# Bipolar Disorders

Dr. Ahmad Almadani

MBBS, MPH, FRCPC, FAPA

# Bipolar I vs. Bipolar II

## Bipolar I

Manic episode

≥ 7 days

Significant functional impairment and/or hospitalization

An initial episode of mania is considered diagnostic, even without a history of depression

## Bipolar II

Hypomania
≥ 4 days

Never a manic episode

must have experienced one or more major depressive episodes with at least one hypomanic episode

# Criteria for Manic Episode

A. A distinct period of **abnormally and persistently elevated, expansive, or irritable mood** and a**bnormally and persistently increased activity or energy**, lasting **at least 1 week** and present most of the day, nearly every day (or any duration if hospitalization is necessary).

B. Accompanied by at least 3 of the following (4 if mood is only irritable):

1. Inflated self-esteem/grandiosity
2. Decreased need for sleep
3. More talkative than usual
4. Flight of ideas
5. Distractibility
6. Increase in goal-directed activity/psychomotor agitation
7. Excessive involvement in pleasurable but high risk activities

C. Mood disturbance is **severe enough to impair functioning and/or requires psychiatric hospitalization and/or psychotic symptoms are present**

D. Symptoms not due to a substance or a general medical condition

# Criteria for Hypomanic Episode

A. A distinct period of **abnormally and persistently elevated, expansive, or irritable mood** and a**bnormally and persistently increased activity or energy, lasting at least 4 consecutive days** and present most of the day, nearly every day

B. At least 3 of the same symptoms as manic episodes (4 if mood is irritable).

C. Mood disturbance is associated with a change in functioning that is uncharacteristic of the individual when non-symptomatic.

D. Mood changes are observable by others.

E. Mood disturbance is **not severe enough** to cause marked impairment in functioning, psychiatric **hospitalization is not needed**, **and psychotic symptoms are not present**

F. Symptoms are not due to a substance or a general medical condition

# Criteria for Major Depressive Episode

A. At least 2 weeks of persistently sad mood and/or a lack of interest and pleasure

B. At least 5 of the following present for at least 2 weeks:

1. Depressed mood
2. Decreased interest
3. Decreased/increased appetite, weight loss/gain
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or lack of energy
7. Feelings of worthlessness or inappropriate guilt
8. Diminished ability to think/concentrate and/or make decisions
9. Thoughts of death, suicidal ideation, suicide plans, and/or suicide attempt

C. Significant impairment in functioning

D. Symptoms not due to a substance or a GMC

Major depressive episode could be part of major depressive disorder (MDD) or bipolar disorders (BAD). **However, MDD and BAD CAN NOT COEXSIST TOGTHER**

# Some Specifiers for Bipolar Disorder

- With rapid cycling
- With melancholic features
- With atypical features
- With psychotic features
  - Mood-congruent
  - Mood-incongruent
- With catatonia
- With peripartum onset

# "With Rapid Cycling" Specifier

- At least 4 episodes of mood disturbance in the previous 12 months
- Episodes must meet criteria for a manic, hypomanic, or major depressive episode
- Episodes must be separated by either partial or full remission for at least 2 months or a switch to an episode of opposite polarity

# Characteristics of Rapid Cycling Patient

- Higher incidence in bipolar II subtype
- **Higher incidence of suicide attempt**
- Higher incidence in **women**
- **Earlier age of onset**
- **Longer duration** of illness
- Higher **morbidity**

# "With psychotic features" Specifier

- Mood-congruent
- Mood-incongruent

# "With peripartum onset" specifier

Mood symptoms occur during pregnancy or within 4 weeks following delivery

# Clinical Presentation and Diagnosis

- Bipolar Disorder most **often starts with depressive episode** (70-75%)
- 10% experience only manic episodes
- Manic/hypomanic episodes have, in general, a rapid onset
- Bipolar disorder is a **recurrent, episodic illness**

# Distinguishing BDI and BDII

- Many clinicians incorrectly assume that BDII is a milder form of BDI
- However, **BDII is at least as disabling as BDI**
- Epidemiologic, clinical, genetic, and neuroimaging studies emphasize that **BDI and BDII are distinct**

Gelenberg, A.J. "Treating Bipolar II Depression." *Biological Therapies in Psychiatry*. Oct 2010: 33(10).

