جامعة الملك سعود
King Saud University

MEDICINE 438's REVIEW OF

CLINICAL PSYCHIATRY

Mood Disorders Part I: Bipolar and Related Disorders

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Objectives

- Differentiate between bipolar disorder-I and bipolar disorder-II and differentiate between a manic and a hypomanic episode.
- Emphasize the impact of bipolar disorders on patients' lives.
- Recognize the early onset and chronic course of bipolar disorder.
- List some medical and psychiatric differential diagnoses, risk factors, and comorbidities associated with bipolar disorders.
- Describe common and severe side effects of mood stabilizers (namely lithium, valproic acid, and lamotrigine).

ACADEMIC LEADER
TA
TARIQ ALANEZI

EDITING FILE

IMPORTANT TEXTBOOK LECTURER'S NOTES EXTRA GOLDEN NOTES

◄ Tips to Tolerate DSM-5

- Mnemonics are widespread for each condition, our teamwork will ensure their inclusion whenever possible
- Impairment of function and ruling out organicity should automatically be memorized for all disorders unless when rarely stated otherwise

◄ Criteria for a Manic Episode

A	A distinct period of **abnormally and persistently elevated, expansive, or irritable mood and abnormally 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)(DIG FAST) 1. Distractibility. 2. Indiscretion: Excessive involvement in pleasurable but high risk activities 3. Grandiosity, inflated self-esteem 4. Flight of ideas 5. Activity: Increase in goal-directed activity/psychomotor agitation 6. Sleep: Decreased need for sleep 7. Talkativeness: More talkative than usual
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.

The criteria for a hypomanic episode is the same except

- It lasts at least 4 or more days
- No marked impairment in functioning

◄ Criteria for a Major Depressive Episode

Depression Is Worth Solidly Memorizing Extremely Grueling Criteria. Sorry.

A. Must have at least **five** of the following symptoms for at least **two weeks** **(must include either number 1 or 2)**

1. Depressed mood most of the time.
2. Interest: Loss of interest (anhedonia).
3. Weight: Change in appetite or weight (↑ or ↓).
4. Sleep: Insomnia or hypersomnia
5. Motor: Psychomotor agitation or retardation
6. Energy: Fatigue or loss of energy
7. Guilt: excessive feeling of guilt or worthlessness
8. Concentration: Diminished concentration
9. Suicide: Recurrent thoughts of suicide and death

TABLE 6–1. DSM-5 bipolar and related disorders

Bipolar I disorder
Bipolar II disorder
Cyclothymic disorder
Substance/medication-induced bipolar and related disorder
Bipolar and related disorder due to another medical condition
Other specified bipolar and related disorder
Unspecified bipolar and related disorder

B. The symptoms cause impairment in social, occupational functioning.
C. The episode is not attributable to a substance or a medical condition.

Major depressive episode could be part of major depressive disorder (MDD) or bipolar disorders (BAD). However, MDD and BAD cannot coexist together.

- The occurrence of a manic episode merits the diagnosis of bipolar disorder

Mania

- Lasts at least 7 days
- Causes severe impairment in social or occupational functioning
- May necessitate hospitalization to prevent harm to self or others
- **May have psychotic features (50% of hospitalized patients have psychotic features)**
- **NOT a medical diagnosis**
- **Always coupled with impaired judgement**
- **Mania is hypothesized to be a defensive mechanism against horrific life event**

Hypomania

- **Lasts at least 4 days**
- No marked impairment in social or occupational functioning
- Does not require hospitalization
- **No psychotic features**
- Many patients have chronic mild depression, may be difficult to differentiate hypomania from depression remission
  - Exert more scrutiny in your history taking and include family members to identify the pathology from a return to normalcy
- **NOT a medical diagnosis**

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**
- Depression is not a requirement for the diagnosis

Bipolar II

- Hypomania
- ≥ 4 days
- Never a manic episode
- **Must have experienced one or more major depressive episodes** with at least one hypomanic episode (if the criteria doesn't meet major depression, consider cyclothymic disorder)
- The genetics of bipolar II is of higher penetrance than bipolar I (greater risk of developing the bipolar phenotype if the family had type II)
- Depression is a requirement for the diagnosis

