Bipolar Disorder

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Key Points

1. Understand the nature of Bipolar Disorder and its different types
2. Understand the new enthusiasm for lithium
3. Understand the use of other important drugs: aripiprazole, lamotrigine, risperidone, lurasidone, and quetiapine
4. Recognize the value of psychotherapy
5. Know how to best help a family member with Bipolar Disorder

To qualify as a full manic episode, manic symptoms must last for:

A. Two Days
B. Four Days
C. One week
D. Two weeks

C. One Week

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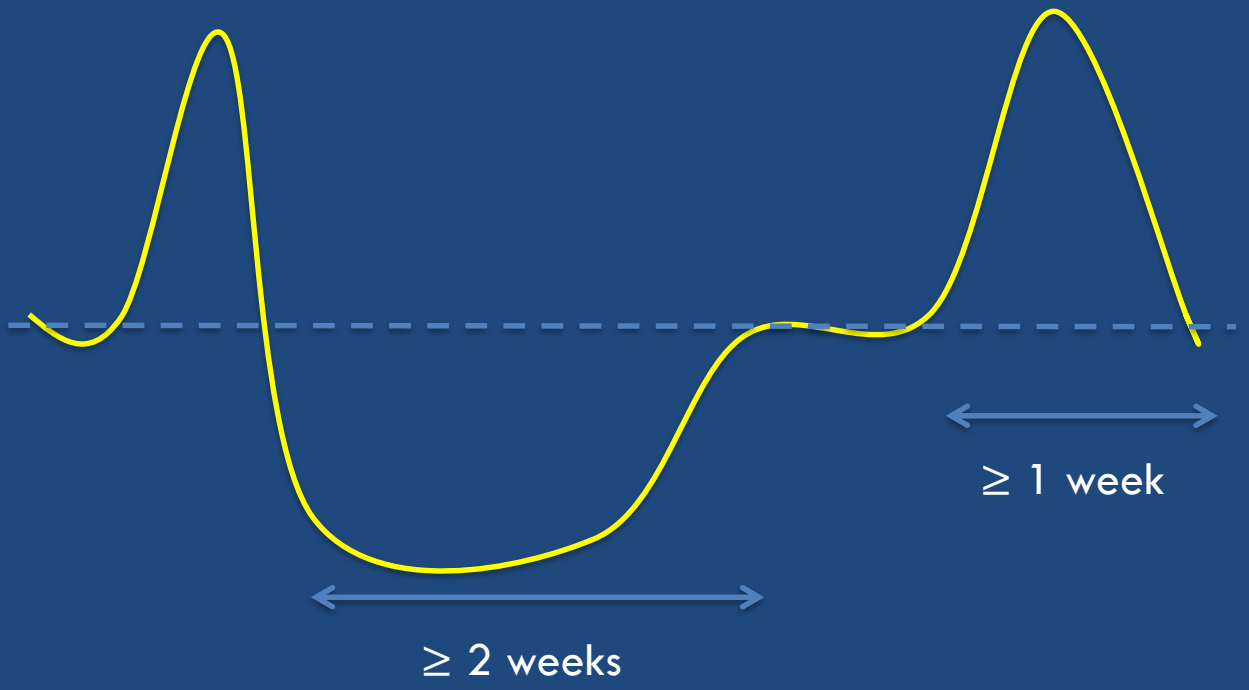
B. Four Days
C. One week
D. Two weeks

Bipolar I Disorder



Criteria for Bipolar Mania

A. Persistently elevated, expansive *or irritable* mood, lasting ≥ 1 week

B. ≥ 3 of the following

1. Flight of ideas, sense that thoughts are racing
2. Decreased *need* for sleep
3. More talkative or pressure to keep talking
4. Increased energy (leading to increased productive activity or agitation)
5. Distractibility
6. Excessive involvement in pleasurable activities that have a high potential for painful consequences
7. Inflated self-esteem or grandiosity

