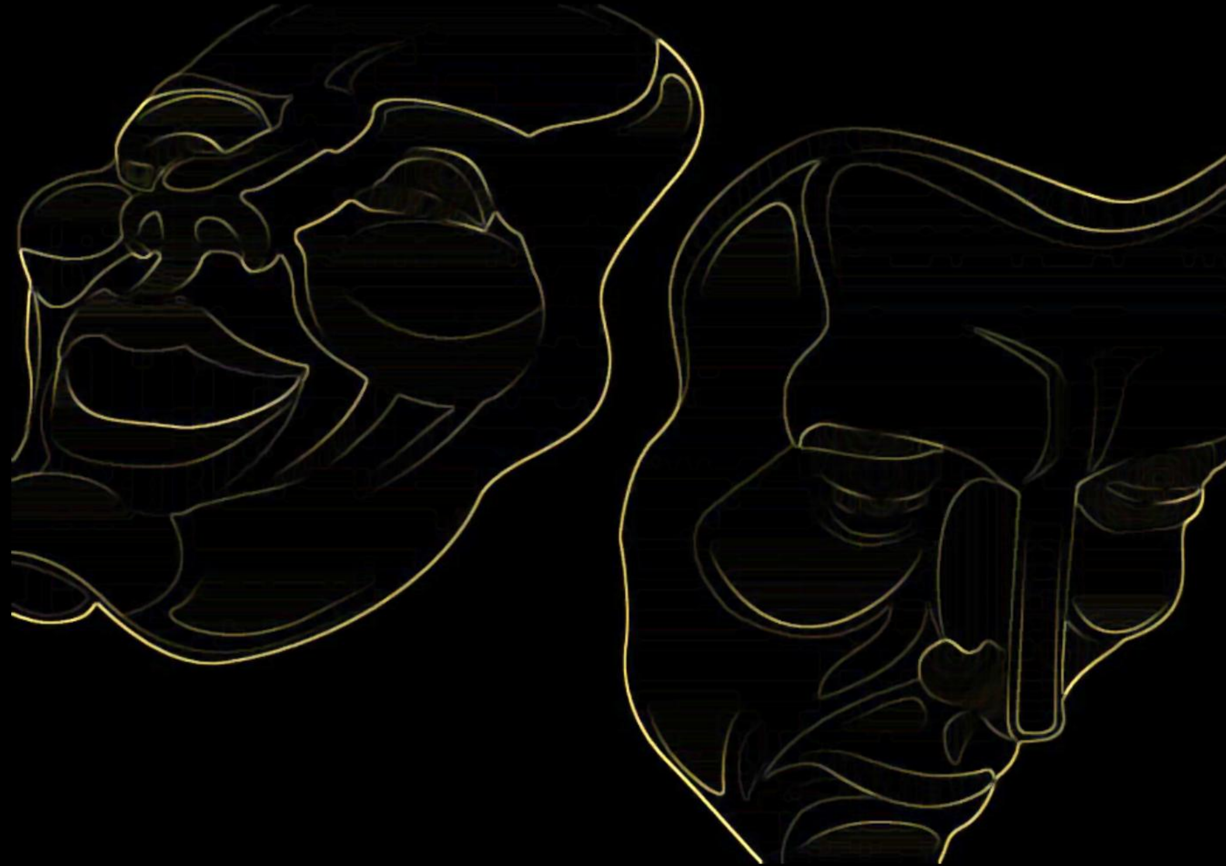
Comorbidity in bipolar disorder



OUTLINE

- INTRODUCTION
- ROLE OF GENDER
- PSYCHIATRIC COMORBIDITIES
- MEDICAL COMORBIDITIES
- DISORDERS RELATED TO PHARMACOLOGIC TREATMENT
- FUTURE CONSIDERATIONS
- REFERENCES

INTRODUCTION

- Comorbidity refers to the occurrence of two syndromes in the same patient
- Clinical comorbidity is defined as one disorder influencing the course of, outcome of, or treatment response to a second coexisting disorder
- may be caused by genetic linkage or shared environmental exposures