◄ Bipolar I

- Bipolar I disorder involves episodes of mania and of major depression; however, episodes of major depression are not required for the diagnosis. **It is also known as manic-depression.**

Diagnosis and DSM-5 Criteria

  - **The only requirement for this diagnosis is the occurrence of a manic episode**
  - **The interval between episodes can extend to months or years and the function between episodes may be excellent**

- **Etiology**
  - Biological, environmental, psychosocial, and genetic factors are all important.
  - **First-degree relatives of patients with bipolar disorder are 10 times more likely to develop the illness.**

◄ Bipolar II

- Recurrent major depressive episodes with **hypomania.**

Diagnosis and DSM-5 Criteria

- **History of one or more major depressive episodes and at least one hypomanic episode.**
- **Remember: If there has been a full manic episode, even in the past, or if the patient ever has a history of psychosis, then the diagnosis is bipolar I, not bipolar II disorder.**
- Again, depression is a requirement for the 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
- 40%-70% concordance rate among monozygotic twins, and 5-25% among dizygotic twins
- **Some patients have a mixed presentation of manic and depressive symptoms in the same episode (laughs one second and cries the next)**
  - **The presence of mixed presentation is associated with** ↑ episodes, ↑ alcohol abuse and ↑ suicide attempts

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

Compared with **BDI**, **BDII** experience:

1. **More frequent** and more protracted episodes of **depression**
2. **More chronic** course of **illness**
3. **Less likely to return to premorbid functioning** between episodes
4. Higher **risk of suicide (10-19%) - 15x that of the general population**
5. More **rapid cycling**

Predictors of poor outcome: (1) Substance abuse, (2) rapid cycling, (3) psychosis, (4) poor compliance (5) residual affective symptoms

Sign/symptom	Mania	Depression
Appearance	Colorful/ strange makeup or dress style	Disinterest in personal grooming or hygiene
Mood	Prolonged Euphoria, excessively optimistic heightened irritability	Feelings of sadness Suicidal Ideation
Speech	Talking fast and loudly Difficult to interrupt (pressured speech driven by their rapid succession of ideas [flight of ideas])	Slowed, monotonous, monosyllabic
Activity	Risk-taking Impulsive Restlessness	Difficulty initiating tasks Decreased psychomotor activity Diminished interest in hobbies
Sleep	Decreased need for sleep	Early morning waking with insomnia OR Hypersomnia and daytime napping
Cognition	Distractible Difficulties planning, reasoning and decision making	Reduced ability to concentrate Problems with memory
Self-Perception/Thinking	Exaggerated self-confidence Grandiose ideas	Reduced self-esteem Guilt Pessimistic thoughts Hopelessness
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)	

◄ Specifiers for Bipolar Disorders

Specifiers are extensions of DSM-5 diagnoses

- They are used to further classify certain disorders into new subcategories
- Specifiers may indicate a specific treatment to an established diagnosis
- The same specifiers apply for depression with the exception of rapid cycling

Rapid Cycling Specifier	• At least 4 episodes of mood disturbance in the previous 12 months. Like in a Pt. who have had 4 episodes (2 major depressive episodes + 1 mania episode + 1 hypomania episode).
	• 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. That is how we differentiate it from untreated or partially treated bipolar.
	• 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 comorbidity and morbidity

Peripartum Onset Specifier	• Mood symptoms occur during pregnancy or onset within 4 weeks following delivery.
Psychotic Features Specifier	• Characterized by the presence of delusions and/or hallucinations. • Mood-congruent or mood-incongruent.

Melancholic features	During depressed episode
	One of the following:
	• Loss of pleasure in all or almost all activities and/or lack of reactivity to usually pleasurable stimuli (does not feel better even temporarily when something good happens).
	• **Three (or more) of the following:**
	  ○ Distinct quality of mood (profound despondency, despair, empty mood).
	  ○ Depression is worse in the morning.
	  ○ Early morning awakening (at least 2 hours before usual awakening)(terminal insomnia)
	  ○ Marked psychomotor agitation or retardation.
	  ○ Significant anorexia or weight loss.
	  ○ Excessive or inappropriate guilt.

