433 Teams

PSYCHIATRY

Lecture 2

Bipolar Disorder I & II

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Bipolar Disorder

☒ Manic Episode

A. distinct **period** of abnormally and persistently **elevated, expansive, or irritable mood**, lasting at least **1 week**.

B. During the period of mood disturbance **≥ 3 of the following** (4 if mood is irritable):

1. Inflated self-esteem or **grandiosity**.
2. Decreased need for sleep.
3. Pressured speech.
4. Racing thoughts or flight of ideas.
5. Distractibility (reduced concentration).
6. Increase in goal-directed activity (socially, at work, or sexually).
7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g.,engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The symptoms **do not meet criteria for a mixed episode.**

D. Significant distress or **impairment in functioning**.

E. Not due to substance abuse, a medication or a general medical condition (e.g., hyperthyroidism).

Manic-like episodes that are clearly caused by antidepressant treatment should not count toward a diagnosis of bipolar I disorder

❖ Etiology

- **Genetic**:

  - ✓ **one parent** with bipolar I >**25 % chance** of mood disorder in child.
  - ✓ **Two parents** with bipolar I > **50 % chance** of mood disorder in child.
  - ✓ Concordance rates for monozygotic twins are approximately 75%, and rates for dizygotic twins are 5 to 25%.
  - ✓ Some studies found some defects in **chromosomes 5, 11 and X**.

- **Neurochemical:** disturbance in biogenic amines (**norepinephrine, serotonin, and dopamine).**

- **Psychosocial:** psychosocial stresses may trigger manic or mixed episode in a vulnerable persons.

❖ Manic-like episodes may be induced by;

A. **Medications**; e.g. steroids , antidepressants.
B. **Medical diseases**; e.g. Hyperthyroidism, SLE, Multiple sclerosis.
C. **Substance abuse**; e.g. stimulants

▪ Mixed Episode

≥ 1 week of both manic and depressive symptoms occurring simultaneously nearly every day (e.g. overactive overtalkative patient may have at the same time profound depressive thoughts including suicidal ideas) **>>> Bipolar I disorder**

▪ Alternating Affective Sates

Manic and depressive features **follow one another** in a sequence of rapid changes in a short time (e.g. a manic patient may be intensely depressed for few hours and then quickly becomes manic) **>>> Bipolar I disorder**

❖ Psychotic features

may occur in severe cases of mania:

A.Mood - congruent hallucinations;

- ✓ e.g. voices talking to the patient about his special powers.
- ✓ Occasionally visual hallucinations (e.g. seeing Angels).

B.Mood-congruent delusions;

- ✓ usually grandiose delusions (e.g. being a prophet, a prince)
- ✓ Patients with delusional disorder (grandiose type) have long-lasting grandiose delusions but no manic features; pressure of speech, racing thoughts, flight of ideas e.t.c. Some manic patients develop delusions of persecutions or of reference

		Hypomanic episode	Manic episode
1	**Minimum Duration**	**4 days**	**7 days**
2	**Severity**	**Not severe enough to cause marked impairment in social or occupational functioning**	**Causes severe impairment in social or occupational functioning.**
3	**Features**	**No psychotic features (hallucinations/delusions).**	**May have psychotic features.**
4	**Diagnosis**	**Bipolar II disorder**	**Bipolar I disorder**
5	**Management**	**Does not require hospitalization**	**Usually necessitates hospitalization to prevent harm to self or others**.

Bipolar I Disorder

- ✓ **(**It was known as **manic-depressive disorder).**
- ✓ Patient has met the criteria for a full manic or mixed episode, usually sufficiently severe to require hospitalization.
- ✓ Depressive episodes may/may not be present **(episodes of major depression are *not* required for the diagnosis).** However, most patients with bipolar I disorder experience MDE and manic or mixed episodes (20% of patients experience only manic episodes).
- ✓ **Epidemiology**: onset usually 18-30 years. Lifetime prevalence: 1% .

A- Bipolar I Disorder, Single Manic Episode

Patients who are having their first episode of bipolar I disorder MDE **cannot be distinguished from patients with MDD.** Thus, according to DSM-IV-TR, patients **must be experiencing their *first* manic episode to meet the diagnostic criteria for bipolar I disorder** *(*Bipolar I Disorder, ***Single*** Manic Episode).

B- Bipolar I Disorder, Recurrent

- ✓ When there are other episodes (whether manic, mixed, or MDE) after the first manic episode, DSM-IV-TR specifies diagnostic criteria **for *recurrent* bipolar I disorder.**
- ✓ Recurrent bipolar I disorder is specified based on the Symptoms of the most recent episode: bipolar I disorder, most recent episode manic; hypomanic; depressed; or mixed.
- ✓ Manic episodes are considered **distinct when** they are **separated by at least 2 months without significant symptoms of mania or hypomania**. Between manic episodes, there may be interspersed normal (euthymic) mood or MDEs.