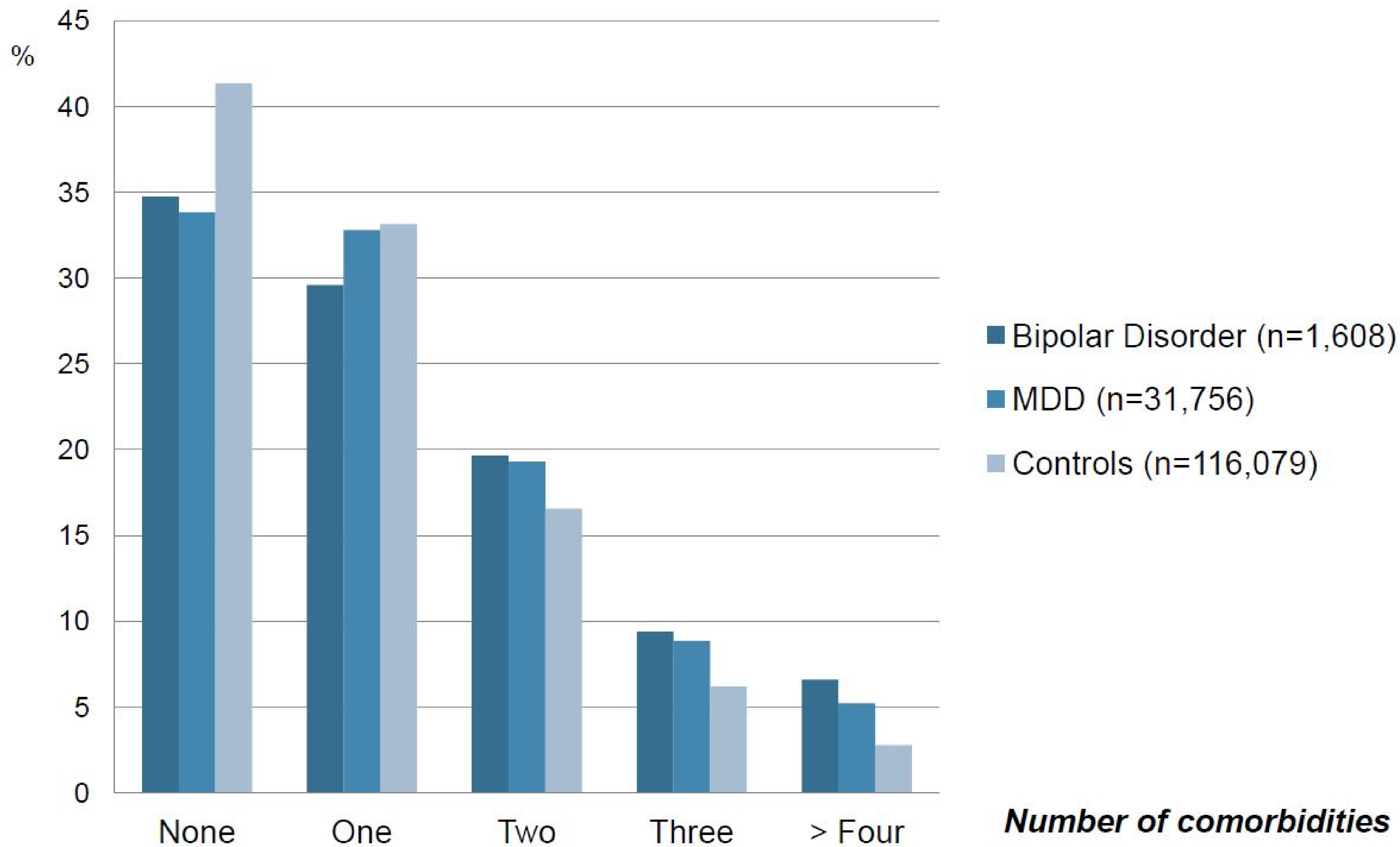
INTRODUCTION

- Bipolar prevalence : 1-2.4% (USA vs Global)
- 60 to 80% patients experience mood episode within the past two years, despite ongoing treatment
- Both psychiatric and medical comorbidity is highly prevalent (lifetime psychiatric comorbidity in bipolar I samples range from 50% to 70%)
- impacts clinical outcome (poor outcomes)
- The life expectancy of patients with BD is reduced by ten years or more

- Coexistence of other Axis I disorders and Axis II personality disorders with bipolar disorder complicates psychiatric diagnosis and treatment
- bipolar symptoms of mood disturbance, anxiety, and psychosis overlap with those of other psychiatric conditions
- unclear whether medical disorder is truly comorbid, a consequence of treatment, or both
- General medical conditions might be under detected

TABLE 1. Comorbidity of Bipolar Disorder With Other Disorders

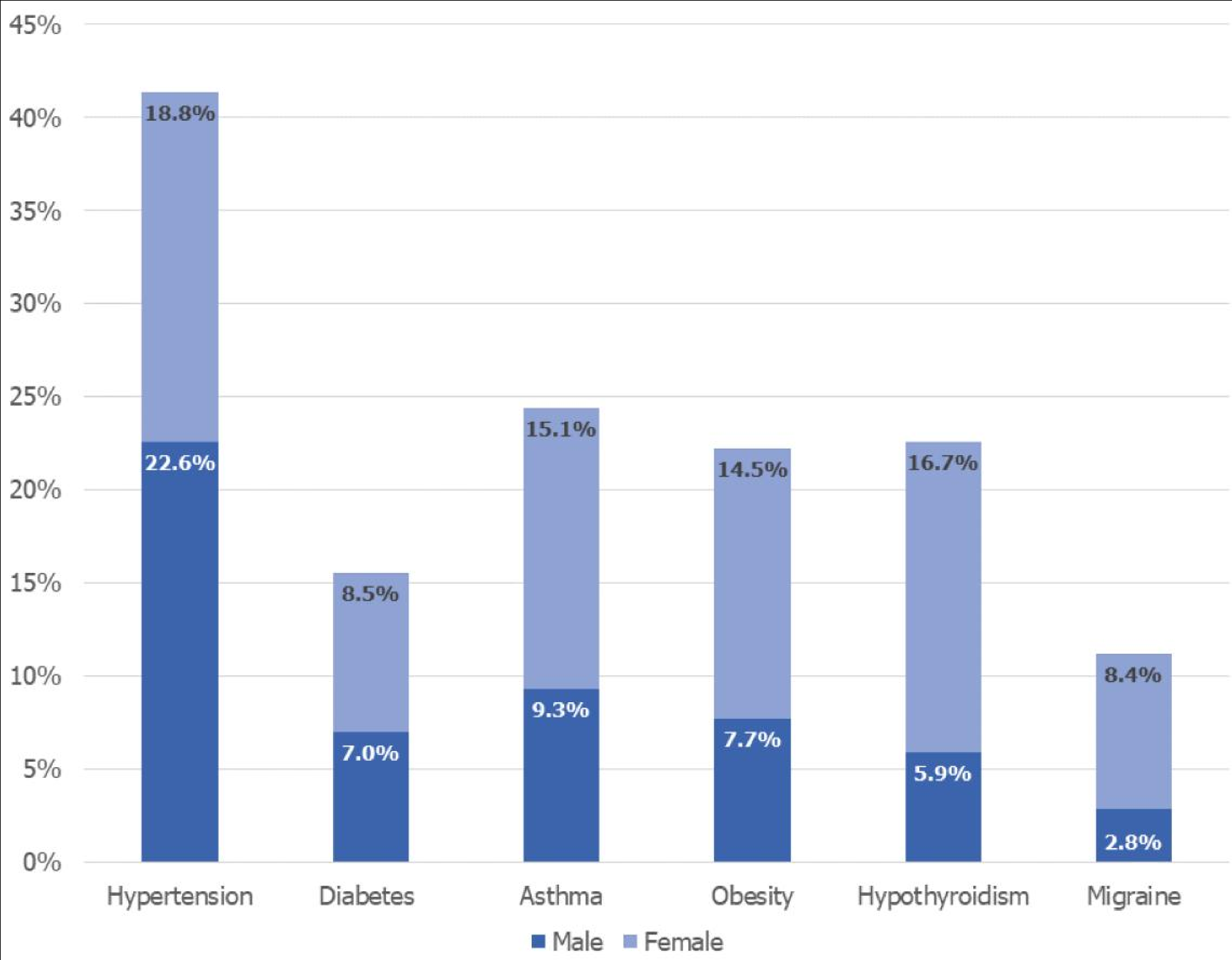
Comorbid Condition	Mean Rate of Comorbidity (%)	Percentage Range Across Studies (%)
Any Axis I disorder	65	50–70
Substance use disorder	56	34–60
Alcohol abuse	49	30–69
Other drug abuse	44	14–60
Anxiety disorder	71	49–92
Social phobia	47	
PTSD	39	
Panic disorder	11	3–21
OCD	10	2–21
Binge-eating disorder	13	
Personality disorder	36	29–38
Migraine	28	15–40
Overweight	58	
Obesity	21	
Type 2 diabetes	10	
Hypothyroidism	9	