- **Compared with BDI, BDII experience:**
  - More frequent and more protracted episodes of depression
  - More chronic course of illness
  - More days depressed over lifetime
  - Less likely to return to premorbid functioning between episodes
  - High risk of suicide
  - More rapid cycling

# Symptom presentation: Mania

| Symptom | Mania |
|---|---|
| Appearance | Colorful/ strange makeup or dress style |
| Mood | Prolonged Euphoria, excessively optimistic heightened irritability |
| Speech | Talking fast and loudly<br>Difficult to interrupt |
| Activity | Risk-taking<br>Impulsive<br>Restlessness |
| Sleep | Decreased need for sleep |
| Cognition | Distractible<br>Difficulties planning, reasoning and decision making |
| Self-Perception/Thinking | Exaggerated self-confidence<br>Grandiose ideas |

Others:

- Circumstantiality (eventually return to the main point)
- Tangentiality (never reaching the essential point)
- Flight of ideas (rapid speech that changes focus based on association, distractions, or plays on words)

# Symptom Presentation: Depression

| Symptom | Depression |
|---|---|
| Appearance | Disinterest in personal grooming or hygiene |
| Mood | Feelings of sadness<br>Suicidal Ideation |
| Speech | Slowed, monotonous, monosyllabic |
| Activity | Difficulty initiating tasks<br>Decreased psychomotor activity<br>Diminished interest in hobbies |
| Sleep | Early morning waking with insomnia<br>OR<br>Hypersomnia and daytime napping |
| Cognition | Reduced ability to concentrate<br>Problems with memory |
| Self-Perception/Thinking | Reduced self-esteem<br>Feelings of worthlessness and guilt<br>Pessimistic thoughts<br>sense of hopelessness |

# Diagnosing Bipolar Disorder

- Family history
- Symptoms presentation
- Establishing the premorbid mood baseline for a particular individual
- Questionnaires
  - Depression (several scales available)
  - Mood Disorders Questionnaire (screening tool)
  - Hypomania/mania (YMRS:Young Mania Rating Scale)
- Longitudinal evaluations
- Prospective mood diaries

# Mood diary example

**Mood Diary** **Month/Year:** _____

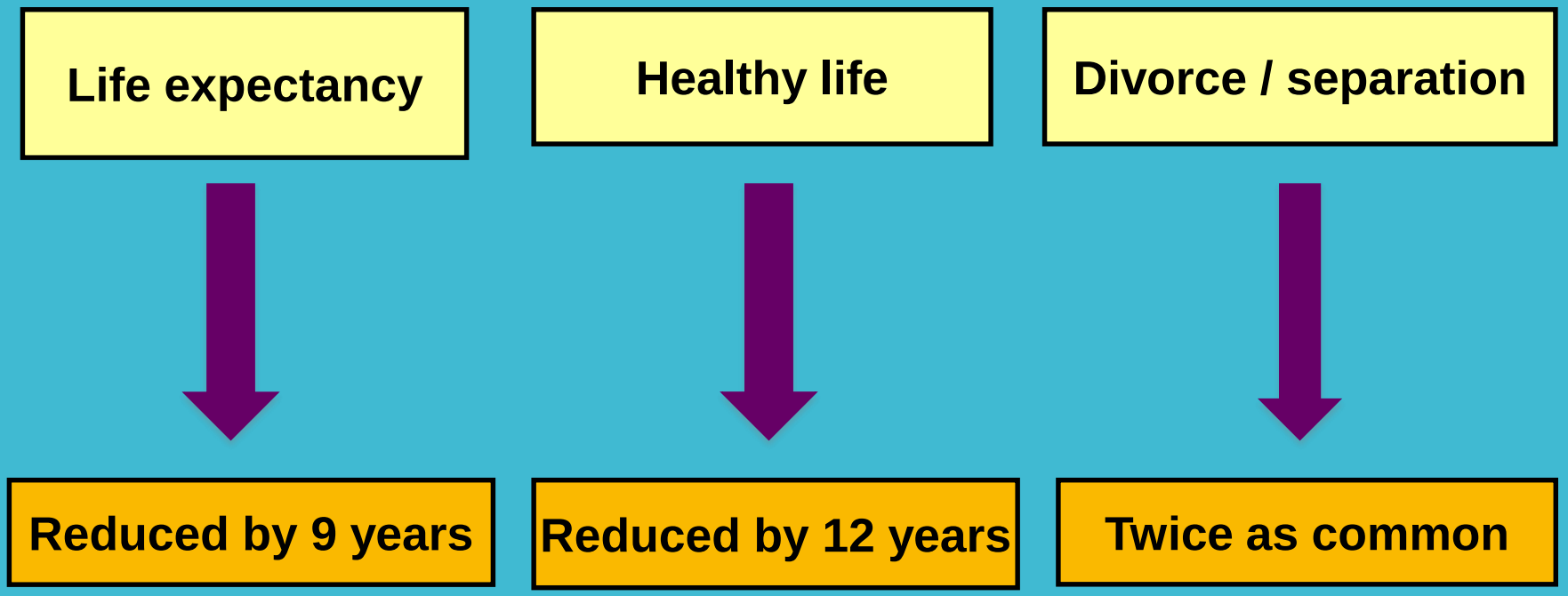
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 ↑ 2 ↑ 1 Normal Mood 1 ↓ 2 ↓ 3 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Anxiety 1-2-3* | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Irritability 1-2-3* | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Sleep # of hours | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Menstrual Cycle | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alcohol # of drinks | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

