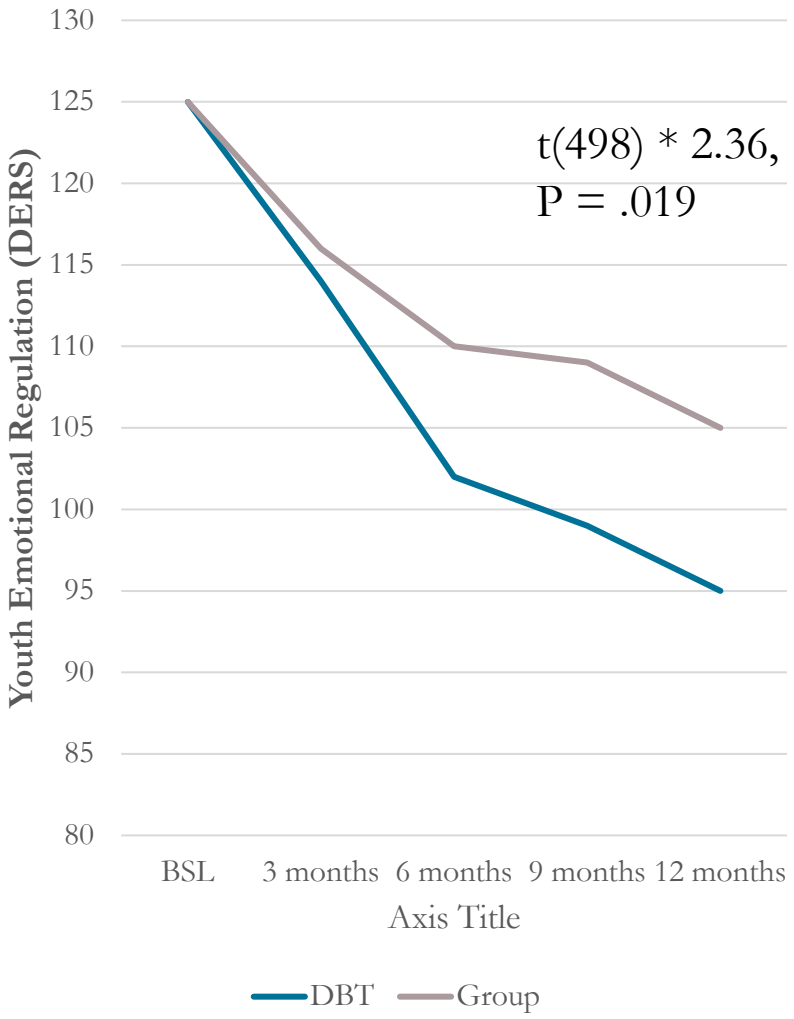
DBT for adolescents with self harm



- 49% had remission of self harm behavior at end of study.
- Reduced substance use
- Parents involved in multi-family group and parents used more DBT skills post treatment.

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Alexsis Treatment I: Mini-DBT

Step 1: Validation and Dialectics

- **Validation:** The therapist validates that the teen's pain is real and that the conflict with their peer or family feels catastrophic. "It is really disappointing when you planned something with friends"
- **The Dialectic**: The therapist holds the position that while the teen's feelings make sense, their *current way of coping* (suicidal ideation) is not effective for building a "life worth living." Alternatives to SI, how SI will lead Alexis, "where she wants does NOT want to be"

Alexsis Treatment I: Mini-DBT

- Step 2: Identifying the "Link" (Chain Analysis). The therapist conducts a **Behavioral Chain Analysis** to understand the upheaval.
  - **Vulnerability Factors:** Are you stressed? Hungry? Already stressed about other issues
  - **Prompting Event:** Mom setting limits
  - **Links**: The thoughts (“Mom wants to ruin my life"), body sensations (tight chest), and emotions (shame/anger) that led to the urge to self-harm
- Step 3: Crisis Management using **TIPP**
  - **Temperature:** Splashing cold water on the face to trigger the mammalian dive reflex and slow the heart rate.
  - **Intense Exercise:** Brief, high-intensity movement to "burn off" emotional energy.
  - **Paced Breathing:** Slowing down the breath to signal safety to the brain.
  - **Paired Muscle Relaxation**

Alexis Treatment III

- Provider able to defuse crisis in session with DBT techniques.
- Mood history not consistent with BP. No periods of mania or hypomania, rather chronic depression and irritability.
- History consistent with poor school performance despite high ability due to inattention, ADHD-RS appears validated.
- Early history consistent with dynamics of BPD.