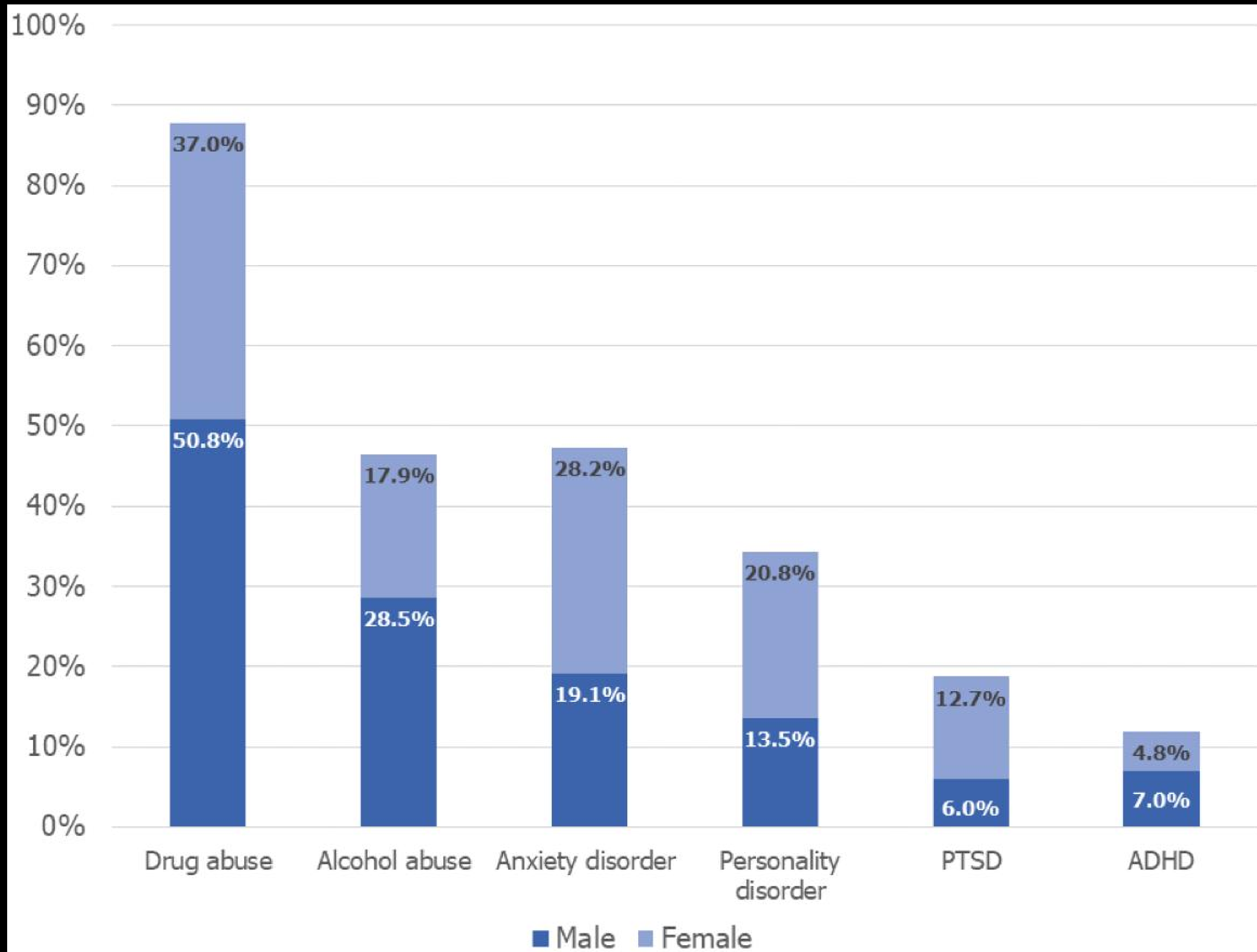
%
45
40
35
30
25
20
15
10
5
0
None
One
Two
Three
> Four
Number of comorbidities
Bipolar Disorder (n=1,608)
MDD (n=31,756)
Controls (n=116,079)

GENDER DIFFERENCES

- Except for substance use disorders, medical and psychiatric comorbidity is more common in women than in men
- bipolar women have much higher prevalence of alcohol and substance use disorders than do women in community samples
- Thyroid disease, obesity, and anxiety disorders are more prevalent in bipolar women



45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
18.8%
22.6%
8.5%
7.0%
15.1%
9.3%
14.5%
7.7%
16.7%
5.9%
8.4%
2.8%
Hypertension
Diabetes
Asthma
Obesity
Hypothyroidism
Migraine
Male
Female


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
37.0%
50.8%
17.9%
28.5%
28.2%
19.1%
20.8%
13.5%
12.7%
6.0%
4.8%
7.0%
Drug abuse
Alcohol abuse
Anxiety disorder
Personality disorder
PTSD
ADHD
Male
Female

Anxiety Disorders

- Anxiety disorders and substance use disorders that cluster together in bipolar patients can pose a therapeutic challenge as well as a diagnostic dilemma (overlap in terms of common symptoms)
- In general lower rates in BDI vs BDII and early onset acts as risk factor
- Patients with comorbid anxiety disorders more often reported pharmacologically induced hypomanic episodes
- Anti anxiety compounds often have risk of switch and destabilizing the course
- Preferable therapeutic options includes CBT

Generalized Anxiety Disorder

- meta-analysis shows lifetime prevalence 13.3%
- anticonvulsant such as lamotrigine or valproate or an atypical antipsychotic such as quetiapine or olanzapine plus fluoxetine in optimized dosage show efficacy
- Gabapentin also useful in treating comorbid anxiety
- agomelatine and vortioxetine are also effective in treating GAD
- duloxetine and venlafaxine not recommended due to their potential higher risk of mood destabilization

Social Anxiety Disorder

- National Comorbidity Survey reported 39 percent patients with any type of bipolar disorder have Social anxiety disorder
- Bipolar II disorder may be the common link in comorbidity between social phobia and alcohol abuse
- pregabalin and gabapentin are preferred options
- CBT effective in treating primary SAD and in comorbid patients as well

Panic Disorder

- 14 to 27 percent of pts have panic disorder
- up to 35 percent report experiencing panic attacks
- Post hoc evidence that gabapentin is useful in severe PD
- addition of an atypical antipsychotic such as quetiapine or risperidone may be appropriate