Bipolar II Disorder

- ✓ Patient has **at least one major depressive episode** and **at least** one **hypomanic episode**, **but *no* manic episode**.
- ✓ If there has been a full manic or mixed episode even in the past, **then the diagnosis is bipolar I disorder, not bipolar II**
- ✓ .Features are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder.
- ✓ The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- ✓ Epidemiology; onset usually 18- 30 years. Lifetime prevalence: 0.5%. Slightly more common in women.

SEASONAL AFFECTIVE DISORDER

- Recurrent major depressive episodes that **come with shortened day light in winter and disappear during summer** (may be followed by hypomania). Absence of clear-cut seasonally changing psychosocial variables.

- Characterized by atypical features of depression: hypersomnia, hyperphagia (carbohydrate craving), weight gain, increased fatigue. Related to abnormal melatonin metabolism. Treated with exposure to light (artificial light for 2 – 6 hours a day). It may occur as part of bipolar I or II disorders.

Rapid Cycling Bipolar I or II Mood Disorders

- ✓ **≥ 4 alternating mood episodes** (MDE, Manic, Hypomanic or Mixed) in the previous 12 months, **separated by intervals of 2-3 days**.
- ✓ It is usually more chronic than non-rapid cycling disorders.
- ✓ Around 80 % are lithium-treatment failures. **Carbamazepine and sodium valproate are usual agents of choice.**

CYCLOTHYMIC DISORDER

- ✓ **Less severe** bipolar mood disorder **with continuous mood swings**;
- ✓ alternating periods of **hypomania** and **moderate depression**.
- ✓ It is **non-psychotic** chronic disorder.
- ✓ It starts in late adolescence or early adulthood.
- ✓ The treatment is similar to the bipolar mood disorder

❖ Course and Prognosis of bipolar disorders

If left untreated, most manic episodes will resolve within 8 -12 weeks (rarely last longer than 24 weeks). The risk of recurrence is particularly high (50 %). About 80 % of manic patients eventually experience a full depressive episode. About 50 % will have multiple relapses with good interepisodic functioning. Chronic deterioration may occur in up to 30 % of bipolar patients. The prognosis is much better than schizophrenia, but there is a wide variation; some people having their lives repeatedly disturbed, whilst others experience only a single episode. Some individuals have years of normal functioning between episodes. Others have episodes in clusters. Some patients have rapidly cycling episodes. As the disorder progresses, the time between episodes often decreases. After about five episodes, however, the interepisodic interval often stabilizes at 6 - 9 months. Patients with bipolar I disorder have a poorer prognosis than do patients with major depressive disorder.

❖ Treatment of Bipolar Mood Disorder

A- Short-term treatment (for acute manic or mixed episode):

- ✓ **Hospitalization** can provide a secure, protective environment. The initial task is to quieten the agitation that commonly occurs.
- ✓ This is usually accomplished with **antipsychotic medication**; **typical** (e.g. **haloperidol** 10 -20 mg or **chlorpromazine** 400-800 mg) or **atypical** (e.g. **olanzapine** 10-20 mg, or **risperidone** 4-8 mg). They reduce psychotic symptoms and over-activity.
- ✓ **Haloperidol** is a potent antipsychotic, **less sedative** and **causes less postural hypotension compared with chlorpromazine,** which is sometimes the drug of choice in mania for its sedative property.
- ✓ When the manic patient settles (usually within weeks), he can be treated as an outpatient with close observation and frequent assessment. Antipsychotics can then be reduced gradually and carefully.

B- Long-term treatment

Mood disorders often recur and have relapsing course, thus preventive (prophylactic) treatment is required :

- **Lithium** has been found effective in preventing recurrence of manic-depressive episodes.
- **Carbamazepine** appears to be as effective as lithium in the prophylaxis of bipolar mood disorder, and can be **considered in patients who are intolerant of lithium or who respond poorly to lithium** (e.g**. rapid-cycling mood disorders).**
- **Sodium valproate** has been **found effective in patients with refractory bipolar illness**, even when there has been a poor response to lithium and carbamazepine. Combination of lithium with carbamazepine can be used, particularly in rapid-cycling disorders, and combination of lithium with sodium valproate has been shown to be effective in the treatment of resistant patients.