*1 = Mild 2 = Moderate 3 = Severe

Comments: _____

# Epidemiology

# Impact of Bipolar Disorder on Patients' Lives




**Results for patients developing bipolar disorder in their mid-20s**

Coryell W et al. The enduring psychosocial consequences of mania and depression. Am J Psychiatry 1993; 150: 720-727.
Scott J. Psychotherapy for bipolar disorder. Br J Psychiatry 1995; 167: 581-588.

# Course and Prognosis

# Predictors of Poor Long-Term Outcome

- Substance abuse
- Rapid cycling
- Psychosis
- Poor compliance
- Ongoing residual affective symptoms

# Bipolar Disorder and Suicide

- **Bipolar II more** at risk of suicide
- Completed Suicide: 10 – 19%

  **(15 times that of the general population)**

# Differential Diagnoses

- Unipolar Depression (major depressive disorder)
- Substance Abuse (cocaine, amphetamine)
- Attention Deficit Hyperactivity Disorder (ADHD)
- Personality Disorders (borderline, narcissistic)
- Organic Mood Disorders
- Schizoaffective Disorder

# Bipolar Disorder vs. Substance Abuse

- For diagnostic clarity, longest possible period of abstinence is optimal (6 months – 1 year)
- **The onset of bipolar disorder usually precedes that of substance use disorder**. Then bipolar disorder could be considered a risk factor for the development of substance use disorder

# BD vs. ADHD

**Bipolar Disorder**

- Onset of clear-cut symptoms after age 8
- Onset with dysthymia or depression
- Episodicity
- Family history of mood disorders
- Variable or negative response to stimulants
- Response to mood stabilizers

**ADHD**

- Onset of clear-cut symptoms before age 7
- Onset of hyperactivity or disruptive behaviors
- Continuous
- Family history of disruptive disorders
- Response to stimulants
- Variable or no response to mood stabilizers

# Bipolar Disorder vs. Borderline Personality Disorder

**Bipolar Disorder**

- Biphasic mood dysregulation
- Mood symptoms meet threshold criteria for MDD
- Reasonable functioning during euthymic episode
- Family history of bipolar disorder

**Borderline Personality Disorder**

- Mood dysregulation in the depressive spectrum
- Mood symptoms often do not reach threshold for MDD
- Dysfunction persists even in euthymic periods
- Family history of deprivation and abuse

# Medical Conditions and Medications Reported to Precipitate Manic Episodes

*Manic-Depressive Illness*, 2nd edition, F.K. Goodwin & K.R. Jamison, 2007, p.139-140

**Table 10–5.** Selected causes of secondary mania

**Neurological conditions**
Frontotemporal dementia
HIV encephalopathy
Huntington's disease
Multiple sclerosis
Psychomotor seizures
Stroke (temporal, right hemispheric)
Traumatic brain injury
Tumors
Viral encephalitis
Wilson's disease

**Other systemic conditions**
Carcinoid
Cushing's syndrome
Hyperthyroidism
Niacin deficiency
Postoperative delirium
Puerperal postpartum psychosis
Vitamin $B_{12}$ deficiency

**Medications and substances**
Alcohol
Amantadine
Amphetamines
Anabolic steroids
Antidepressants
Cocaine
Corticosteroids/corticosteroid withdrawal
Cyclobenzaprine
Dextromethorphan
Dopamine agonists (levodopa, pramipexole)
*Hypericum perforatum* (St. John's wort)
Isoniazid
Methylphenidate and other stimulants
Modafinil
Phencyclidine
Procarbazine
Propafenone
Sympathomimetic amines (e.g., ephedrine)
Thyroid preparations
Zidovudine

# Medical Conditions and Medications Reported to Precipitate Depressive Episodes

# Secondary to Neurological Condition

- Cerebrovascular disease
- Dementia
- Epilepsy
- Huntington's disease
- Multiple Sclerosis
- Parkinson's
- Postconcussional disorder
- Sleep apnea
- Stroke
- Subarachnoid hemorrhage