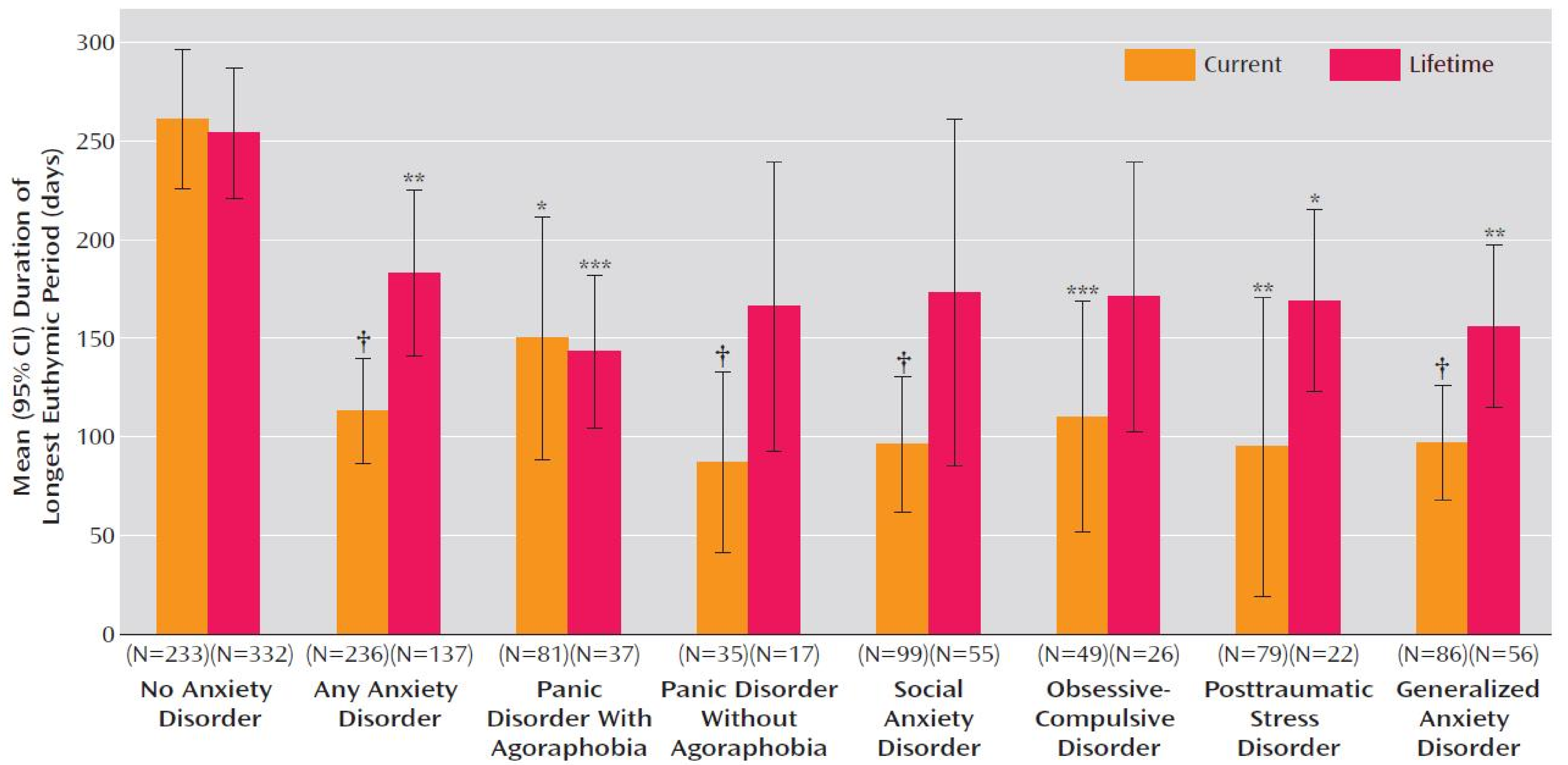
Obsessive–Compulsive Disorder and Related Disorders

- 10 to 25 percent of patients with bipolar disorder have a lifetime history of OCD
- Sexual and religious obsessions tend to be more common and their severity tends to wax and wane over lifetime
- clinical significance of the comorbidity between OCD and bipolar disorder is yet unclear – chronicity of course

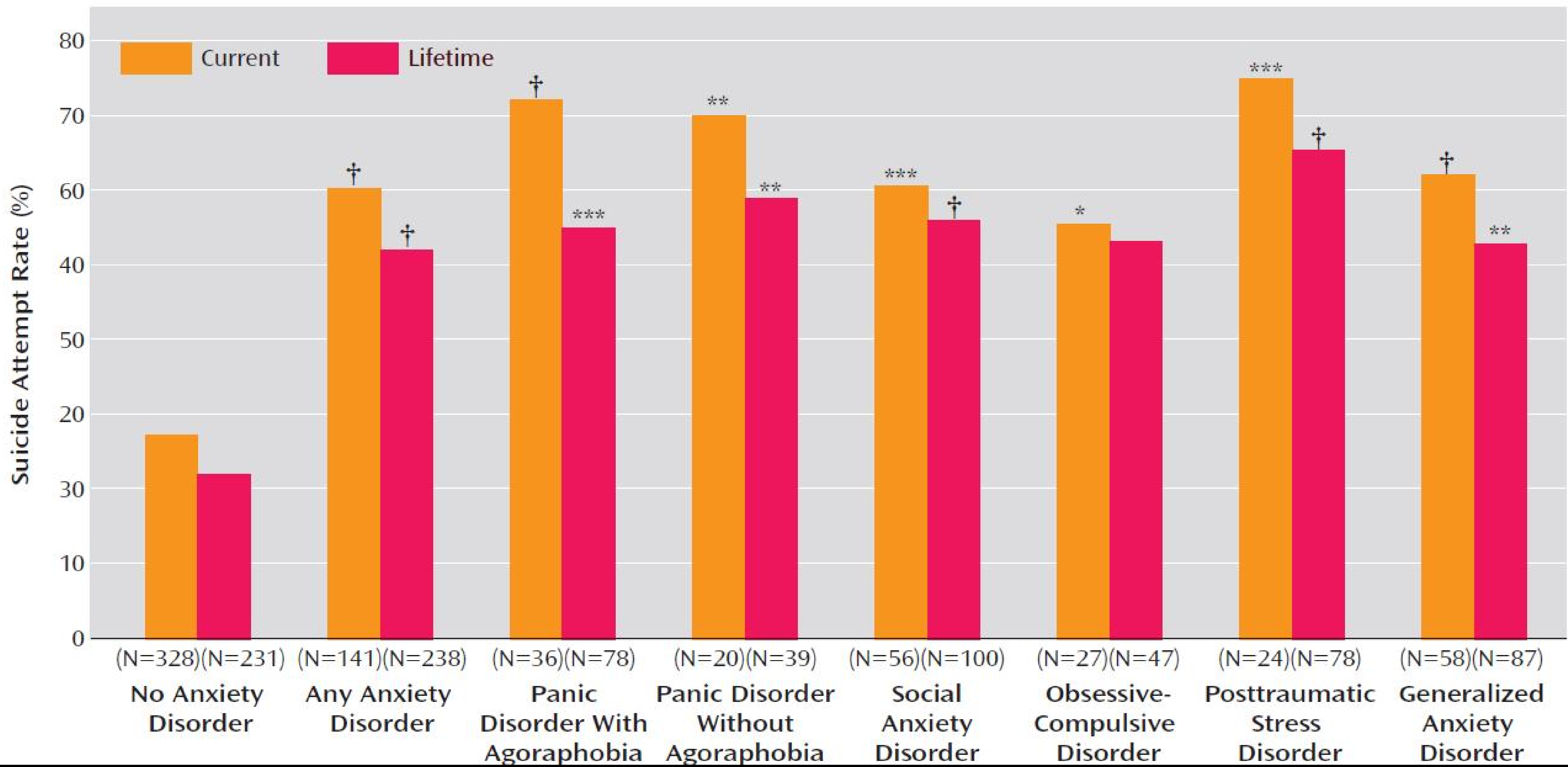
- treatment with lamotrigine, topiramate, or atypical antipsychotics such as risperidone, aripiprazole, olanzapine or quetiapine is effective in treating primary refractory OCD
- clomipramine not recommended in bipolar patients due to higher risk of manic switch

Post-Traumatic Stress Disorder

- range from 16 to 39 percent in patients with bipolar disorder
- Childhood sexual abuse, adult sexual assault, and adult survival of the suicide, homicide, or accidental death of a close friend or relative
- Anticonvulsants preferred particularly due to efficacy in reducing cravings for alcohol as abuse common in PTSD
- Atypical antipsychotic mono or adjunctive therapy beneficial for in treating symptoms of intrusion