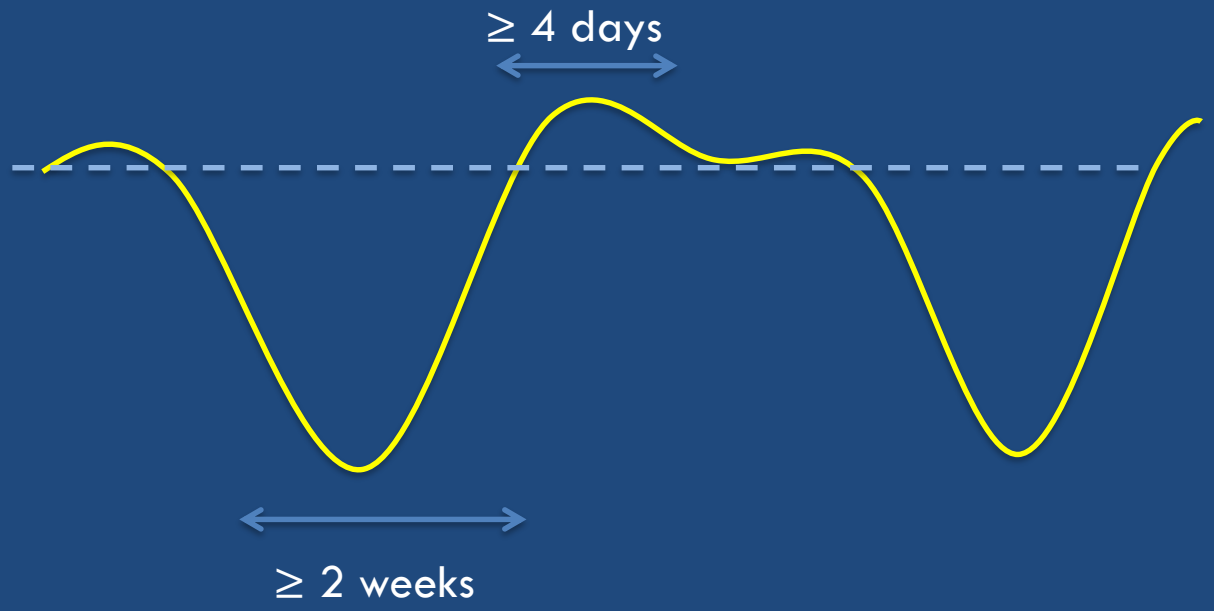
Criteria for Bipolar Depression

same as major depressive episode in major depressive disorder:

≥ 5 of the following sx, lasting ≥ 2 weeks:

1. Depressed mood
2. Diminished interests or pleasure
3. Weight loss, or weight gain
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. *Fatigue or loss of energy (leaden paralysis)*
7. Feelings of worthlessness or guilt
8. Problems thinking, concentrating
9. Recurrent thoughts of death, or SI

Bipolar II Disorder



Bipolar II Dis

Hypomanic Episodes

- *Same* as Bipolar I but sx present for ≥ 4 days
- Change in mood/functioning must be unequivocal and observable by others
- Not severe enough to cause marked impairment in functioning.

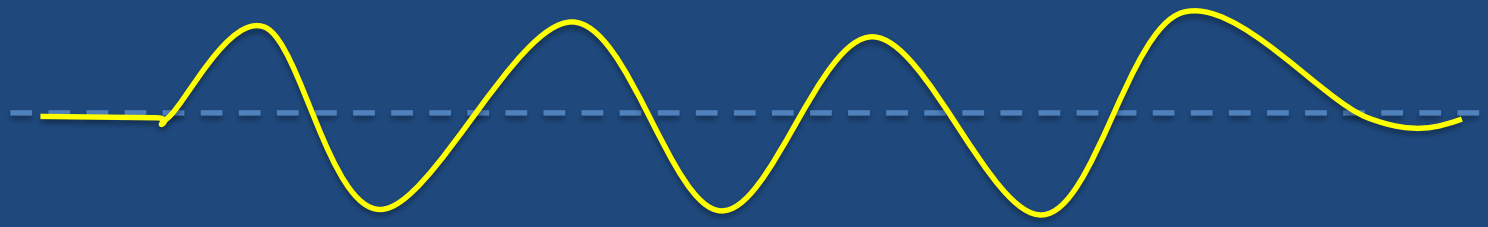
Depressions

- *Same* as for Bipolar I, Major Depressive Dis

Note: suicide risk just as high in Bipolar II as in Bipolar I

(lifetime risk 6 - 15%)