Alexis- Treatment IV

- SSRI not effective, tapered off – 50 mg q d x 1 week, then DC (could immediately DC if side effects clearly present)
- Alexis was started on Concerta 18 mg q am, titrated to 54 mg q am over 3 weeks, improved school performance, fewer outbursts.
- Drug testing to discourage THC use
- Mother and daughter enrolled in DBT program- individual for Alexis, parent group for mother
- With time, Alexis was able to move beyond immediate mood regulation to dealing with object relation level issues

Clozapine in Youth

- Clozapine treatment show reduced rates of:
  - Hospitalizations
  - Emergency Department visits
  - Reduced suicidality
  - Reduced suicide mortality
  - Lower all-cause mortality rate compared to other antipsychotics

- Reviews consistently report the incidence of agranulocytosis in pediatric patients to be between 0.6% and 1.0%. Is **NOT** higher than in adults.
- Studies on pediatric patients report a wide range, with some finding that **13% to 31%** of youth on clozapine experience at least one episode of mild or moderate neutropenia (ANC < 1500/mm^3), higher than in adults.
- Risk factors: Younger age, male, African ancestry

Meltzer HY, et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial Arch Gen Psychiatry 60:82, 2003
Adnan et al. Clozapine for Management of Childhood and Adolescent-Onset Schizophrenia: A Systematic Review and Meta-Analysis. J Child Adolesc Psychopharm. 32:2, 2022

Maher et al. JAACAP 23:110, 2013
Schneider et al. European Psychiatry 29:1, 2014

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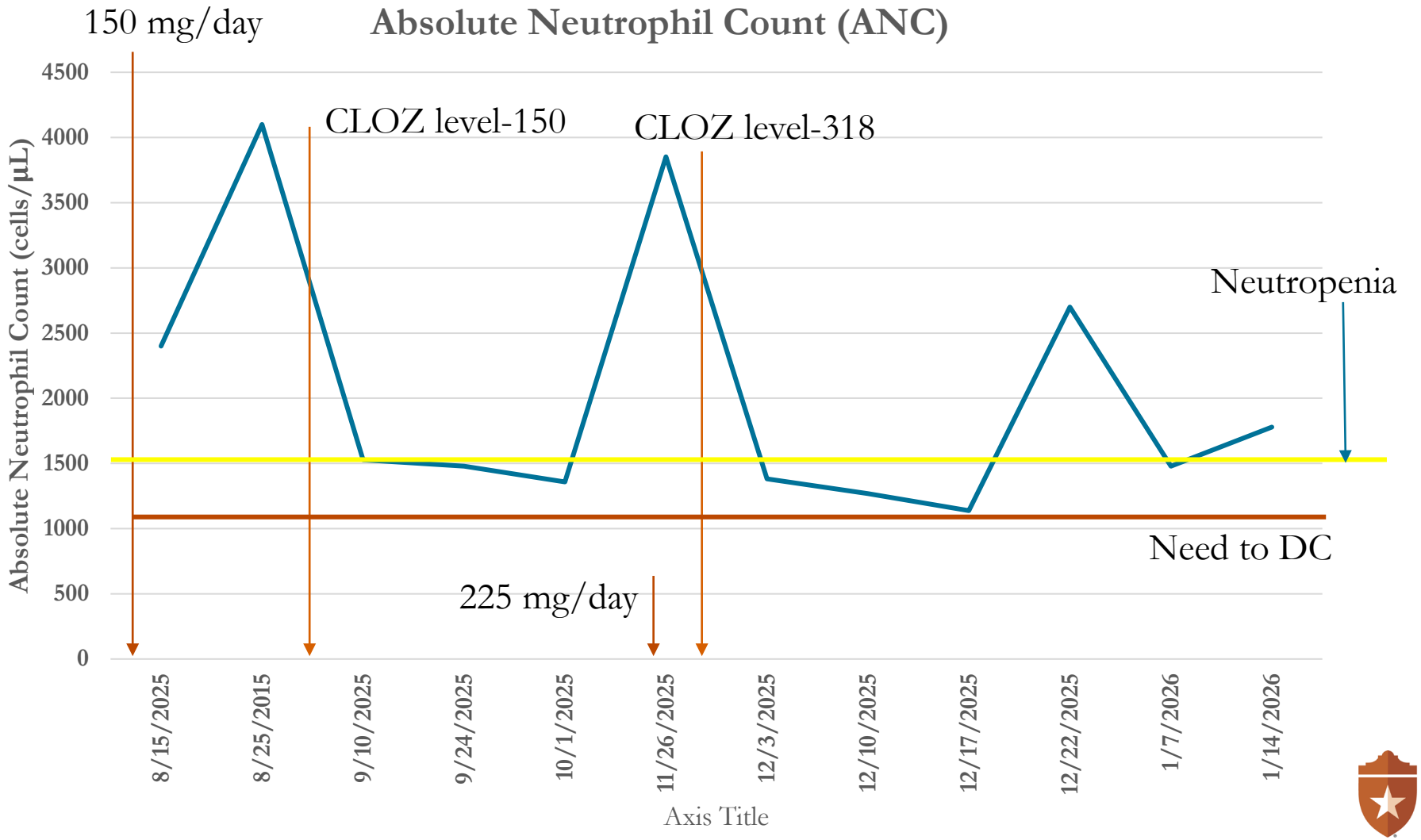
Case Study –Mac Treatment I