Mean (95% CI) Duration of Longest Euthymic Period (days)
300
250
200
150
100
50
0
Current
Lifetime
**
*
***
†
†
†
***
**
*
**
†
(N=233)(N=332)
No Anxiety Disorder
(N=236)(N=137)
Any Anxiety Disorder
(N=81)(N=37)
Panic Disorder With Agoraphobia
(N=35)(N=17)
Panic Disorder Without Agoraphobia
(N=99)(N=55)
Social Anxiety Disorder
(N=49)(N=26)
Obsessive-Compulsive Disorder
(N=79)(N=22)
Posttraumatic Stress Disorder
(N=86)(N=56)
Generalized Anxiety Disorder


Current
Lifetime
Suicide Attempt Rate (%)
80
70
60
40
50
20
30
10
0
†
†
†
**
***
**
***
†
*
***
†
†
**
(N=328)(N=231)
No Anxiety Disorder
(N=141)(N=238)
Any Anxiety Disorder
(N=36)(N=78)
Panic Disorder With Agoraphobia
(N=20)(N=39)
Panic Disorder Without Agoraphobia
(N=56)(N=100)
Social Anxiety Disorder
(N=27)(N=47)
Obsessive-Compulsive Disorder
(N=24)(N=78)
Posttraumatic Stress Disorder
(N=58)(N=87)
Generalized Anxiety Disorder

Alcohol and Substance Use Disorders

- 52·3% of patients with bipolar I and 36·5% of patients with bipolar II disorder had a lifetime diagnosis of substance use disorder
- men twice as likely as women to have a comorbid substance use disorder
- prevalence of current smoking among individuals with bipolar I disorder range from 30 to 70%
- violent crimes reported in a longitudinal study of 3743 individuals with bipolar disorder was associated with substance abuse comorbidity

Comorbid Mood Disorders* and Substance Abuse

	Any substance abuse or dependence (%)	Alcohol dependence (%)	Alcohol abuse (%)
Any Mood Disorder	32.0	4.9	6.9
Any Bipolar Disorder	56.1	27.6	16.1
Bipolar I	60.7	31.5	14.7
Bipolar II	48.1	20.8	18.4
Unipolar Depression	27.2	11.6	5.0

- strong relationship between lifetime AUD/SUD and suicide attempts in BPAD individuals
- impulsivity is a shared characteristic of BPAD and AUD/SUDs – possible genetic basis
- Early onset BPAD is associated with the development of SUDs and is related to a more severe course of illness
- patients intoxicated with stimulants such as cocaine or methamphetamine can appear manic
- increasing evidence that cannabis use can act as a risk factor for the development of bipolar as well as psychotic disorders

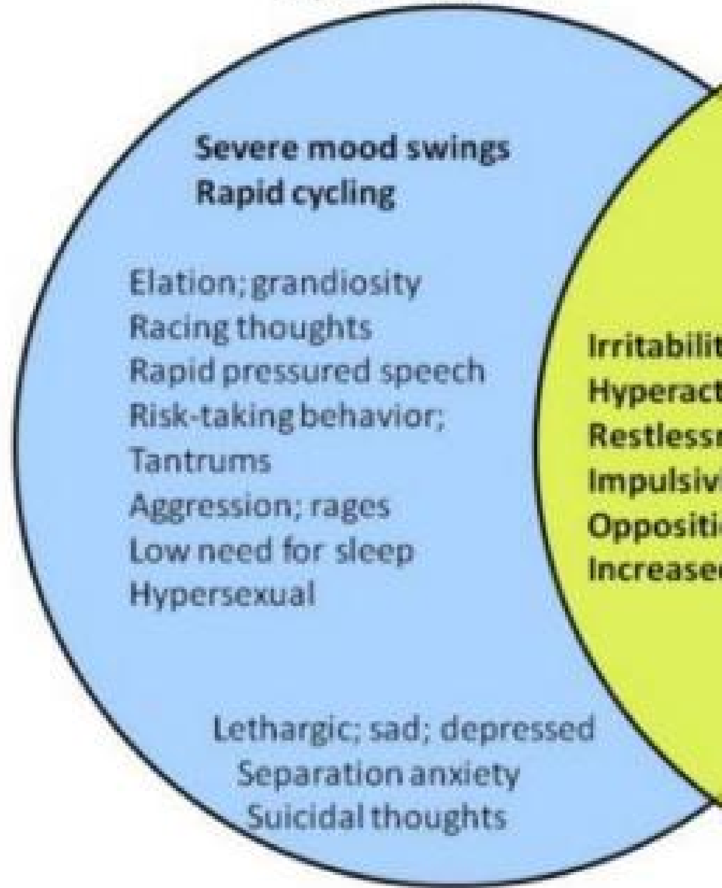
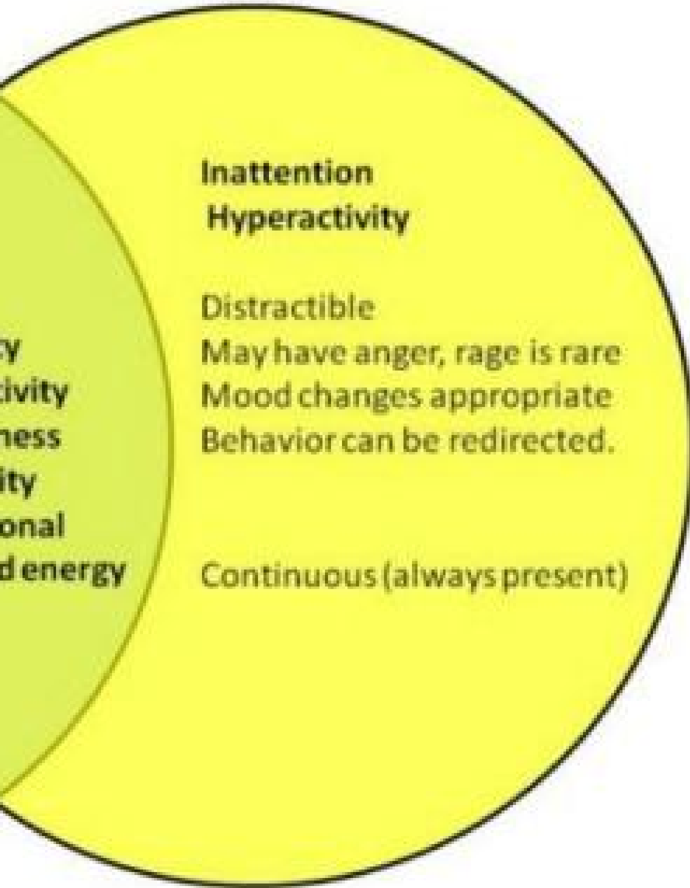
- several studies have reported that substance abuse is a predictor of poor response of bipolar disorder to lithium
- evidence that valproate effective in reducing various indices of alcohol use in bipolar patients with comorbid alcohol use
- Lamotrigine, gabapentin and topiramate have shown efficacy
- disulfiram not recommend in bipolar patients given its inhibitory effects on dopamine β-hydroxylase and the potential for worsening of mania
- Valproate, lamotrigine, quetiapine, and risperidone mono or add-on therapy appears to provide some benefit in patients with cocaine abuse