MOOD STABILIZERS

☒ LITHIUM

❖ **Mechanism of action**:

The exact mechanism is unknown, however it is thought that it stabilizes neuronal activities (decreases sensitivity of postsynaptic receptors and inhibits release of neurotransmitters). **Before starting lithium**, a **note should be made of any other medications taken by the patient and a physical examination should be carried out. Prerequisite laboratory test: Renal functions and electrolytes / Thyroid functions/ ECG if cardiac disease is suspected. Pregnancy test (if indicated).**

❖ **Contraindications:**

Renal or cardiac failure / Recent myocardial infarction / Chronic diarrhea sufficient to alter electrolytes. First trimester of pregnancy (fetal cardiac anomalies)

Lithium is not recommended in children.

❖ **Side effects:**

 Fine tremor/ Gastric discomfort and diarrhea **/**Dry mouth, metallic taste , Fatigue **/**Weight gain

- Reversible hypothyroidism / Reversible nephrogenic diabetes insipidus (polyuria – polydepsia) due to blockade of ADH – sensitive adenylcyclase in distal tubules.

- **Toxicity** (course tremor, ataxia, confusion, diarrhea, vomiting…).

❖ Drug interactions:

Several drugs increase lithium concentration and may lead to Lithium toxicity: **Thiazide diuretics / NSAID)/Angiotension - converting enzyme inhibitors e.g. lisinopril / Haloperidol high doses (e.g. 40 mg/day).**
Lithium may potentiate the effect of muscle relaxants. This is important when a patient undergoes an operation or ECT. It may potentiate extrapyramidal side effects of antipsychotics. It may precipitate 5 - HT syndrome if given with SSRIs.

The recommended plasma concentrations are:
- 0.9 - 1.2 mmol / liter (during acute phase)
- 0.4 - 0.8 mmol / liter (for prophylaxis)

Dose is 300 - 450 mg twice or three times a day.

Plasma concentration requires continuous measurement because the narrow therapeutic index of lithium (therapeutic and toxic levels are close). Toxic levels ≥ 9.9 mmol / liter.
Plasma level should be measured **12 hours after the last dose**.

☒ Carbamazepine (Tegretol)

Carbamazepine (Tegretol) was first used to treat epilepsy and trigeminal neuralgia. Then, it has been used for decades as a first-line agent for acute and maintenance treatment for bipolar I disorder. Studies suggest that carbamazepine may be especially effective in persons who are not responsive to lithium.

In acute mania: carbamazepine is typically effective within **the first 2 weeks of treatment in 50 -70 % of cases.**

Prophylaxis: carbamazepine is effective in preventing relapses, particularly among patients with mood disorders and schizoaffective disorders. It is effective in controlling **impulsive and aggressive** behavior in persons of all ages who are not psychotic (e.g. borderline personality disorders, mentally retarded, head trauma Sequelae)

.**Doses:** starting dose is usually 200 mg two times a day. (in children 100 mg / day). It can be increased gradually to 600 – 1000 mg. Therapeutic concentration for psychiatric indications is 8 – 12 ug per mil.

Side effects: It is relatively well tolerated. **The most common side effects are mild and transient; Mild GI (gastric discomfort, nausea, vomiting, constipation, diarrhea, and**

anorexia) and CNS (sedation, drowsiness, vertigo, blurred vision and ataxia). It occasionally causes syndrome of secretion of inappropriate antidiuretic hormone (SIADH) through activation of vasopressin receptor function (hyponatremia +/- water intoxication). **Rarest but serious adverse effects**: hepatitis, pancreatitis, serious skin reactions **(**Stevens-Johnson syndrome**),** and blood dyscrasias (agranulocytosis and aplastic anemia).

Drug Interactions: As a result of prominent induction of hepatic CYP 3A4, It decreases serum concentrations of numerous drugs (e.g. oral contraceptives, warfarin, haloperidol, valproate). (When carbamazepine and valproate are used in combination, the dosage of valproate may need to be increased and the dosage of carbamazepine should be decreased, because valproate displaces carbamazepine binding on proteins.)

☒ Valproate

(Depakine Depakene, Depakote): It is used for the treatment of acute manic episode associated with mood and schizoaffective disorders.

Doses: starting dose is usually **250 mg twice**/day. It can be increased gradually to 2500 mg**/**day.

Common side effects include Mild GI **(gastric discomfort, nausea, vomiting, and anorexia) and CNS (sedation, drowsiness, dysarthria, and ataxia).**

Rarest but serious adverse effects; fatal hepatotoxicity, **pancreatitis**, **and fetal neural tube defects (e.g., spina bifida**) , 2-4% in women who take valproate **during the first trimester of the pregnancy**. **Daily folic acid supplements reduce the risk of neural tube defects.**

☒ Other anticonvulsants used as mood-stabilizers:

Lamotrigine (Lamictal), Topiramate (Topamax), Gabapentin (Neurontin), Pregabalin (Lyrica), Levetiracetam (Keppra), and Tiagabine (Gabitril).

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