Cyclothymic Disorder



Hypomanic spells last < 4 days

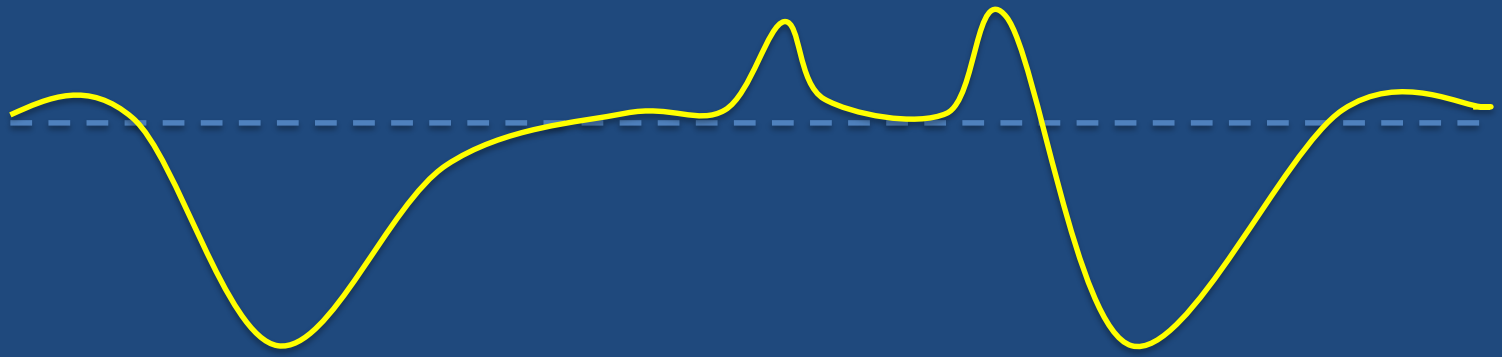
Depressive spells last < 2 weeks

During a 2-yr period, hypomanic or depressed half the time

15-50% develop Bipolar I or Bipolar II Dis

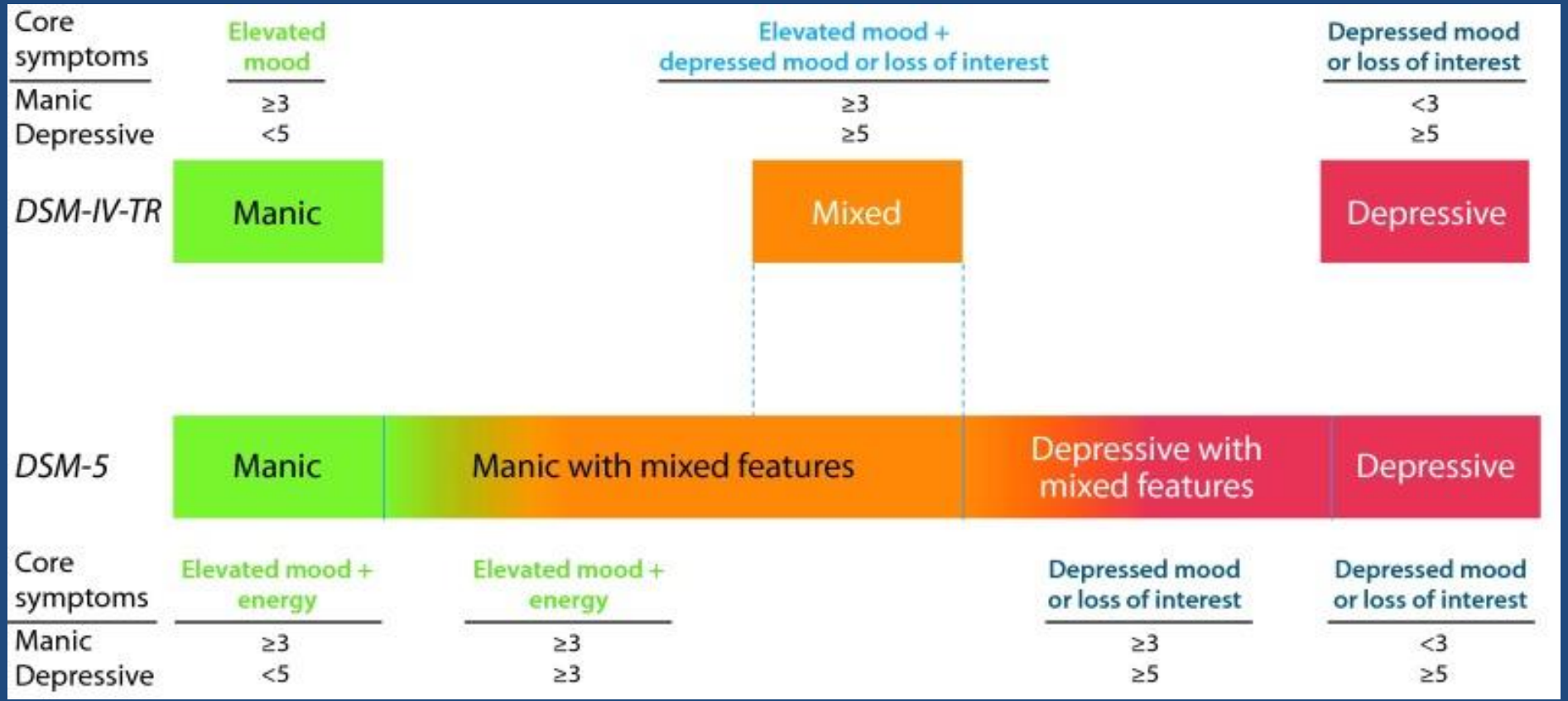
Treatment similar to Bipolar II Dis

Bipolar Disorder Unspecified



- Depressive spells > 2 wks but hypomanic spells last < 4 days, or -
- Depressive and hypomanic sx failing to meet full criteria for BD or Cyclothymic Disorder

Bipolar Mixed States – Considered Part of Mania or Depression



Bipolar Disorder - FAQs

Cause

- Unknown
- Genetic component: 10% offspring of parent with BD have bipolar spectrum dis (vs 0.8% of controls)
- Offspring are twice as likely as controls to suffer from a serious psychiatric disorder of any type

Prevalence

- Bipolar I Dis – 1%
- Bipolar II Dis – 2-3%
- Cyclothymic Dis and Bipolar Unspec – 2-3%

Bipolar Disorder - FAQs

Patients who also have Substance Use Disorders

- Bipolar I Dis – 42%
- Bipolar II Dis – 26%

Suicide Risk

- 25-50% attempt suicide; 6-15% complete
- Suicide risk same or greater in Bipolar II

Socioeconomic Burden of BD

- 6th leading cause of disability-adjusted life-yrs
- Costs in 1991 - $7 billion direct, $45 billion including indirect costs
- Majority of patients with Bipolar I Dis are unemployed, living in households with low income
- Most report relationship problems, divorce rates are high

Notable People believed to have (or had) Bipolar Disorder

- Demi Lovato
- Catherine Zeta-Jones
- Carrie Fisher
- Vivian Leigh
- Jean-Claude Van Damme
- Sinéad O’Connor
- Vincent van Gough
- Virginia Woolf
- Jane Pauley
- Mariette Hartley
- Patty Duke
- Meriwether Lewis
- Winston Churchill
- Margot Kidder
- Brian Wilson
- Amy Winehouse
- Ashley Judd

Missed Diagnosis

The typical person with bipolar disorder goes how many years before accurate diagnosis after first seeking help?

A. 1 year
B. 2 years
C. 3-5 years
D. 6-10 years

D. 6-10 years

Depending on how onset is defined:

- Patients are ill for up to 10 years before dx of bipolar disorder
- Patients see an average of 4 physicians before diagnosis made

A. 1 year
B. 2 years
C. 3-5 years
D. 6-10 years

Why is Diagnosis Missed?