Eating Disorders

- 13% met criteria for binge-eating disorder, whereas an additional 25% met criteria for a partial binge-eating syndrome (Kruger et al)
- Binge eating > bulimia nervosa > anorexia nervosa
- Aggregation patterns suggesting common familial causal factors

Attention-Deficit Hyperactivity Disorder

- prevalence of ADHD ranges from 9 to 30 percent
- Bipolar patients with ADHD tend to have an earlier age at onset of mood symptoms, more frequent mood episodes, more suicide attempts, and other psychiatric comorbidities
- ADHD symptoms persist during euthymia and cause SOF impairment
- Persistent impulsivity and impaired ability for sustained attention despite treatment with mood stabilizing medications and absence of other symptoms of mood episodes - suspect for ADHD



Bipolar Disorder
ADHD
Severe mood swings
Rapid cycling
Elation; grandiosity
Racing thoughts
Rapid pressured speech
Risk-taking behavior;
Tantrums
Aggression; rages
Low need for sleep
Hypersexual
Lethargic; sad; depressed
Separation anxiety
Suicidal thoughts
Irritability
Hyperactivity
Restlessness
Impulsivity
Oppositional
Increased energy
Inattention
Hyperactivity
Distractible
May have anger, rage is rare
Mood changes appropriate
Behavior can be redirected.
Continuous (always present)
Medscape

- ADHD pharmacotherapy treatments can destabilize the course of bipolar disorder
- Atomoxetine associated with mania and hypomania or mood dysregulation or irritability in 33% of patients with ADHD
- bupropion is often the first choice
- Clonidine has also been reported to be effective
- In non responders, adjunctive modafinil or mixed amphetamine salts or methylphenidate could be considered
- Watch out for emergence of manic symptoms

Personality Disorders

- may complicate the diagnosis and course of bipolar disorder
- greater severity of residual mood symptoms than those without comorbid personality disorders, even during bipolar remission
- more frequent history of alcohol and substance use disorder
- Obsessive-compulsive and histrionic personality disorders most commonly diagnosed comorbid personality disorders
- mania in BD I and depression in BD II are predictive of some hypochondriac aspects

- Across studies approximately 10% of patients with Borderline PD had bipolar I disorder and another 10% had bipolar II disorder
- mood cycling in bipolar II disorder may be difficult to distinguish from cyclothymic temperamental and borderline personality disorder
  (affective instability, impulsivity, disinhibition on antidepressants)
- Research considering whether Borderline PD considered part of bipolar spectrum - differing conclusions
- more frequent history of substance abuse and childhood symptoms of ADHD
- divalproate may be safe and effective in borderline personality disorder and comorbid bipolar II disorder

Table : Preferred pharmacological treatments for comorbid psychiatric disorders commonly associated with bipolar disorder based on controlled data

Comorbid psychiatric disorder	Preferred treatments
Alcohol abuse or dependence	Divalproex, carbamazepine, topiramate[a]
Other substance abuse or dependence	Lithium
Panic disorder	SSRI[a]
Social phobia	SSRI[a], gabapentint
Obsessive–compulsive disorder	Risperidone, SSRI[a], quetiapine, olanzapine
Post-traumatic stress disorder	Risperidone, lamotrigine, olanzapine
Bulimia nervosa	Lithium, topiramate[a]
Anorexia nervosa	Lithium, olanzapine
Impulse control disorder (pathological gambling)	Lithium, SSRI[a]
Attention-deficit hyperactivity disorder	Mixed amphetamine salts/stimulants[a]
Personality disorder (borderline personality disorder)	Divalproex, lamotrigine, SSRIs[a], oxcarbazepine, atypical antipsychotic drugs

MEDICAL COMORBIDITIES

- unclear whether a medical disorder is truly comorbid or causative agent (Organic affective disorder)
- Many neurological disorders can cause “secondary mania,” including strokes, tumors, head trauma, CNS infection, and degenerative disorders

Migraine

- Migraine prevalence is higher in bipolar II disorder (33-54%)
- overall lifetime prevalence of migraine 64 to 77% in the bipolar II subgroup
- Compared with patients without migraine, those with migraine were younger, more educated, more likely to be employed, had fewer psychiatric hospitalizations, and initially presented for symptoms of depression rather than hypomania

Irritable bowel syndrome

- meta-analysis of retrospective cohort studies show positive correlation - However, potentially important confounders, such as antidepressant use, were not adjusted for
- evidence that both disorders may share inflammatory and stress-related aetiologies which could give rise to this association

Vascular Bipolar Disorder

- Vascular mania, or vascular bipolar disorder, refers to subcortical infarcts presenting with manic symptoms
- Patients are typically older, with late-onset bipolar disorder, cognitive impairment, and extensive subcortical white matter hyperintense lesions on brain magnetic resonance images
- Younger bipolar patients may have similar hyperintensities, but their pathophysiologic significance is still unknown

- **Cushing’s Syndrome**
  - Cushing’s syndrome is caused by the prolonged hypersecretion of cortisol Patients may present with a clinically significant mood disturbance
- **Asthma**
  - lifetime severe asthma was associated with a fivefold increase in the probability of bipolar disorder
- **Multiple sclerosis**
  - MS patients had a higher lifetime prevalence of MDD, bipolar type I, bipolar II and cyclothymia

Hypertension

- common comorbidity among BD inpatients -31.1% prevalence in US studies
- Also present with other comorbidities such as MetS
- Individual life style choices important