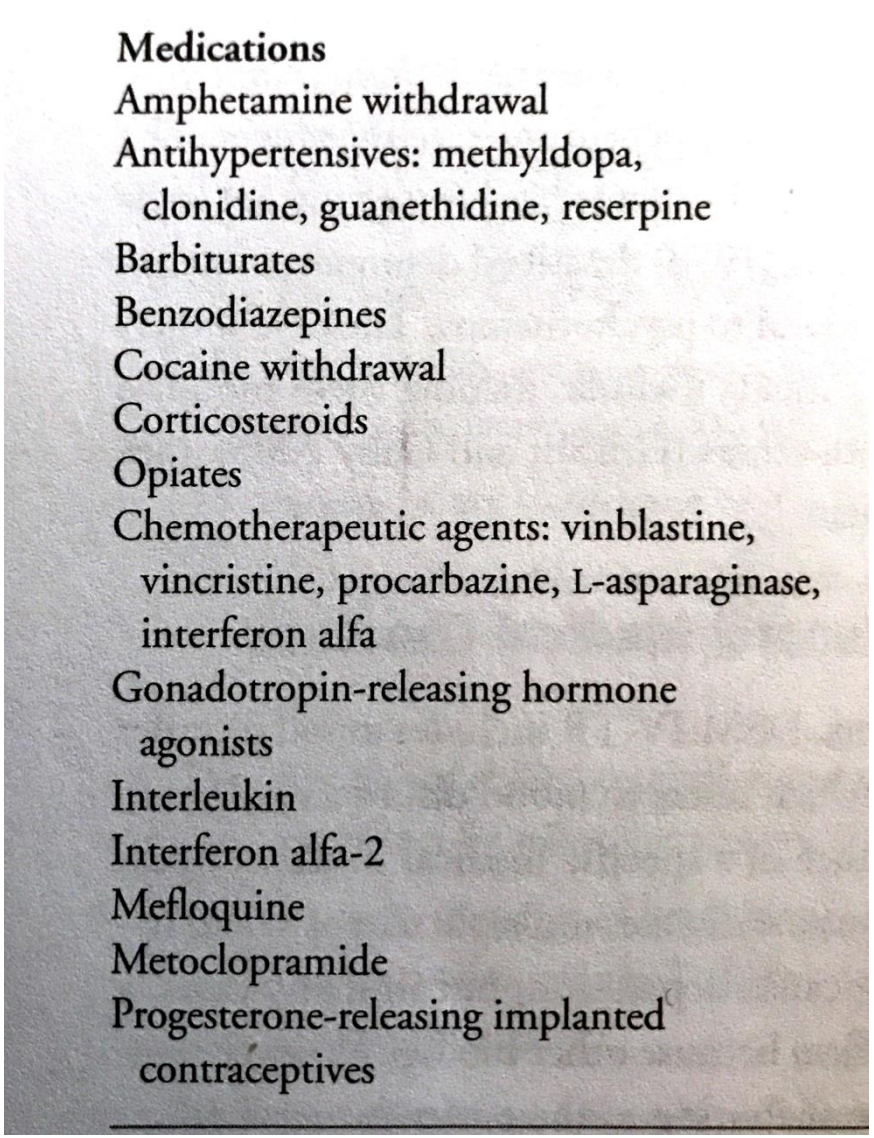
# Secondary to Endocrine Disorders

- Addison's Disease
- Cushing's syndrome
- Hypopituitarism
- Hyperthyroidism

# Secondary to Infections

- Encephalitis
- Epstein–Barr virus
- Hepatitis
- HIV
- Pneumonia
- Post-influenza
- Tertiary syphilis

# Secondary to Medications



**Medications**

Amphetamine withdrawal

Antihypertensives: methyldopa, clonidine, guanethidine, reserpine

Barbiturates

Benzodiazepines

Cocaine withdrawal

Corticosteroids

Opiates

Chemotherapeutic agents: vinblastine, vincristine, procarbazine, L-asparaginase, interferon alfa