- Patients tend to present when depressed, underreporting manic and (especially) hypomanic episodes.

Why is Diagnosis Missed?

1. Patients tend to present when depressed or anxious, underreporting manic and (especially) hypomanic episodes.

2. Patients may not recognize their own hypomanic symptoms as being abnormal

3. Substance abuse can cloud the clinical picture

4. Spectrum of hypomanic symptoms can be difficult to separate from “normal” mood variation

"I medicate first and ask questions later."

Treatment of Bipolar Disorder

Pharmacological Tools
- Mood Stabilizers
- Anti-manic agents
- Medications for bipolar depression
- Medications for sleep and anxiety

Psychotherapeutic Tools
- Psychoeducation for patient and family
- Intensive Out-patient Program
- CBT, Life coaching

Substance Use Disorder treatment, if needed

Mania FDA Approved Med for Bipolar Disorder

Drug	Trade Name	Mania	Depression	Maintenance
Lithium		+		+
Valproate	**Depakote**	+		
Lamotrigine	**Lamictal**			+
Risperidone	**Risperdal**	+		+
Olanzapine	**Zyprexa**	+	+ with fluoxetine	+
Quetiapine	**Seroquel**	+	+	+
Aripiprazole	**Abilify**	+		+
Lurasidone	**Latuda**		+	
Ziprazidone	Geodon	+		
Cariprazine	Vraylar	+		
Cabamazepine ER	Tegetrol ER	+		
Oxcarbazepine	**Trileptal**			

Lithium is considered the best choice for Bipolar I Disorder for all of the following reasons, except:

A. It protects the brain from lasting injury associated with bipolar mania
B. It reduces manic symptoms more rapidly than other drugs approved for mania
C. It is the only medication repeatedly shown to reduce the risk of suicide
D. 40-80% of patients respond to lithium

B: Lithium is *not* the most rapidly acting bipolar medication

Lithium often takes 1-2 wks to reduce manic symptoms. Antipsychotics and valproate (Depakote) work faster

A. Protects the brain
B. Acts most rapidly
C. Reduces risk of suicide
D. 40-80% response rate

Lithium - Benefits

- 40-80% response rate in bipolar mania
- Reduces manic *and* depressive episodes
  - 1/3 are “excellent” lithium responders
  - 1/3 are partial responders
  - 1/3 have limited response
- Reduces suicide risk by 60-70%
- Neuroprotective
- Many patients have minor if any side effects

Lithium – predictors of good response

- Positive family history of bipolar dis
  (especially a positive family history of response to lithium)
- Classic euphoric manic episodes
- Full remission between episodes
- Later onset
- Pattern of mania, followed by depression
- Good adherence