Atypical features	During depressed episode
	• Mood reactivity (mood brightens in response to positive events).
	• **Two (or more) of the following:**
	  ○ Significant weight gain or increase in appetite.
	  ○ Hypersomnia.
	  ○ Leaden paralysis (heavy, leaden feelings in arms or legs).
	  ○ Long-standing pattern of interpersonal rejection sensitivity causing functional impairment.

Catatonia	• **Three (or more) of the following symptoms:**
	  ○ Stupor (no psychomotor activity).
	  ○ Catalepsy (passive induction of a posture held against gravity). If you position the pt, they will stay in that position
	  ○ Waxy flexibility (slight resistance to positioning by examiner).
	  ○ Mutism.
	  ○ Negativism (no response to instructions or external stimuli).
	  ○ Posturing (spontaneous adoption of posture against gravity). If the pt position themselves in a certain position and freeze. Active not passive.
	  ○ Mannerism (odd caricature of normal actions). Non goal directed movement.
	  ○ Stereotypy (repetitive, abnormal non-goal directed movements).
	  ○ Agitation.
	  ○ Grimacing.
	  ○ Echolalia.
	  ○ Echopraxia (mimicking another's movements)
	Treat with benzodiazepines (first-line), ECT (2nd line)

Anxious	• 2 of the following 5 symptoms across an episode: 1) feeling keyed up or tense, 2) feeling unusually restless, 3) difficulty concentrating because of worry, 4) fear that something awful might happen, and 5) a feeling that one might lose control of himself/herself • Higher suicide risk, less responsive to treatment, higher duration of illness
Seasonal pattern	• Related to time of the year.
Mixed Features	• Depressed features are present during the majority of the days of mania or hypomania. (Mixed refers to a rapid switch between depressed and manic status).

◄ Bipolar Disorder and ADHD

Bipolar Disorder	ADHD
Onset of clear-cut symptoms after age 8	Onset of clear-cut symptoms before age 7
Onset with dysthymia or depression	Onset of hyperactivity or disruptive behaviors
Episodicity	Continuous
Family history of mood disorders	Family history of disruptive disorders
Variable or negative response to stimulants	Response to stimulants
Response to mood stabilizers	Variable or no response to mood stabilizers

◄ Bipolar Disorder and Borderline Personality Disorder

Bipolar Disorder	Borderline Personality Disorder
Biphasic mood dysregulation	Mood dysregulation in the depressive spectrum
Mood symptoms meet threshold criteria for MDD	Mood symptoms often do not reach threshold for MDD
Family history of bipolar disorder	Family history of deprivation and abuse
Reasonable functioning during euthymic episode	Dysfunction persists even in euthymic periods

◄ Secondary Causes of Depressive Episodes

1. **Neurological diseases**
   a. Cerebrovascular disease (subarachnoid hemorrhage, ischemic stroke)
   b. Motor and Systemic (Parkinson's, multiple sclerosis, huntington)
   c. Others (Dementia, epilepsy, central sleep apnea, postconcussional disorder)

2. **Endocrinopathies**
   a. Adrenocorticopathies (Addison's and Cushing's)
   b. Hyperthyroidism
   c. Hypopituiarism

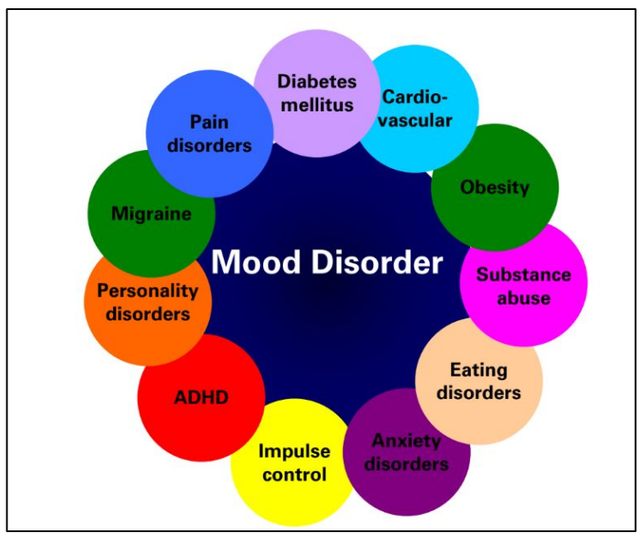
3. **Infections**
   a. Viral (HIV, EBV, hepatitis)
   b. Infectious pneumonia and encephalitis
   c. Tertiary syphilis
   d. Post-influenza