Gonadotropin-releasing hormone agonists

Interleukin

Interferon alfa-2

Mefloquine

Metoclopramide

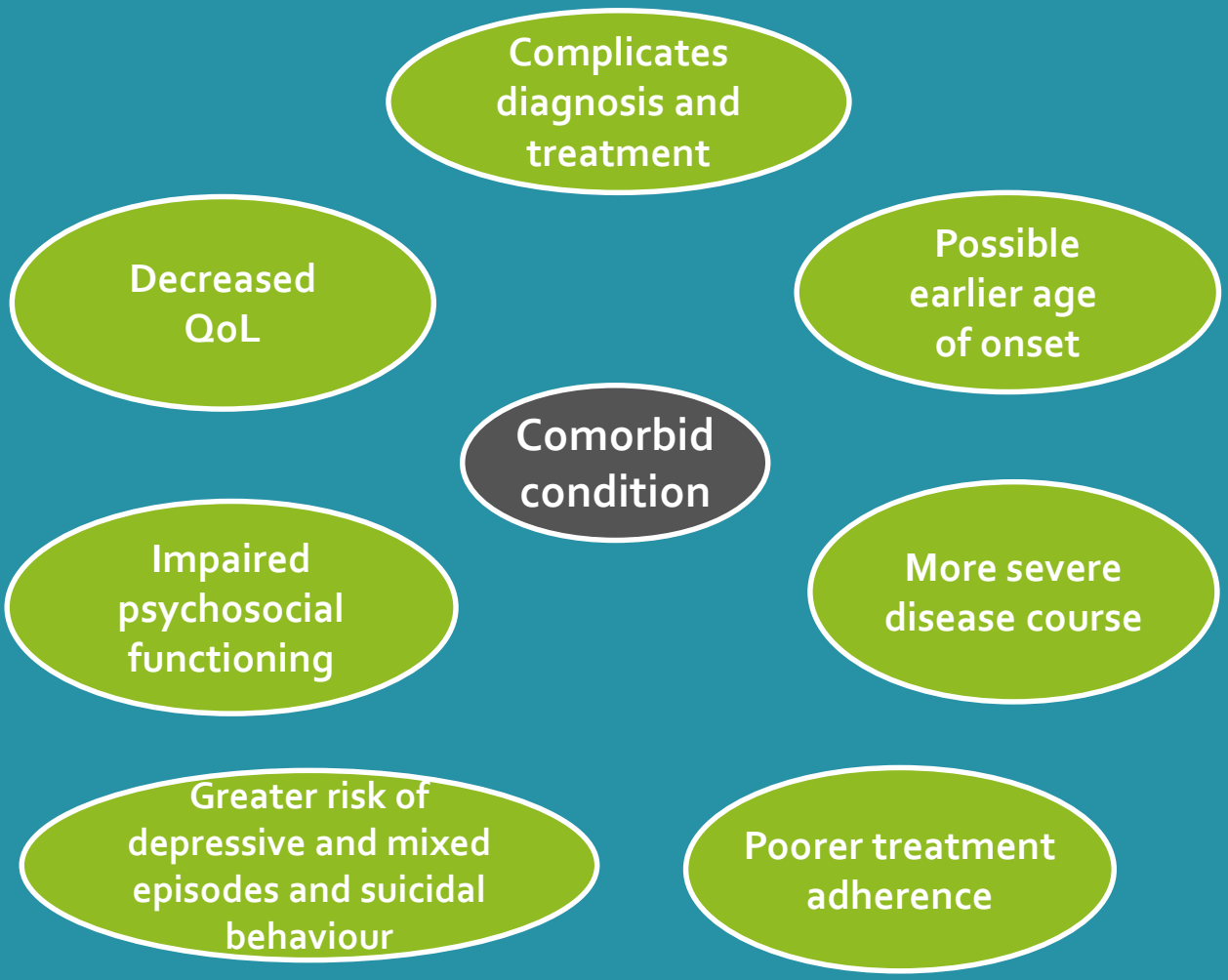
Progesterone-releasing implanted contraceptives

# Secondary to Other condition

- Alcoholism
- Anemia
- Heavy Metal poisoning
- Hypercalcemia
- Hypomagnesaemia
- Hyopkalemia
- Systemic lupus erythematosus

