The source of the following condensed material is Up-To-Date.
Bold font-definitely know; Regular font-know; *Italics font-supplemental*

Treatment of Bipolar Disorder

1. In treating a manic or hypomanic episode of bipolar disorder, what is the goal?
    - The goal is remission such that at most only 1-2 symptoms of mild intensity persist. If symptoms include psychosis, resolution of psychosis is required.
    - Patients with subsyndromal symptoms of mania are at increased risk of relapse

2. What is the difference between a severe acute manic episode and a moderate acute manic episode?
    - A manic episode is considered **severe** if there is:
        - **dangerousness** (suicidal ideation or behavior; homicidal ideation or behavior; aggressive behavior; poor judgment that place patient or others at imminent risk of being harmed)
        - **psychotic features** (hallucinations or delusions)

3. What is the general approach to treatment of acute mania or hypomania?
    - Drug classes commonly used:
        - Lithium
        - Anticonvulsants
        - Antipsychotics
        - Benzodiazepines- primarily used as adjunctive treatment for insomnia, agitation, or anxiety
    - Severe manic episode
        - Combination therapy (lithium plus antipsychotic; valproate (Depakote) plus antipsychotic)
    - Moderate/mild manic episode, hypomanic episode
        - Monotherapy: lithium, anticonvulsants, or antipsychotics

4. How long does a medication regimen need to be given to tell if it is working?
    - While there is no formally established timeline, in general need to allow for 2 weeks.

5. What are predictors of a good response to medication?
    - Clinical features that consistently predict a good response have not been identified.

6. If a medication works for a patient but the patient stops the medication and has a relapse, is the medication less likely to be effective?
    - While this concern is raised, the few studies that have looked at this question suggest this is not the case.

7. For bipolar patients who relapse often, what is the treatment recommendations?
    - The evidence supports using medication combinations for acute and maintenance treatment of these relapses

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Severe Manic Episode Treatment

1. What is the first line medication treatment recommendation for a severe manic episode?
    - The combination **(Lithium plus an antipsychotic or valproate plus an antipsychotic)** has been shown to be more effective than lithium or valproate monotherapy. Also, the time to response is significantly shorter.
        - Antipsychotic recommended (in alphabetical order):
          Aripiprazole (Abilify), Haloperidol (Haldol) or other first generation antipsychotics, Olanzapine (Zyprexa), Quetiapine (Seroquel), or Risperidone (Risperdal)

2. How is Lithium or valproate (Depakote) plus which antipsychotic to be used chosen?
    - No head-to-head trials have compared antipsychotics in combination with lithium or valproate. Thus the choice between Lithium and valproate, and the choice of which antipsychotic is based on other factors which include:
        - Past response to medications, side effect profiles, comorbid medical conditions, potential for drug-drug interactions, drug preparation (IM, oral disintegrating or pill), patient preference, and cost

3. What is done for treatment resistant patients?
    - A severe manic episode that does not respond to one medication combination should then be treated with a second medication combination. Generally Lithium is switched to valproate (Depakote) or vice versa.

- For patients who do not respond to Lithium plus an antipsychotic or valproate (Depakote) plus the same antipsychotic it is suggested to do a trial of a third medication combination but with a different antipsychotic. The choice between lithium and valproate is based on a clinical judgement of the efficacy and tolerability of the prior two trials.

4. What is done for treatment refractory patients?
    - A patient who has not responded to 4-6 medication combinations is considered treatment refractory.
    - Treatment options at this point include:
        - **Electroconvulsive therapy (ECT)**
        - **Lithium or valproate (Depakote) plus clozapine (Clozaril)**

Treatment of Hypomania & Mild to Moderate Mania

1. What is the first line medication treatment recommendation for hypomania and mild to moderate manic episodes?
    - Monotherapy is commonly used for initially treating hypomania and mild to moderate mania
    - Reasonable choices include

Aripiprazole (Abilify)	Paliperidone (Invega)		Carbamazepine (Tegretol)
Haloperidol (Haldol)	**Quetiapine (Seroquel)**		**Lithium**
Olanzapine (Zyprexa)	**Risperidone (Risperdal)**		**Valproate (Depakote)**

    - Other factors in addition to the efficacy and frequency of treatment discontinuation for any reason that may be considered and lead to a recommended medication include:
        - Patient's past response to medication
        - Past response of patient family members with bipolar disorder to medications
        - Specific symptoms
        - Adverse drug effects
        - Comorbid medical illness
        - Concurrent medications (risk of drug-drug interactions)
        - Cost
    - Since all patients with bipolar disorder should receive maintenance therapy, long term implications of treatment from maintenance therapy also need to be considered:

2. What is done for treatment resistant patients?
    - If the patient's manic episode does not respond to the monotherapy trial within two weeks of reaching the target dose or if the patient does not tolerate the medication then the medication should be tapered and discontinued. A second monotherapy medication trial should be started in conjunction with the tapering and discontinuation of the first medication.
    - If a patient has not responded to 3-5 monotherapy trials, the next suggested step would be a trial of Lithium plus an antipsychotic or valproate (Depakote) plus an antipsychotic.