Lithium – Side Effects

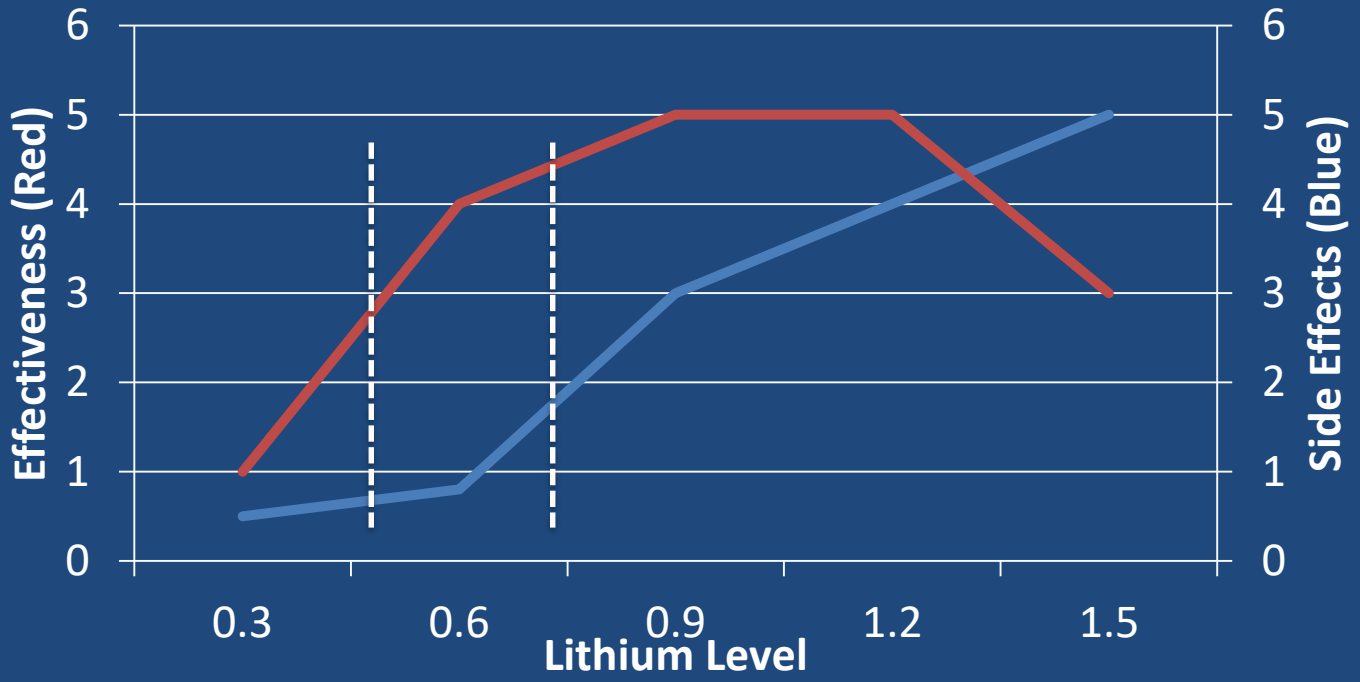
dose dependent

- Within therapeutic range (0.4 – 1.2)
  - Tremors
  - GI disturbance (nausea, diarrhea)
  - Increased urination → increased thirst
  - Increased appetite → increased weight
  - Acne (in adolescents)
- Above therapeutic range(1.2 – 1.6)
  - Marked tremors
  - Incoordination
- > 1.7 potential dangerous toxicity

Lithium Levels: finding the sweet spot

initial target for acute full mania: 0.8 – 1.0 mmol/L

for hypomania or maintenance: 0.4 - 0.6 mmol/L



Lithium Dosing

- Adults: start at 300mg twice/day; check level in one week and adjust
- Dose in single dose at night unless SEs require divided dosing.
- Average eventual dose: 900-1200mg/day
- Children and the elderly: start at 300mg daily, check level in a week and adjust

Check dose and adjust for daily NSAIDs, ACE-Inhibitors

Lithium – managing side effects

Nausea – change to ER preparation

Diarrhea – avoid ER preparation

Tremors – low dose propranolol (e.g., 20mg bid)

Emotional/cognitive dulling – lower dose

Polyuria – add HCTZ

Increased appetite – dietary strategies

Hypothyroidism – augment with oral thyroid medication

Lithium – SEs with long-term use

Hypothyroidism

- may develop in first year of treatment, sometimes resolves spontaneously

Kidney toxicity

- may develop in < 5% after many years of use

Parkinsonsism

- Infrequent to rare, sometimes seen after years of use

Hypercalcemia (high calcium levels from elevated parathyroid hormone)

- Studies found incidence of 12-15% in long-term users, cause uncertain.

Lithium: Laboratory Monitoring

Day #7

Lithium level, along with other baseline labs:
Creatinine, TSH, calcium; EKG in elderly or in patient with h/o heart disease

1st month:

Recheck Li level ~ 7 days after each dose increase until target level achieved

1st year:

Li level Q 3mo; creatinine, Calcium and TSH (thyroid) q6 mo

2nd year and beyond:

Li level, creatinine, calcium and TSH q6mo
24-hr creatinine clearance test if creatinine rising