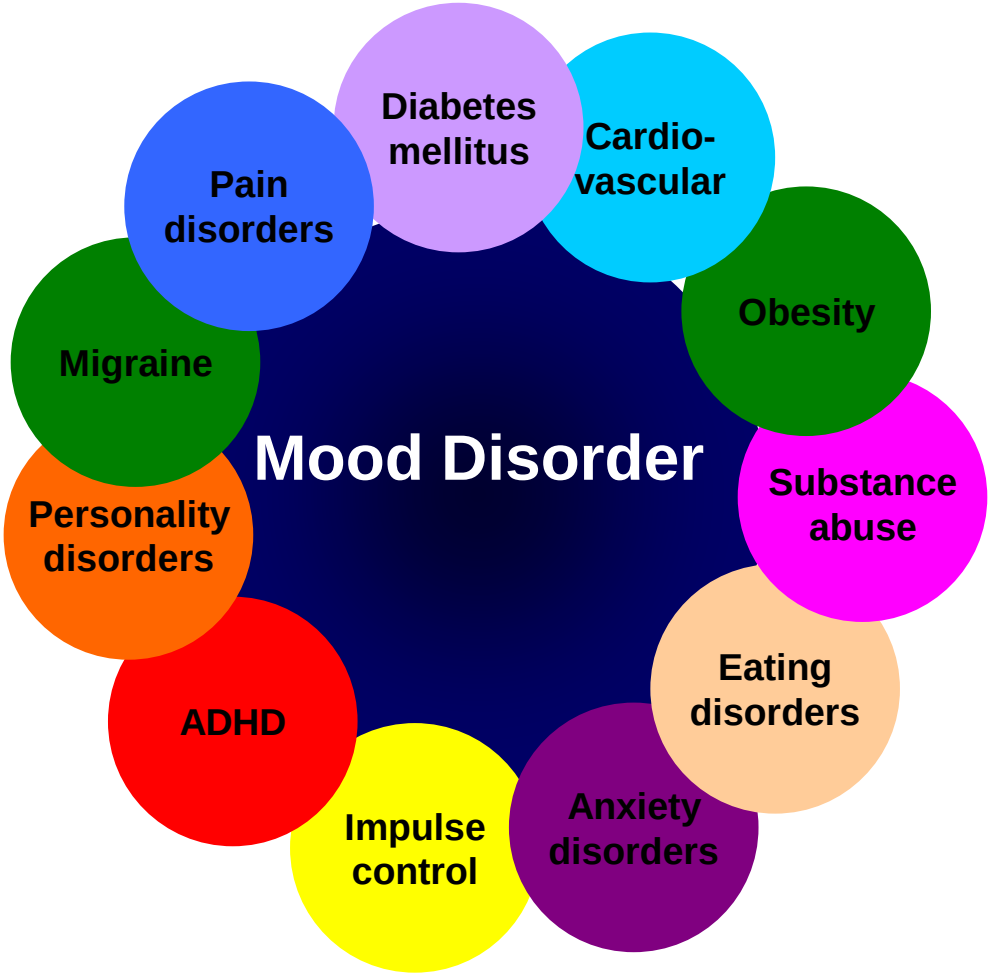
# Bipolar Disorder and Psychiatric/Medical Comorbidities

# Comorbid Conditions Complicate Diagnosis and Management of Bipolar Disorder




**References**
Colom F et al. Clinical factors associated with treatment noncompliance in euthymic bipolar patients. J Clin Psychiatry 2000; 61: 549-555.
Keller MB. Prevalence and impact of comorbid anxiety and bipolar disorder. J Clin Psychiatry 2006; 67 (Suppl 1): 5-7.
Pollack LE, Cramer RD, Varner RV. Psychosocial Functioning of People with Substance Abuse and Bipolar Disorders. Subst Abus 2000; 21: 193-203.
Vieta E, Colom F, Corbella B, Martinez-Aran A, Reinares M, Benabarre A, Gasto C. Clinical correlates of psychiatric comorbidity in bipolar I patients. Bipolar Disord 2001; 3: 253-258.

# Medical and Psychiatric Comorbidities




- The prevalence of psychiatric/medical comorbidities in bipolar disorder is **high**
- **Cardiometabolic disorders most common specific cause of premature mortality**

# Etiological Theories of Bipolar Disorder

Yatham, L., & Malhi, G. (2001). *Bipolar Disorder*. New York: Oxford University Press.

# Neurotransmitter System Abnormalities

Monoaminergic

Cholinergic

Glutamatergic

GABA-ergic

Glucocorticoid

Peptidergic

# HPA axis Function

HPA abnormalities have been demonstrated in all phases of bipolar disorder

# Neuroimaging and Neurophysiological Findings

Several areas in the brain are involved

# Family Studies and Genetics

- A **family history of BD is one of the strongest and most consistent risk factors** for the development of this condition

# Circadian Rhythms in Bipolar Disorder

- Changes in sleep, day time activity and energy levels are important in acute mania and depression
- Changes in sleep-wake cycle and represent core features of BD with sleep abnormalities in about 90% during acute episodes
- **Even in euthymia, sleep abnormalities persist**
- **Changes in sleep is highly predictive of impending mental illness presentations**
- **Sleep disturbance is the most common prodrome of mania**

# Environmental Risk Factors

- **Life events** can influence both the onset and relapse of BD
- **Childhood adversities** relate to earlier onset of the disorder and greater comorbidities
- **Stress** precipitates episodes, but its role diminishes as the illness progresses
- **Complications during pregnancy or delivery**