4. **Others**
   a. Anemia
   b. Electrolyte abnormalities (hypercalcemia, hypomagnesemia, hypokalemia)
   c. Heavy metal poisoning
   d. SLE
   e. Alcoholism

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

◄ Comorbidities

- Complicate the diagnosis and management of bipolar disorder. Possible **earlier age** of onset.
- More severe disease course.
- Poorer treatment adherence.
- Greater risk of depressive and mixed episodes and suicidal behavior.
- Impaired psychosocial function.
- Decreased quality of life
- The prevalence of psychiatric/medical comorbidities in bipolar disorder is high
- Cardiometabolic disorders most common specific cause of premature mortality



◄ Bipolar Disorder and 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.
- Therefore **bipolar disorder could be considered a risk factor** for the development of substance use disorder.

◄ Etiological Theories of Bipolar Disorder

1. **Neurotransmitter System Abnormalities:** (Monoaminergic, Cholinergic, Glutamatergic, GABA—ergic, Glucocorticoid, Peptidergic).
2. **HPA axis Function:** HPA abnormalities have been demonstrated in all phases of bipolar disorder.
3. **Neuroimaging and Neurophysiological Findings:** Several areas in the brain are involved.
4. **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 Rhythm in Bipolar Disorder

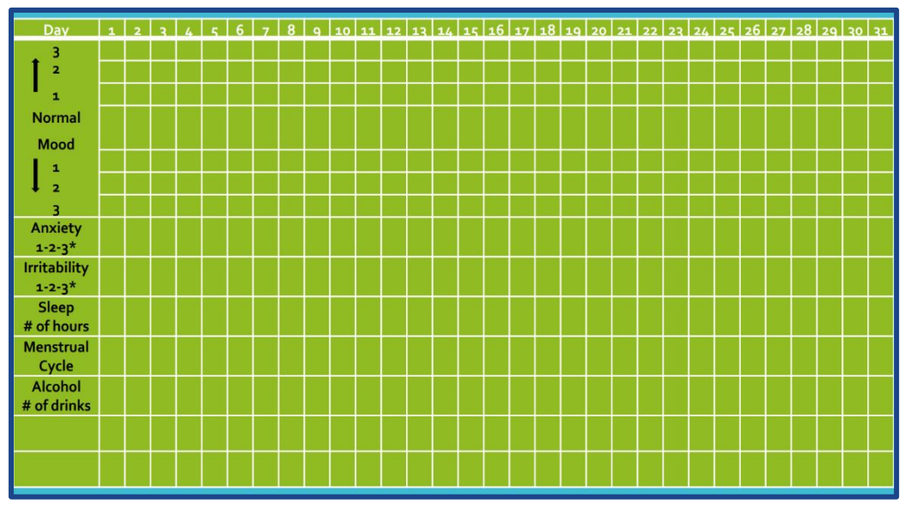
- Changes in sleep, daytime activity and energy levels are important in acute mania and depression.
- Changes in sleep-wake cycle and **represent core features of BD** with sleep abnormalities in about 90% during acute episodes
- Even in euthymia, sleep abnormalities persist.
- **Changes in sleep is highly predictive of impending mental illness presentations.**
- **Sleep disturbance is the most common prodrome of mania.**
- Change in sleeping pattern is a very important symptom and usually appear first in the patient

◄ 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

◄ 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



An example of a mood diary

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

- Life expectancy → reduced by 9 years
- Healthy life → reduced by 12 years
- Divorce or separation → twice as common

◄ Bipolar Disorder and Suicide

- Bipolar II more at risk of suicide
- Completed Suicide: 10-19% (15 times that of the general population).
- Suicide rates are even higher than depression.

◄ Differential Diagnoses

- Unipolar depression (MDD)
- Substance abuse (cocaine, amphetamine)
- ADHD
- Personality disorders (borderline, narcissistic)
- Organic mood disorders.
- Schizoaffective disorder.