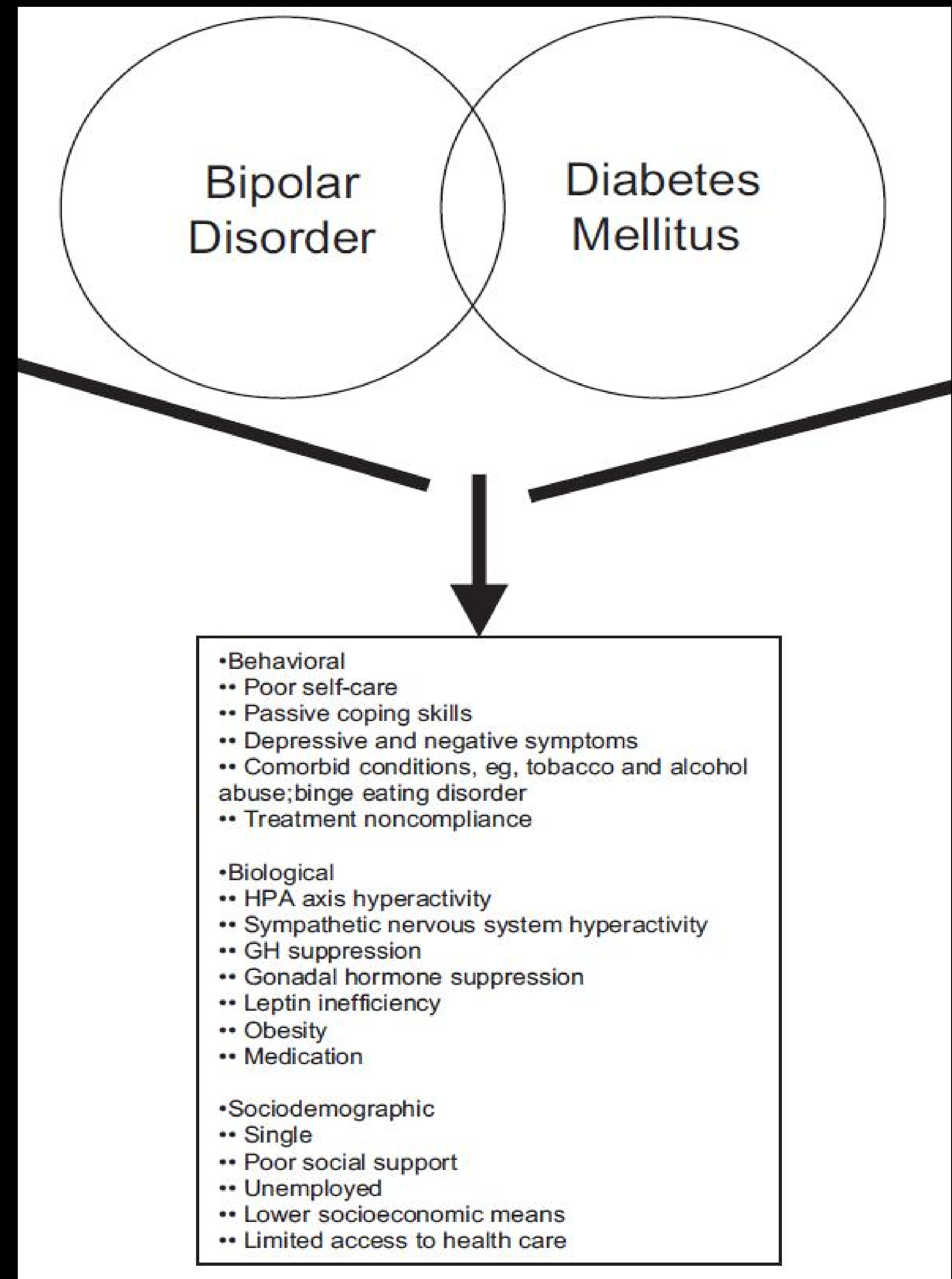
MEDICAL DISORDERS RELATED TO PHARMACOLOGIC TREATMENT

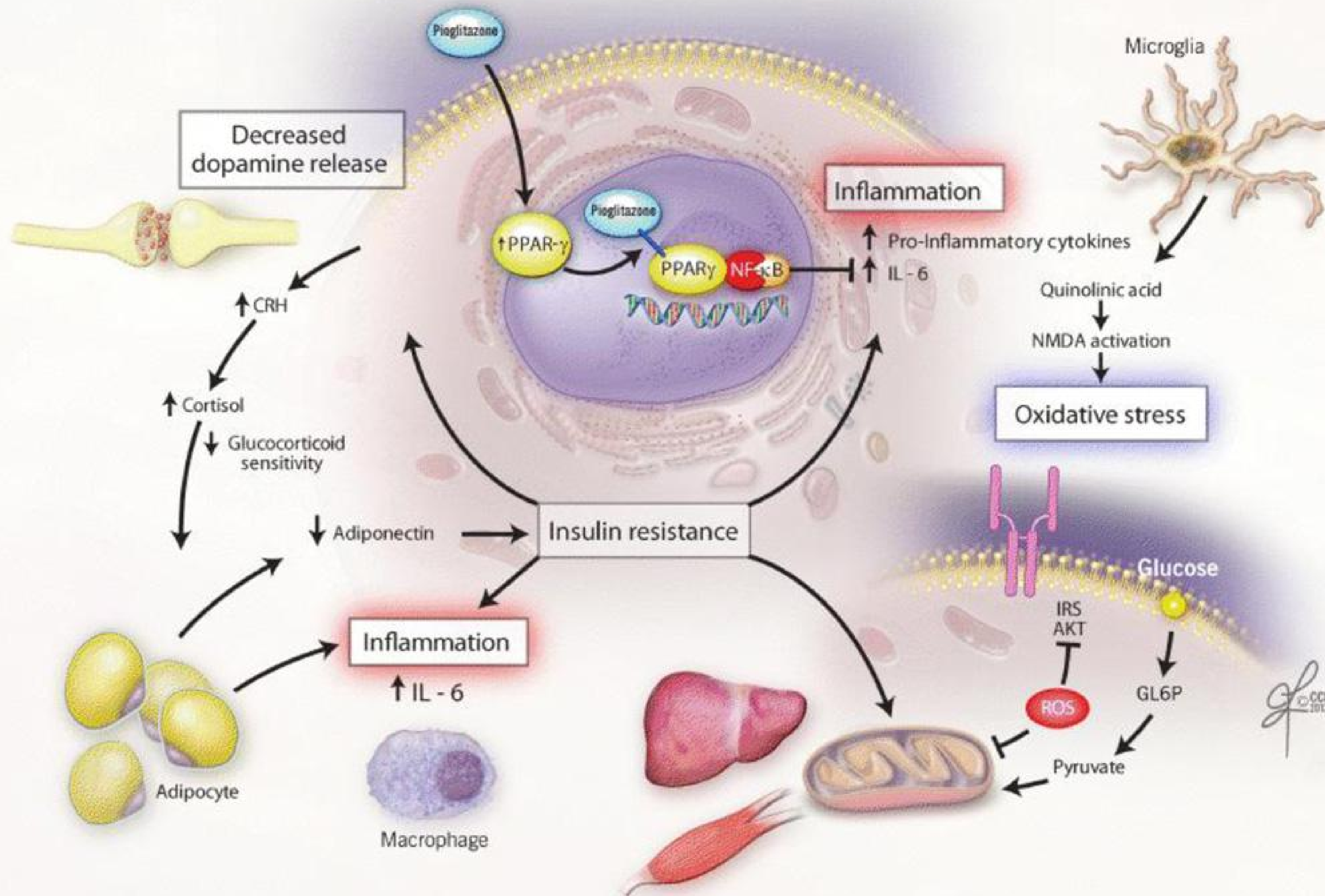
- **Obesity**
- treatment of bipolar disorder may worsen obesity
- risk factors for weight gain and obesity in patients with bipolar disorder include comorbid binge-eating disorder; the number of depressive episodes, excessive carbohydrate consumption; and low rates of exercise
- hypothesis that substance abuse and pathological over-eating may be a phenotypic expression of a competing brain reward system

- Over 12 months, 71% of patients taking valproate and 43% of those taking carbamazepine gained weight
- Lithium has been associated with weight gain, which is a major factor leading to poor compliance with treatment
- Risk of weight gain is increased for antipsychotic- naive patients and may not be dose dependent
- Topiramate may reduce psychotropic drug-induced weight gain and binge eating in euthymic patients without affecting mood

- **Diabetes Mellitus (Type 2)**
- possible mechanisms of comorbidity are unclear :
  1. genetic relationship
  2. hypercortisolemia induced diabetes
  3. diabetic vascular lesions contributing mania
  4. effect of psychotropic medications and associated weight gain