Treatment of Mania and Hypomania

- Bipolar I Mania with psychosis
  - Lithium + antipsychotic (e.g., risperidone 2-6mg)
  - 2nd line: valproate +/- antipsychotic
- Bipolar I Mania without psychosis
  - Lithium, addition of antipsychotic optional
  - 2nd line: valproate +/- antipsychotic
- Bipolar II Hypomania
  - Quetiapine, aripiprazole – or focus on stabilization by starting lithium or lamotrigine

Depression

Drug	Trade Name	Mania	Depression	Maintenance
Lithium		+		+
Valproate	**Depakote**	+		
Lamotrigine	**Lamictal**			+
Risperidone	**Risperdal**	+		+
Olanzapine	**Zyprexa**	+	+ with fluoxetine	+
Quetiapine	**Seroquel**	+	+	+
Aripiprazole	**Abilify**	+		+
Lurasidone	**Latuda**		+	
Ziprazidone	Geodon	+		
Cariprazine	Vraylar	+		
Cabamazepine ER	Tegetrol ER	+		
Oxcarbazepine	**Trileptal**			

Treatment of Depression

Quetiapine

- Low doses (50-200mg) good for depression
- Higher doses good for mania (200-600mg)
- Highest doses good for psychosis (300-800mg)
- Anxiolytic and hypnotic effects
- Side Effects:
  - Sedation
  - Increased appetite → weight gain
  - Possible elevation of TGs, glucose (monitoring required if used for maintenance)
  - Akasthisia, movement disorders

Treatment of Depression

Lurasidone

- Only proven useful for depression (and schizophrenia)
- Easy dosing (start with 20mg, increase to 60-80mg)
- Side Effects:
  - Sedation
  - Akasthisia, movement disorders
  - Expensive (> $1,000/mo)

Treatment of Depression

Lamotrigine

- Officially approved as a mood stabilizer
- Not approved for bipolar depression but widely accepted as having antidepressant effects in many patients
- Not effective for mania (though may prevent hypomania in Bipolar II)
- Side Effects:
  - Many patients report no side effects
  - 5% develop benign rash
  - < 1/1,000 develop Stevens-Johnson Syndrome

Treatment of Depression

Aripiprazole (Abilify)

- Officially approved for mania and stabilization
- Not approved for bipolar depression but accepted as often having antidepressant effects in many patients
- Side Effects:
  - Antidepressant effects achieved at low doses (2-5mg)
  - Low doses have low side effects
  - Possible SEs: sedation, increased appetite, akasthisia
  - If continuing, monitor lipids and glucose
- Expensive (> $1,000/mo)

What about antidepressants?

- Antidepressants generally ineffective in bipolar I depression
  - 2010 analysis of 15 studies involving 2373 showed no benefit over placebo
- Antidepressant given in the absence of a mood stabilizer or antipsychotic can trigger manic switch or rapid cycling
  - Venlafaxine and TCAs > SSRIs and buproprion
- A subcategory of patients with bipolar II depression may be responsive to antidepressants
- If patients reports past response, appropriate to try

Maintenance

Drug	Trade Name	Mania	Depression	Maintenance
Lithium		+		+
Valproate	**Depakote**	+		
Lamotrigine	**Lamictal**			+
Risperidone	**Risperdal**	+		+
Olanzapine	**Zyprexa**	+	+ with fluoxetine	+
Quetiapine	**Seroquel**	+	+	+
Aripiprazole	**Abilify**	+		+
Lurasidone	**Latuda**		+	
Ziprazidone	Geodon	+		
Cariprazine	Vraylar	+		
Cabamazepine ER	Tegetrol ER	+		
Oxcarbazepine	**Trileptal**			

Bipolar Maintenance

- **Lithium** – best efficacy, suicide reduction
- **Lamotrigine** – lowest side effects
  - But less likely to prevent or treat mania
  - An attractive option in Bipolar II if hypomania not a major concern
- **Quetiapine, aripiprazole** –
  - Raise dose for breakthrough mania, lower for dep'n
- **Risperidone** – not helpful for breakthrough dep'n
  - Associated with more SEs than alternatives
- **Olanzapine** – efficacy for breakthrough mania, dep'n
  - Can cause medically serious wt gain, elevated glucose

Bipolar Maintenance

Off-label options:

- Valproate (Depakote) – efficacy as mood stabilizer close to that of lithium
  - Start at 500-1,000mg, average eventual dose 1,500mg
  - On initiation, monitor CBC, LFTs and valproate level
    - 40-80 therapeutic for some, 80-100 best for mania (but more side effects)
  - 2/3 experience weight gain; GI SEs common

- Oxcarbazepine (Trileptal)
  - Can work for mild mania, stabilization; not for depression
  - Start at 300mg bid, average eventual dose 600mg bid
  - Unlike carbamazepine, no blood dyscrasias
  - Well tolerated, minimal effects on weight

Summary of Pharmacological Treatment

- Full Mania – lithium or valproate (may be combined), +/- antipsychotic (e.g., risperidone or quetiapine), especially if psychotic
- Hypomania – low dose antipsychotic; or lithium, oxcarbazepine
- Depression – quetiapine, lurasidone, lamotrigine or aripiprazole
- Mixed States – mood stabilizer + quetiapine
- Maintenance for Bipolar I - Li > valproate > antipsychotic (quetiapine, aripiprazole)
- Maintenance for Bipolar II – lamotrigine, Li, low-dose quetiapine, aripiprazole, ? Oxcarbazepine, ?? antidepressant

Psychotherapy for Bipolar Disorder improved outcomes

Reduces distress and illness severity by:

- Addressing stressors that can trigger or contribute to bipolar or manic episodes
- Addressing substance abuse, self-medication
- Addressing effects of illness on self-esteem
- Improving adherence
- Assisting family members in understanding the illness and how to help
- Facilitating communication with physician

Psychotherapy for Bipolar Disorder

Reduces functional impairment by helping patient to:

- Bear residual symptoms and breakthrough episodes
- Gain coping skills to allow continuation of school, employment
- Establish rhythms of work, sleep and diet shown to improve mood stability
- Continue social/recreational activities, even if at a reduced pace

"Fake it until you make it"

“Okay, maybe I need to change my life, or maybe you could just tweak my medication.”

Self-Help for Bipolar Disorder

- DBSA
- NAMI
- Overcoming Bipolar Disorder: A Comprehensive Workbook for Managing Your Symptoms and Achieving Your Life Goals – *by Mark Bauer, et al*

How Can Families Help?

- Help patient and other family members understand the illness as a treatable brain disorder
- Help get patient into treatment and assist in adhering to treatment recommendations
- Communicate important observations with care providers – and, carefully, with patient himself/herself
- Get patient involved with NAMI, DBSA, other self-help
- Encourage exercise, and a daily structure, to help maintain function during periods of depression or hypomania
- Assist with obtaining disability, if appropriate

When Standard Out-Patient Care is Not Enough

- IOP – Intensive Out-Patient Program

  When more intensive work is required to stabilize moods and improve ability to manage symptoms and improve function

- PHP – Partial Hospital Program

  The most intensive kind of treatment to prevent (or shorten) in-patient treatment

- Hospitalization

  Generally short-term, for stabilization of acutely ill individuals at risk of self-harm, or of doing serious harm to personal and family affairs.

- Residential Treatment –

  For patients who require long-term stabilization with full-time staff and support. Hard to get insurance authorization for this.

One more time…

1. **Key to diagnosis: doctors must ASK about past mania/hypomanic symptoms**
   - Energized, racing thoughts, extra-talkative, decreased need for sleep, lasting for a few days – 4 for bipolar II, 7 for bipolar I
   - Ask a family member
2. **Lithium reduces suicide and produces best outcomes:**
   - Level of 0.4-0.6 often works, reduces side effects and improves adherence
   - Dosing in single bedtime dose improves adherence
   - Labs (creat, Ca, TSH and Li level) quarterly first year, then every 6 mo
3. **Other useful drugs:**
   - **Lamotrigine** for bipolar II
   - **Quetiapine/aripiprazole** – doses go up/down for breakthrough mania/dep'n
   - **Risperidone** for acute mania, psychosis, **Lurasidone** for depression
4. **Psychotherapy can make a big difference in facilitating function and fulfillment**