Treatment

- **Mood Stabilizers**: **Lithium**, valproic acid, carbamazepine and lamotrigine
- Lamotrigine
- Carbamazepine
- We can use antipsychotics, and benzodiazepines (but are generally discouraged)
- Antipsychotics are the preferred initial therapy in agitated patients
- All 2nd generation antipsychotics are approved for the treatment of acute mania except clozapine
- Avoid prescribing antidepressants before prescribing a mood stabilizer as this may induce mania or hypomania

Treatment Essentials

Acute mania and hypomania	Mild to moderate (mild to moderate functional impairment)	Monotherapy with: • Mood stabilizer (Lithium, valproic acid) • Atypical antipsychotics (e.g., olanzapine, quetiapine) • Consider augmenting the therapy with antipsychotics for the first few weeks if lithium is chosen
	Severe (psychosis or >3 of DIG FAST, or severe impairment)	Combination therapy • Mood stabilizer (Lithium, valproic acid) • Antipsychotics (e.g., haloperidol, quetiapine, risperidone)
	Special cases	• No response to initial treatment (after one or two weeks): Change the choice of mood stabilizer and/or antipsychotic. • Refractory or severe mania: Consider electroconvulsive therapy (ECT). • Pregnancy: Lithium (continued but not initially prescribed during pregnancy), antipsychotics or ECT **(safest)** • Agitated patients: Atypical antipsychotics are the preferred initial therapy
Acute depression	Atypical antipsychotics + mood stabilizer	
Long-term maintenance therapy	Most patient will need lifelong therapy to prevent relapses • Lithium (preferred option) • Valproic acid, lamotrigine and atypical antipsychotics • Refractory or severe cases: Atypical antipsychotics + lithium or valproic acid	

◄ Lithium

- **First-line** (the most important medication in bipolar)
- More effective in preventing high. It is less effective but yet effective to prevent lows.
- Lithium **is the only drug that decreases risk of suicide attempts and completions.**
- Low therapeutic index. It might get to the toxic level.
- Elimination half-life is **8-12hrs** in manic patients and **18-36hrs** in euthymic patients (manic patients have an increased GFR)
- Mechanism of action: inhibits IP3 and glycogen synthase kinase 3β (GSK-3)
    - Stimulates neurogenesis (higher grey matter volume in bipolar patients following administration)
    - Induction of brain-derived neurotrophic factor and VEGF → neuroprotection and mood improvement

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

.**Pre Lithium investigations**

- **Thyroid Function Test**
- **Creatinine Level**
- **ECG**

- Onset of action: ~5-14 (5-7) days. That's why when we use it we should combine it with another drug that will work faster. Antipsychotics (or sometimes, benzodiazepines) are indicated when rapid control is needed
- **100% renal excretion (almost entirely through the kidney, yet found in other bodily fluids e.g., saliva[1], semen or breastmilk)**
- **Levels should be checked monthly in the first 3 months then every 3 months**
    - The concomitant use of thiazides or NSAIDs should be avoided
- Reduces the **frequency and severity** of manic episodes
    - Most patients will have breakthrough episodes

Other indications

1. As an augmentation to prevent suicide in unipolar depression (not in acute situations)
2. Schizoaffective disorder
3. Aggression in dementia and intellectual development disorder
4. Cluster headache prophylaxis

FOOTNOTES

1. A spouse might therefore complain of a "metallic taste" with kissing

- Side effects can be mild or severe:

Mild	• Fine Tremor (worse with high doses, caffeine, and neuroleptics). Treat with propranolol if severe or persistent • Reversible agranulocytosis. • Rash. • Hair loss. • Cognitive Impairment1 • Sedation[1] • Acne. • Nausea / vomiting / diarrhea / dry mouth. • Excessive thirst (polydipsia), polyuria. Diabetes insipidus. Treat with fluid replacement and either amiloride, spironolactone, triamterene and reduce dosage of lithium. • Weight gain (+3.8 kg over one year).
Severe	• Psoriasis exacerbation. • **Hypothyroidism (reversible upon discontinuation, blocks iodine uptake)(Suspect hypothyroidism if symptoms of depression appears during the course of treatment. Treat with levothyroxine)** • Hyperparathyroidism (downregulates CaSR on parathyroid glands → less -ve feedback → hyperparathyroidism) • ECG Changes (reversible flattening of T wave, may also result in SA nodal block) • Nephrogenic Diabetes Insipidus. • Chronic Renal Disease. • Parkinsonian-like symptoms

