THE BIPOLAR SPECTRUM

Bipolar I disorder (mixed mania) ---------- Bipolar II disorder (mixed hypomania) ---------- MDD with mixed features (subsyndromal hypomania) ---------- MDD (non-mixed)

MANIA VS. HYPOMANIA:

Mania	Hypomania
• Time period of at least 1 week* of abnormal mood that is **elevated, expansive** or **irritability** ***** = any time period if hospitalization is required • Significant increase in goal-directed activity or energy • The disturbance causes significant social/occupational functioning • Hospitalization is required or **psychotic features** are present • Episode is not the result of a substance (drugs of abuse, meds, treatment, medical condition) o EXCEPTION: antidepressants can cause a polarity switch	• Period of abnormally and continually elevated, expansive, or irritable mood with increased activity or energy for **at least 4 consecutive days** • Impairment in social or occupational functioning **is not severe** • Hospitalization is **not required,** and there are **no psychotic symptoms** • Episode not attributable to a drug of abuse, a med, or other txt o EXEPTION: antidepressants can precipitate an episode
3 of the following (or 4, if mood is only characterized as **irritable** [rather than expansive or elevated]) • Inflated self-esteem of grandiosity • Decreased need for sleep • Increased quantity of speech, or speech that is pressured • Engaging in activities that can result in detrimental outcomes	• Flight of ideas or subjective racing thoughts • Easily distracted • Increased goal directed activity or psychomotor agitation

MAJOR DEPRESSIVE EPISODE:

- The criteria for a major depressive episode associated with bipolar disorder are the same used to diagnose a MDD with major depressive disorder

BIPOLAR DISORDER SUBTYPES

BIPOLAR I DISORDER:

- Diagnosis can be made after ONE (1) manic episode
- A hypomanic or depressive episode may occur before or after the manic episode
- Not explained by a diagnosis categorized as a schizophrenia spectrum disorder

BIPOLAR II DISORDER:

- One hypomanic episode and at least one major depressive episode
- No history of a manic episode
- Depressive symptoms or frequent alteration between depression and hypomania result in clinically significant distress or impairments of functioning

CYCLOTHYMIC DISORDER:

- Uncommon
- For at least 2 years, there are significant periods of hypomanic and depressive symptoms that never met full criteria
- Significant distressed or impaired functioning
- During this time period, at least 50% of time is spent with hypomanic or depressive symptoms

SPECIFIERS FOR BIPOLAR AND RELATED DISORDERS:

- Specifiers are included with a diagnosis to provide additional information regarding a specific patient
- Can guide pharmacologic decision making
- More than 1 specifier may be given

ANXIOUS DISTRESS:

- **At least 2 anxiety sx** present during current or most recent episode
- May further specify the severity based on number of symptoms
- **Feeling keyed up/tense, unusually restless, difficulty concentrating** because of worry/fear of losing control

RAPID CYCLING:

- At least 4 separate mood episodes (mania, hypomania or depressive) have occurred in the previous 12 months
- Episodes are separated by partial or full remission, or there is a switch to the opposite polarity that is not caused by a substance or another medical condition (EXCEPTION: ANTIDEPRESSANTS)

IMPACT OF RAPID CYCLING:

- More likely to have an earlier lifetime onset of symptoms
- Cycling often begins with depressive sx and can result from antidepressant use
- Women more likely than men
- Rapid cyclers are at increased risk for suicide attempts

MIXED FEATURES:

- Manic or hypomanic episode with mixed features = full criteria met for a manic or hypomanic episode with at least **3 symptoms of depression**
- Depressive episode with mixed features = full criteria met for a major depressive episode with at least **3 symptoms of mania/hypomania**
- NOTE: When criteria are met for both a full manic and full depressive episode, the diagnosis should be manic episode, with mixed features

IMPACT OF MIXED FEATURES:

- A manic episode with mixed features = greater irritability and more severe mood lability compared with non-mixed
- Dysphoric mood, excessive guild, and suicidality = predominate depressive symptoms
- Increased number of lifetime episodes, increased risk of suicidality, longer time to episode resolution

OTHER SPECIFIERS:

- Melancholic features
- Atypical features
- Psychotic features
- With catatonia
- With peripartum onset
- With seasonal pattern

GOALS OF THERAPY:

- Remission (of current mood episode)
- Maintenance of response
- Prevention of relapse
- Full functional recovery (most challenging)

TREATMENT PHARMACOLOGY:

- BZDs and Mood Stabilizers modulate GABA & glutamate
- Clozapine, quetiapine, olanzapine and VPA are suggested activate DNA-demethylation of GABAergic gene promoters to correct downregulation

TREATMENT SCNEARIOS – ACUTE:

MANIC EPISODE:

- Reduce agitation, aggression, and impulsivity to prevent harm to self or others
- First line options = **lithium, valproate, or SGA**
  - Lithium for purely euphoric mania episodes
  - SGA better if aggression is present
- Combination of lithium or VPA with an SGA may be more effective than these agents alone (esp. with psychotic features)
- BZDs have anti-manic properties; can be used as short-term adjunctive treatment for psychomotor agitation, anxious features or **sleep restoration**
- Antidepressants should be tapered and discontinued when possible

MANIC EPISODES WITH MIXED FEATURES:

- Consideration of **VPA, carbamazepine or SGA**
  - SGA as monotherapy or in combo with mood stabilizer
- Presence of mixed features is a predictor of lithium non-response
- Antidepressants should be avoided
- *NOTE: so far, no studies have primarily enrolled individuals meeting criteria for mania with mixed features specifiers*

ACUTE MAJOR DEPRESSIVE EPISODES:

- **Lithium, lamotrigine,** quetiapine, olanzapine-fluoxetine, lurasidone
  - Last 2 may be used in Bipolar I and II
  - **Quetiapine** first line in bipolar II depression
- VPA cannot be used for depression monotherapy
- Aripiprazole and ziprasidone = negative results in bipolar depression

ANTIDEPRESSANTS AND MANIC SWITCH:

- Antidepressants should not be used as monotherapy
  - Studies demonstrate no improvement of depressive sx
  - Should be used in conjunction with mood stabilizer
- Risk of manic switch lower with SSRI or bupropion, higher with SNRI & TCA
  - Switch from depression to activated state may not be seen after 10 weeks of treatment
  - Mood dysregulation = classic hypomania or manic episode, worsening depression, emergence of dysphoria and irritability
  - D/C when worsening irritability/dysphoria, mixed sx, rapid cycling, emergence of polarity switch, lack of benefit

DEPRESSIVE EPISODES WITH MIXED FEATUERS:

- New DSM-V diagnosis = limited evidence
- Lurasidone and olanzapine +/- fluoxetine reported to have benefits in post-hoc analysis
- *Antidepressant monotherapy in MDD with subsyndromal hypomania may be associated with higher rate of suboptimal therapeutic outcomes when compared to MDD without subsyndromal hypomania*

TREATMENT OF ACUTE MANIA OR DEPRESSION EPISODES WITH PSYCHOTIC FEATURES:

- Psychotic symptoms are seen in both acute bipolar manic and depressive episodes
  - More common in bipolar mania
- **Antipsychotics** are recommended when **psychotic features** are present

CONTINUATION TREATMENT:

- Therapy continued 2-4 months following acute response (during which time the risk of **relapse is high**)
- Optimize treatment, prevent adverse reactions, **ensure adherence**, prevent polarity switching, or relapse

MAINTENANCE TREATMENT:

MAINTENANCE THERAPY:

- Once there is mood stability for approx. 3 months during continuation txt
- Focus on the continued improvement of functioning
- Ongoing use of acute/continuation medications
  - Least number of agents at minimum effective dosage
  - Monotherapy = ideal
  - NOTE: greater risk of recurrence when mood stabilizers are abruptly discontinued versus tapered
- **Prophylaxis** against **future mood episodes**
  - Not all agents are equal in their ability to prevent manic and depressive episodes
    - Quetiapine = best coverage
    - Lamotrigine = poor anti-manic but best for depression

STRATEGIES TO CHOOSE MAINTENACE THERAPY:

- Most recent episode of polarity
- Polarity of “index episode” (first episode presented)
- More frequently presenting pole of illness
- +/- frequent, recent, or severe mania

TIPS:

- Select medications that have a low relative risk of weight gain and metabolic syndrome
- Maintenance dose should generally be no less than half of the initial clinically effective dose, as that can result in reduced effectiveness of relapse prevention