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Case Study: Mac Treatment II

Incident Start Date	Incident Types Requiring Interventions	Incident Start Time	Incident End Time	Duration in minutes	Restraint performed?
09/12/2025	Physical Aggression/Posturing	7:48 AM	7:59 AM	11	1
09/12/2025	Physical Aggression/Posturing	6:14 PM	6:24 PM	10	1
09/13/2025	Damage to Property|Physical Aggression/Posturing	8:50 AM	9:00 AM	10	1
10/31/2025	Physical Aggression/Posturing	8:30 PM	8:40 PM	10	0
11/01/2025	Damage to Property|Physical Aggression/Posturing|Verbal Aggression	8:59 AM	9:21 AM	22	1
11/06/2025	Damage to Property|Physical Aggression/Posturing	7:15 AM	7:55 AM	40	0
11/09/2025		12:01 PM	12:01 PM	0	0
11/10/2025		6:15 PM	7:25 PM	70	0
11/12/2025	Physical Aggression/Posturing	6:25 PM	6:35 PM	10	0
11/15/2025	Physical Aggression/Posturing	5:00 PM	5:20 PM	20	1
11/17/2025	Physical Aggression/Posturing	6:00 PM	6:30 PM	30	0
12/05/2025	Physical Aggression/Posturing	4:39 PM	4:44 PM	5	1

Clozapine increased

No incidents after 12/5/2025
Had good Christmas Pass!
March 2026- ANC normal!

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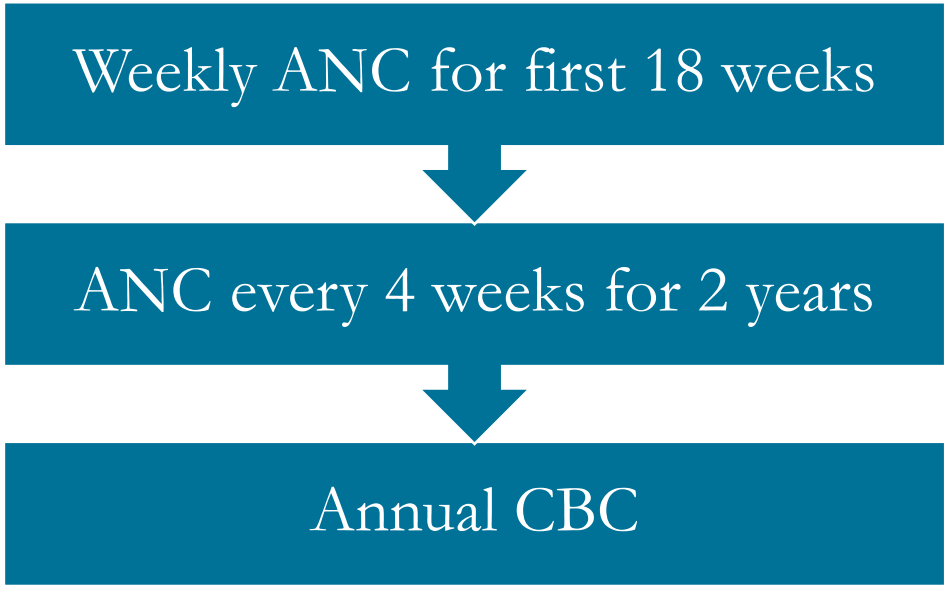
ANC Monitoring



- Severe Neutropenia (ANC <500 cells/mm^3)
  - Overall risk: <0.8%
  - Peak in 30-54 days
  - Highest in 18 weeks
- Neutropenia (ANC < 1500)
  - Overall risk: 4%

ANC threshold: 1000 cells/mm^3

Benign Ethnic Neutropenia <500 cells/mm^3

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Thank you and Questions!
Please visit my Substack:
“Why We Need Psychiatry”
Drstevepsychiatry.substack.com

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