Lithium Toxicity

1. Autonomic instability (arrhythmia, coarse tremors, agitation, dizziness and syncope)
2. Neurological symptoms (Weakness, muscle fasciculations, ataxia, dysarthria, drowsiness, and lethargy)
3. Others (polyuria, polydipsia)

Management

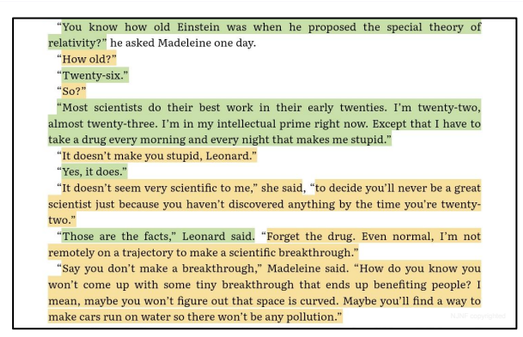
- Discontinue lithium
- IV fluids
- Hemodialysis in severe cases
- Whole bowel irrigation with PEG (floods lithium out of the intestines, rarely needed)

Lithium Contraindications

1. Significant renal impairment
2. Severe dehydration or electrolyte imbalance (kidneys compensate sodium loss with lithium (same ionic charge, +1), this causes excessive accumulation of lithium in the body when sodium or water is lacking)
3. Significant cardiac impairment
4. Psoriasis, DM, ulcerative colitis, diuretic use and senile cataracts: relative contraindication (given cautiously)
5. Discontinued for at least 10-14 days post-MI
6. Myasthenia gravis (blocks ACh release)
7. Pregnancy: especially **first trimester (Ebstein anomaly)**, monitor levels closely in 2nd and 3rd trimesters
   - Excreted in breast milk - discouraged in breastfeeding
   - The teratogenic risk is lower than carbamazepine and valproate
   - Lithium may be continued during pregnancy but use the lowest dose. However if the patient hasn't started any medication, it may be wise to consider alternatives.

FOOTNOTES

1. Cognitive impairment and sedation may at times present as reduced attentiveness and intellectual capabilities in mood disorder patients medicated on psychotropics. The following is an excerpt from Jeffrey Eugenides's The Marriage Plot, illustrating a somewhat classical presentation of these side effects, Leonard was diagnosed with bipolar and is on lithium and anticonvulsants, thus duplicating the sedative effect.



"You know how old Einstein was when he proposed the special theory of relativity?" he asked Madeleine one day.
"How old?"
"Twenty-six."
"So?"
"Most scientists do their best work in their early twenties. I'm twenty-two, almost twenty-three. I'm in my intellectual prime right now. Except that I have to take a drug every morning and every night that makes me stupid."
"It doesn't make you stupid, Leonard."
"Yes, it does."
"It doesn't seem very scientific to me," she said, "to decide you'll never be a great scientist just because you haven't discovered anything by the time you're twenty-two."
"Those are the facts," Leonard said. "Forget the drug. Even normal, I'm not remotely on a trajectory to make a scientific breakthrough."
"Say you don't make a breakthrough," Madeleine said. "How do you know you won't come up with some tiny breakthrough that ends up benefiting people? I mean, maybe you won't figure out that space is curved. Maybe you'll find a way to make cars run on water so there won't be any pollution."

◄ Valproic acid (VPA)

- Another first-line option for bipolar
- Reduces frequency of manic episodes
- More effective than lithium in patients with (1) a mixed presentation, (2) irritable mania, and (3) no response to lithium
- Main mechanism of action: inhibit **GABA transaminase.**
- Can measure its level to guide the dose, among other considerations.
- Particular lab monitoring is required (hepatic panel, CBC, platelet count and a pregnancy test)
- Metabolized in the liver.
- Onset of action is 3-7 **(1-4)** days. Works faster than lithium.
- **Contraindications**:
    - Hepatic disease.
    - Be cautious of drug interactions.
    - **In pregnancy**: Valproate is associated with neural tube defects, cardiac/limb malforms.
- Side effects can be mild or severe
- Preferred to lithium in the treatment of acute mania in children (controversial) and elderly persons
- All women with childbearing potential should take folic acid supplements