# Treatment modalities

# Various Treatment Modalities

- **Medications:**
  - Lithium
  - Valproic acid
  - Lamotrigine
  - Carbamazepine
  - Certain antipsychotics
  - Others
- **Psychotherapy**
- **Neurostimulation** ( electroconvulsive therapy)
- **Others**

# Lithium

- More effective in **preventing high**. It is less effective but yet effective to prevent lows
- Lithium **decreases risk of suicide attempts and completions**

- **Low therapeutic index**

- Dosing - Guided by Plasma Levels;
  - **Elderly - usually require lower doses**
  - Needs dose adjustment in renal impairment
  - Targeted lithium levels varies depending on the stage of illness, among other factors

- **Onset of action: ~5-14 days**

- **100 % renal excretion**

- **Require particular lab monitoring, including the kidney function tests.**

- **Mild Side-Effects:**
  - Fine Tremor (worse with high doses, caffeine, and neuroleptics)
  - Reversible agranulocytosis
  - Rash
  - Hair loss
  - Cognitive Impairment
  - Sedation
  - Acne
  - Nausea / Vomiting / Diarrhea, Dry mouth
  - Excessive Thirst (Polydipsia), polyuria
  - Weight gain (+3.8 kg over one year)

- **Severe side effects:**
  - Psoriasis Exacerbation
  - **Hypothyroidism**
  - Hyperparathyroidism
  - ECG Changes
  - Nephrogenic Diabetes Insipidus
  - Chronic Renal Disease

## Lithium toxicity:

- Symptoms:
  - Coarse tremor
  - Drowsiness
  - Lethargy
  - Weakness
  - Agitation
  - Muscle Fasciculation
  - Ataxia
  - Dysarthria
  - Vomiting, Diarrhea
  - Dizziness, Syncope
  - Arrhythmias
  - Polyuria, Polydipsia

- Management of lithium toxicity:
  - IV fluids ++
  - Might need hemodialysis in certain situations.

## Lithium Contraindications:

- **Significant renal impairment**
- Severe dehydration or electrolyte imbalance
- Significant Cardiac Impairment
- Psoriasis - Relative Contraindication

## Lithium in pregnancy and breast feeding:

- If used during the second and third trimester, the **serum lithium levels should be monitored closely** because of changes in blood volume during pregnancy
- Cross into breast milk and therefore, is generally **discouraged during breast feeding**

# Valproic acid (VPA)

- Main mechanism of action: inhibit GABA transaminase
- Can measure its level to guide the dose, among other considerations
- Particular lab monitoring is required
- **Metabolized in the liver**
- onset of action is 3-7 days

**Mild side effects:**

- Tremor
- agranulocytosis and anemia
- Hair Thinning / Loss
- Sedation
- Benign Rash
- Nausea, Vomiting, Diarrhea
- Weight Gain
- Benign hepatic transaminase elevation

## Severe side effects:

- Osteoporosis / Reduced Bone Density
  Thrombocytopenia
- Hyperammonemic Encephalopathy
- Stevens-Johnson Syndrome
- Polycystic Ovary Syndrome
- Hepatotoxicity
- Acute Pancreatitis
- Interaction with aspirin and warfarin
- HypoNa

## VPA and Polycystic Ovary Syndrome:

- Signs and symptoms;
  - Hyperadrogenism (hirsutism, acne, alopecia)
  - Chronic Anovulation (oligomenorrhea or amenorrhea)
  - Polycystic Overaies on Ultrasonography
- Can lead to **infertility** and **metabolic syndrome**
- **<u>Avoid valproate use in women under 18</u>**

## VPA and Stevens-Johnson Syndrome / SJS/TEN Overlap Syndrome/ Toxic Epidermal Necrolysis:

- Stevens-Johnson Syndrome (<10%) / SJS/TEN Overlap Syndrome (10-30%) / Toxic Epidermal Necrolysis (>30%)
- Prodromal flu-like **systemic symptoms**
- **Mucosal surfaces affected**
- Characteristic lesions with **target-like appearance**

- **Contraindication of VPA: Hepatic disease**
- Be cautious of drug interactions
- In pregnancy: **Valproate is associated with neural tube defects, cardiac/limb malforms**

# Lamotrigine

- Does not interfere with GABA system. Mainly inhibit voltage sensitive sodium channel
- **No elevated LFT**
- No major hematological side effects
- **Weight Neutral**
- **Cognitive side effects are unusual**
- **Helpful in treating depressive symptoms (not effective for manic and hypomanic features)**