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Treatment of Bipolar Depression

1. What medications are used to treat bipolar patients with an acute depressive episode?
    - Antidepressants
        - Fluoxetine (Prozac) plus olanzapine (Zyprexa) [combo drug called Symbyax]
    - **Lithium**
    - Anticonvulsants
        - **Valproate (Depakote)**
    - Second generation antipsychotics
        - **Quetiapine (Seroquel)**
        - **Lurasidone (Latuda)**
        - Olanzapine (Zyprexa)
    - Electroconvulsive therapy (ECT)

2. Are other antidepressants beyond the above Symbyax combination medication used in treatment of acute bipolar depression?
    - Antidepressants have a limited role as an adjunct treatment of acute bipolar depression
    - Use of antidepressants for acute and maintenance treatment of bipolar depression is controversial because of concerns the medications are not effective and may harm patients by causing switches from depression to mania as well as rapid cycling
        - Randomized trials indicate that switching during the treatment of bipolar depression occurred more often with tricyclics (TCA's) *[10-11% switch rate]* or venlafaxine (Effexor*) [12-15% switch rate]*
    - Nevertheless, antidepressants are the most commonly prescribed medications for bipolar depression

3. Is there historical information about patients that may help determine if an antidepressant could be used or should be avoided for treating bipolar depression?
    - Could be used if patient has:
        - history of responding favorably in the past
        - never taken antidepressants

4. Which anti-manic drugs should be used with an antidepressant so as to prevent switching?
    - **Lithium**
    - **Valproate (Depakote)**
    - Carbamazepine (Tegretol)
    - Second generation anti-psychotics
        - **Quetiapine (Seroquel)**
        - **Lurasidone (Latuda)**
        - Olanzapine (Zyprexa)
            - studies have looked at olanzapine plus fluoxetine (Symbyax); it is not known if olanzapine reduces the risk of switching from other antidepressants; is also not known if other second generation antipsychotics reduce the risk of antidepressant-induced switching
    - Switching to mania occurs less often when these anti-manic drugs are used with an antidepressant;
    - **Avoiding antidepressant monotherapy** is consistent with practice guidelines

5. Are antidepressants used in maintenance treatment of bipolar depression?
    - Antidepressants generally do not appear to reduce the risk of depressive episodes

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Maintenance Treatment of Bipolar Disorder

1. What is the first line maintenance treatment of bipolar disorder?
   - First line treatment is usually the same medication regimen that successfully treated the acute hypomanic or manic episode

2. What is the second line maintenance treatment of bipolar disorder?
   - If the patient is not tolerating the first line maintenance therapy the following is the general order of preference for second-line monotherapy
     - **i. Lithium**
       - More widely studied than any other maintenance therapy
       - Reduces risk of relapse by about 30%
       - Reduced risk of suicide
     - **ii. Valproate (Depakote)**
       - Considered third line for female patients of childbearing age due to teratogenicity concerns
       - Reduces risk of relapse by about 30%
     - **iii. Quetiapine (Seroquel)**
       - Studies also shows effectiveness in preventing depression recurrences

3. What is the treatment for patients who relapse often?
   - The evidence supports using medication combinations for acute and maintenance treatment of these relapses
     - **Lithium or valproate (Depakote) plus an antipsychotic**; Antipsychotic may be:
       - quetiapine (Seroquel)
       - risperidone (Risperdal)
       - olanzapine (Zyprexa)
       - aripiprazole (Abilify)
     - ECT-for patients who responded to ECT for acute mood episodes or who failed many ($\geq$5) other maintenance medication regimens
4. What medications are to be avoided in maintenance treatment of bipolar disorder?
   - Antidepressants: are concerns these medications may destabilize patients
   - Benzodiazepines: may be associated with an increased risk of recurrence

5. How long do bipolar patients need maintenance treatment?
   - Patients may require maintenance for many years, some for their entire lives.

Summary

Severe manic episode:

- **lithium or Valproate (Depakote), plus SGA/FGA**
- **Treatment refractory: ECT, lithium or Valproate (Depakote) plus clozaril (clozapine)**

Hypomania & mild to moderate mania

- **Most SGA's**
- **Lithium, Valproate (Depakote), carbamazepine (Tegretol)**
- **Treatment resistant (multiple monotherapy trial failures): lithium or Depakote plus SGA**

Maintenance

- **1st line: Whatever worked in treating acute hypomania or mild to moderate mania**
- **2nd line: Lithium; Valproate (Depakote), quetiapine (Seroquel),**
- 3rd line: Olanzapine (Zyprexa) or Aripiprazole (Abilify) or Risperidone (Risperdal)
- **If relapse often, lithium or Depakote plus SGA/FGA ECT an option**

Bipolar depression

- **"Antidepressants": Symbyax (fluoxetine plus olanzapine)**
- **Lithium**
- **Anticonvulsants: Valproate (Depakote)**
- **SGA's: Quetiapine (Seroquel), Lurasidone (Latuda),** Olanzapine (Zyprexa)
- **ECT**