Mild	• Tremor. • Agranulocytosis and anemia. • Hair Thinning / Loss. • Sedation. • Benign Rash. • Nausea, Vomiting, Diarrhea. • Weight Gain. • Benign hepatic transaminase elevation (does not require dose reduction)

Severe	• Osteoporosis/reduced bone density.
	• Thrombocytopenia.
	• Hyperammonemic encephalopathy.
	• **Stevens-Johnson syndrome (toxic epidermal necrolysis, TEN Overlap Syndrome):** prodromal flu-like symptoms, characteristic target-like lesions. Mucosal surfaces affected.
	• **Polycystic ovary syndrome (Hyperandrogenism (hirsutism, acne, alopecia) + Chronic Anovulation (oligomenorrhea or amenorrhea)**
	  ○ Can lead to infertility and metabolic syndrome
	  ○ Avoid valproate use in women under 18
	• **Hepatotoxicity.**
	• Acute pancreatitis.
	• Interaction with aspirin and warfarin.
	• HypoNa
	• Hepatotoxicity (especially in those under three years of age)

◄ Carbamazepine

- An anticonvulsant
- An alternative to lithium and valproic acid
- Especially effective in rapidly-cycling patients
- Absorption of carbamazepine is slow and unpredictable (effect is apparent after 5-7 days)
- Several drug interactions (induces its own metabolism as well as the metabolism of other hepatically metabolized drugs)
- Order a CBC and an ECG before starting carbamazepine
- Dose may need to be increased after weeks or months because of autoinduction
- Side effects: transient skin rash, impaired coordination, slurred speech, transient leukopenia and rarely aplastic anemia, hyponatremia,
    - Should be avoided in pregnancy and breastfeeding

◄ Lamotrigine

- Does not interfere with GABA system. Mainly inhibit voltage sensitive sodium channel.
- Helpful in treating **depressive symptoms** (not effective for manic and hypomanic features): Especially effective in delaying the occurrence of depressive episodes and may be effective in treating acute ones (antipsychotics are preferred)
- Should not be combined with valproic acid due to increased risk of Steven-Johnson Syndrome
- Can measure its level to guide the dose, among other considerations.
- No elevated LFT.
- No major hematological side effects and weight Neutral.
- Cognitive side effects are unusual.
- **Side effects**:
    - Sedation.
    - Nausea/vomiting/diarrhea.
    - Headache.
    - Others:
        - Benign rash
            - 8.3% of patients
            - Characteristics of benign rash: (1) Spotty, (2) non-tender, (3) itchy
            - No systemic features and no lab abnormalities
        - Stevens-Johnson syndrome/SJS/TEN Overlap syndrome/Toxic epidermal necrolysis

◄ Non Pharmacological Treatment for Mood Disorders

- ECT (for both depression and mania)
    - Helpful in elderly
    - Psychotic depression
    - Catatonia
    - Severe depression
    - Treatment resistant depression
    - At least equal to lithium in efficacy for mania
    - Should not be used with lithium (lowers seizure threshold)
    - Used when pharmacotherapy fails
    - ECT is the most ambiguous and non-specific psychiatric treatment. The induction of seizure-like activity dramatically improves depressive and manic symptoms, some hypothesize a 'dumping hypothesis', whereby synaptic clefts become filled with serotonin and other neuromodulators following a seizure, manifesting as a benign reset to the neurochemical profile of the brain. But nobody really knows what's going on.
        - Has the most rapid onset of action, after the fourth session, almost certainly an improvement
        - It is done three times weekly, therefore the improvement is observed in the beginning of the 2nd week as opposed to SSRIs (3rd week)
- Psychotherapy in Bipolar patients (1) (IPSRT Interpersonal and social rhythm therapy) (2) Supportive psychotherapy, (3) Psycho education
- rTMS (**Repetitive transcranial magnetic stimulation**)(only for depression)

Compared to ECT

- No anesthesia
- No negative effects on neurocognitive functioning
- No driving restrictions
- Used mainly to treat resistant depression
- Noninvasive