**Side effects:**

- Sedation
- Nausea / Vomiting / Diarrhea
- Headache
- Others:
  - Benign Rash
  - Stevens - Johnson syndrome, / SJS/TEN Overlap Syndrome, Toxic Epidermal Necrolysis

## Lamotrigine and benign rash:

- 8.3% of patients
- Characteristics of benign rash:
  - Spotty
  - Non-tender
  - Itchy
  - **No systemic features**
  - **No lab abnormalities**

## Lamotrigine and Stevens - Johnson syndrome / SJS/TEN Overlap Syndrome / Toxic Epidermal Necrolysis :

- Stevens - Johnson syndrome (<10%) / SJS/TEN Overlap Syndrome (10-30%) / Toxic Epidermal Necrolysis (>30%):
- Prodromal **flu-like systemic symptoms**
- **Mucosal surfaces affected**
- Characteristic lesions with **target-like appearance**

# Carbamazepine (CMZ)

- **Absorption of carbamazepine is slow and <u>unpredictable</u>.**
- Several drug interactions
- Several possible side effects
- Dose may need to be increased after weeks or months because of **autoinduction**

# Risk of switch with antidepressants treatment

- Using antidepressants (such as SSRI and SNRI) may carry the risk of switching to hypomania or mania;
  - Sometimes called antidepressant-induced manic or hypomanic episode
  - In general, risk of switch: buproprion < SSRI< SNRI

# Other treatment modalities

- ECT (electroconvulsive therapy)

- Psychotherapy; such as:
  - **Psychoeducation**
  - CBT (cognitive behavioral therapy)
  - Family-focused therapy
  - Interpersonal and social rhythm therapy
  - Others

# Other Bipolar and related disorders

# Bipolar and Related Disorder Due to Another Medical Condition

A. A prominent and persistent period of abnormally elevated, expansive, or irritable mood and abnormally increased activity or energy that predominates in the clinical picture.

B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of another medical condition.

C. The disturbance is not better explained by another mental disorder

D. The disturbance does not occur exclusively during the course of a delirium

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning, or necessitates hospitalization to prevent harm to self or others, or there are psychotic features.

# Substance/ Medication-Induced Bipolar and Related Disorder

A. A prominent and persistent disturbance in mood that predominates in the clinical picture and is characterized by elevated, expansive, or irritable mood, with or without depressed mood, or markedly diminished interest or pleasure in all, or almost all, activities.

B. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2):

(1)The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to a medication.

(2)The involved substance/medication is capable of producing the symptoms in Criterion A.

C. The disturbance is not better explained by a bipolar or related disorder that is not substance/medication-induced.

D. The disturbance does not occur exclusively during the course of a delirium.

E. The disturbance causes clinically significant distress or impairment

# Other Specified Bipolar and Related Disorder

This category applies to presentation in which symptoms characteristic of a bipolar and related disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but **do not meet the full criteria for any of the disorders in the bipolar and related disorders diagnostic class**. The other specified bipolar and related disorder category is used in **situations in which the clinician chooses to communicate the specific reason** that the presentation does not meet the criteria for any specific bipolar and related disorder.

For example: Short-duration hypomanic episodes (2-3 days) and major depressive episodes

# Unspecified Bipolar and Related Disorder

This category applies to presentation in which symptoms characteristic of a bipolar and related disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but **do not meet the full criteria for any of the disorders in the bipolar and related disorders diagnostic class**. The unspecified bipolar and related disorder category is used in **situations in which the clinician chooses not to specify the read that the criteria are not met** for a specific bipolar and related disorder, and includes presentation in which there is insufficient information to make a more specific diagnosis (e.g., in emergency room settings).

# Summary

- Bipolar Disorder types I and II are **chronic, intermittent** lifelong disorders, with strong tendencies for relapse and recurrence of major and minor affective episodes
- Lifetime prevalence: 1-3%
- **Healthy life and life expectancy**: reduced by about 10 years
- **Bipolar II disorder is underdiagnosed** and represents the majority of bipolar patients
- **Bipolar II as compared to Bipolar I** experience more depressive episodes, rapid cycling, and are at higher risk for suicide

- **Depressive pole is predominant** in BD-I and BD-II
- **Psychiatric and medical comorbidities** are common
- Comorbidities complicate diagnosis, treatment, and outcome
- Often associated with **cognitive deficits** (and poor functional outcome)
- **Completed suicide** is higher than in the general population, MDD and Schizophrenia.
- Several pharmacological and non-pharmacological treatments exist.

# Questions and Discussion

# Other references

- DSM-5
- kaplan and sadock's synopsis of psychiatry
- Others