- The prevalence of diabetes 15.6 to 17.2%





Pioglitazone
Microglia
Decreased dopamine release
Inflammation
↑PPAR-γ
Pioglitazone
PPARγ
NF-κB
↑ Pro-Inflammatory cytokines
↑ IL - 6
↑ CRH
Quinolinic acid
NMDA activation
Oxidative stress
↑ Cortisol
↓ Glucocorticoid sensitivity
↓ Adiponectin
Insulin resistance
Glucose
IRS
AKT
Inflammation
↑ IL - 6
ROS
GL6P
Pyruvate
Adipocyte
Macrophage
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- principles of managing DM in BD are not dissimilar from non-psychiatrically affected diabetic patients
- However pts show vulnerability to depression, propensity for impulsivity and suicidal behavior, higher prevalence of cardiovascular disease and smoking, frequent overeating and inactivity, and exposure to weight-gain promoting psychotropic agents
- complications of treatment with atypical antipsychotics include sudden, severe, and occasionally fatal diabetes ketoacidosis, marked increase of serum lipids, especially triglycerides

Table 3 Criteria for Testing for DM in Asymptomatic Adult Individuals

1. Testing for diabetes should be considered in all individuals at age 45 years and above, particularly in those with a BMI 25 kg/m^{2}*, and, if normal, should be repeated at 3-year intervals.

2. Testing should be considered at a younger age or be carried out more frequently in individuals who are overweight (BMI 25 kg/m^{2}*) and have additional risk factors:

- are habitually physically inactive
- have a first-degree relative with diabetes
- are members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- have delivered a baby weighing >9 lb or have been diagnosed with GDM
- are hypertensive (140/90 mmHg)
- have an HDL cholesterol level 35 mg/dl (0.90 mmol/l) and/or a triglyceride level 250 mg/dl (2.82 mmol/l)
- have PCOS
- on previous testing, had IGT or IFG
- have other clinical conditions associated with insulin resistance (e.g., PCOS or acanthosis nigricans)
- have a history of vascular disease

* May not be correct for all ethnic groups. PCOS, polycystic ovary syndrome.

Table I. Type 2 diabetes risk reduction and management in patients with bipolar disorder.

Prevention:
Diet low in simple carbohydrates
Regular aerobic exercise
Address sleep disturbance if present

Screening/surveillance:
Fasting plasma glucose (FPG) every 2–3 years, regardless of bipolar treatment
FPG at 3 and 6 months, then every 6 months if on chlorpromazine, clozapine, or olanzapine
FPG at 6 and 12 months, then every 12 months if on other antipsychotic

Management of medication-induced weight gain or type 2 diabetes:
Diet and exercise (see Prevention)
Consider switching antipsychotic to another mood stabilizer, if possible
If unable to switch, consider adding metformin

Treatment of type 2 diabetes in patients with bipolar disorder:
Non-pharmacologic
- Diet and exercise (see Prevention)
- Weight and glycemic control
- Decrease cardiovascular risk factors
- Ensure vaccinations are up to date

Pharmacologic
- Consider metformin as first-line treatment if non-pharmacologic measures ineffective
- Consider glucagon-like peptidase-1 receptor agonists/analogues or dipeptidyl peptidase-4 inhibitors
- Consider other oral antihyperglycemics
- Consider insulin, if oral antihyperglycemics not effective

Metabolic syndrome (MetS)

- also known as the cardiometabolic syndrome and syndrome X, refers to a cluster of related risk factors for cardiovascular disease : 20 – 25 percent of the world’s adult population have risk factors

	WHO (1999)	NCEP (2001)	IDF (2005)
Required	Insulin resistance*		WC† ≥ 94 cm in men or ≥ 80 cm in women
No. of abnormalities	≥ 2 of:	≥ 3 of:	≥ 2 of:
Obesity	WHR > 0.9 in men or > 0.85 in women; BMI ≥ 30 kg/m^2	WC ≥ 102 cm in men or ≥ 88 cm in women	
Triglycerides	≥ 150 mg/dL	≥ 150 mg/dL	≥ 150 mg/dL
HDL cholesterol	< 40 mg/dL in men or < 50 mg/dL in women	< 40 mg/dL in men or < 50 mg/dL in women	< 40 mg/dL in men or < 50 mg/dL in women
Hypertension	≥ 140/90 mmHg	≥ 130/85 mmHg	≥ 130/85 mmHg
Glucose		≥ 110 mg/dL‡	≥ 100 mg/dL
Microalbuminuria	Albumin/creatinine ratio > 30 mg/g; Albumin excretion rate > 20 mcg/min		

- prevalence of MetS + BPAD range from 16.7% to 67% - different definition for the MetS (NECP ATP III vs consensus criteria)
- prevalence 40-55% in Indian studies
- greater life time episodes of BD, longer duration of illness, greater depressive symptoms, lesser severity of manic symptoms and comparable longer lag period for treatment
- age more than 35 years, number of lifetime depressive episodes and use of olanzapine are strong predictors for development of MetS
- pioglitazone was associated with improvement in depressive symptoms and reduced cardio-metabolic risk

Seasonal pattern and CVD

- continuous variables in SP+ BD patients : higher systolic blood pressure, LDL cholesterol, triglycerides levels, larger abdominal circumference and higher BMI
- covariance analysis : association between SP and significantly higher level of fasting glucose and systolic blood pressure
- Clinical presentations of seasonal bipolar depressions include increased appetite, carbohydrate cravings, weight gain, and hypersomnia
- melatonin may help in seasonal metabolic and circadian dysregulation in BD patients

- **Hypothyroidism**
  - Hypothyroidism an important consequence of treatment with lithium
  - Prospective studies may help determine whether pharmacological thyroid supplementation facilitates recovery from bipolar depression
- **Polycystic Ovarian Syndrome**
  - menstrual abnormalities, hyperandrogenism, and polycystic ovarian syndrome (PCOS) in bipolar disorder have been linked to valproate use
- **Rheumatoid arthritis**
  - Study shows prevalence higher in the bipolar group compared with control groups and general population

- **Renal Failure**
  - Lithium-induced nephrogenic diabetes insipidus is common, and there are some reports of renal failure with lithium
  - Given the association with cardiovascular risk factors, it is not surprising that cardiovascular disease is a leading cause of early death in bipolar disease, second only to suicide

- **Skin Rash**
  - Skin rash, and rarely Stevens-Johnson syndrome, is associated with some of the medications used in the management of bipolar disorder, including carbamazepine and lamotrigine

FUTURE CONSIDERATIONS

- comorbidity associated with earlier onset of bipolar symptoms, more severe course, poorer treatment compliance and response, and worse outcomes related to suicide - thus requiring vigilance
- collaborative care model is required for early diagnosis and management
- more research into efficacy and pharmacotherapy in future trials for comorbid bipolar condition
- conflicting data for medical comorbidities
- greater focus on medical comorbidities other than MetS

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THANK YOU

I have OCD, but I only clean things when I'm in the mood because I'm also bipolar.

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