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**

◄ Cyclothymic Disorder

- **Definition**
  - Alternating periods of hypomania and periods with mild-to-moderate depressive symptoms.
- **Diagnosis and DSM-5 Criteria**
  - Numerous periods with hypomanic symptoms (but not a full hypomanic episode) and periods with depressive symptoms (but not full MDE) for at least 2 years.
  - The person must never have been symptom free for >2 months during those 2 years.
  - No history of major depressive episode, hypomania, or manic episode.
- **Course and Prognosis**
  - Chronic course; approximately one-third of patients eventually develop bipolar I/II disorder.
- Treatment
  - **Antimanic agents (mood stabilizers or second-generation antipsychotics)**

◄ Other DSM-5 Bipolar 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 and Medication Induced Bipolar 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.
- **Includes presentation in which there is insufficient information to make a more specific diagnosis (e.g., in emergency room settings).**

Table 10–5. Selected causes of secondary mania

Neurological conditions	**Medications and substances**
Frontotemporal dementia	Alcohol
HIV encephalopathy	Amantadine
Huntington's disease	Amphetamines
Multiple sclerosis	Anabolic steroids
Psychomotor seizures	Antidepressants
Stroke (temporal, right hemispheric)	Cocaine
Traumatic brain injury	Corticosteroids/corticosteroid withdra
Tumors	Cyclobenzaprine
Viral encephalitis	Dextromethorphan
Wilson's disease	Dopamine agonists (levodopa, pramipexole)
Other systemic conditions	*Hypericum perforatum* (St. John's wort)
Carcinoid	Isoniazid
Cushing's syndrome	Methylphenidate and other stimulants
Hyperthyroidism	Modafinil
Niacin deficiency	Phencyclidine
Postoperative delirium	Procarbazine
Puerperal postpartum psychosis	Propafenone
Vitamin B_{12} deficiency	Sympathomimetic amines (e.g., ephedrine)
	Thyroid preparations
	Zidovudine

◀ 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.

Quiz

1. Which episode is favorable to make more benefit from lithium?
   a. Psychosis.
   b. Acute depression.
   c. Acute mania.
   d. Generalized anxiety disorders.

2. Patient w/ CKD stage 3 and has Bipolar. Which of the following is correct about Lithium in this patient?
   a. Contraindications for lithium.
   b. Use lithium until reach end stage renal failure.
   c. Use lithium 3 times daily.

3. 24 year old boy office worker presented to the psychiatrist with 1 week history of increased activity irritability, sleep deprivation, over talkativeness, believe of having special power (in short manic episode). no history of any psychiatric illness
   a. Bipolar I.
   b. Bipolar II.
   c. Dysthymic Disorder.
   d. Substance Induced Manic Episode.

4. A 34 y/o male came with 4 days history reduced sleep overconfidence, talkativeness what is the most important immediate management?
   a. Clonazepam.
   b. Depot IM haloperidol.
   c. Quetiapine.
   d. Phenytoin

5. 25-year-old male with a 2-week history of agitation, unrealistic ambitions and reduced need for sleep. What's the treatment? (Doctor mentioned that they mean the immediate)
   a. Carbamazepine.
   b. Olanzapine.
   c. Lithium.
   d. Valproic Acid.

Answer Key: 1) C, 2) A, 3) A, 4) C, 5) B

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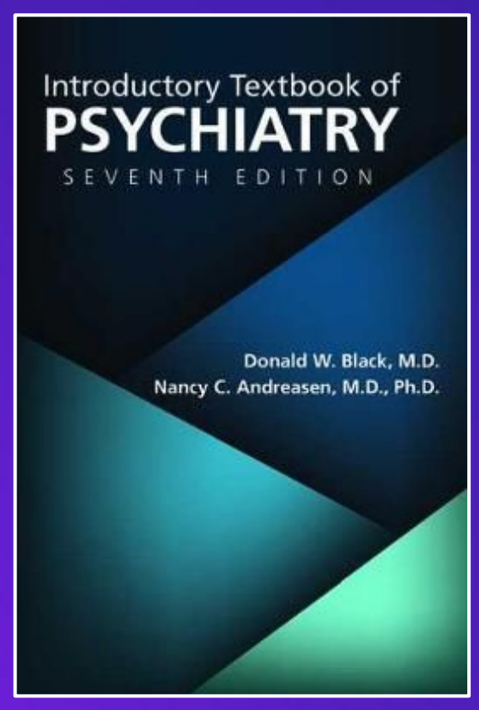

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