MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Treatment of Mania and Psychosis

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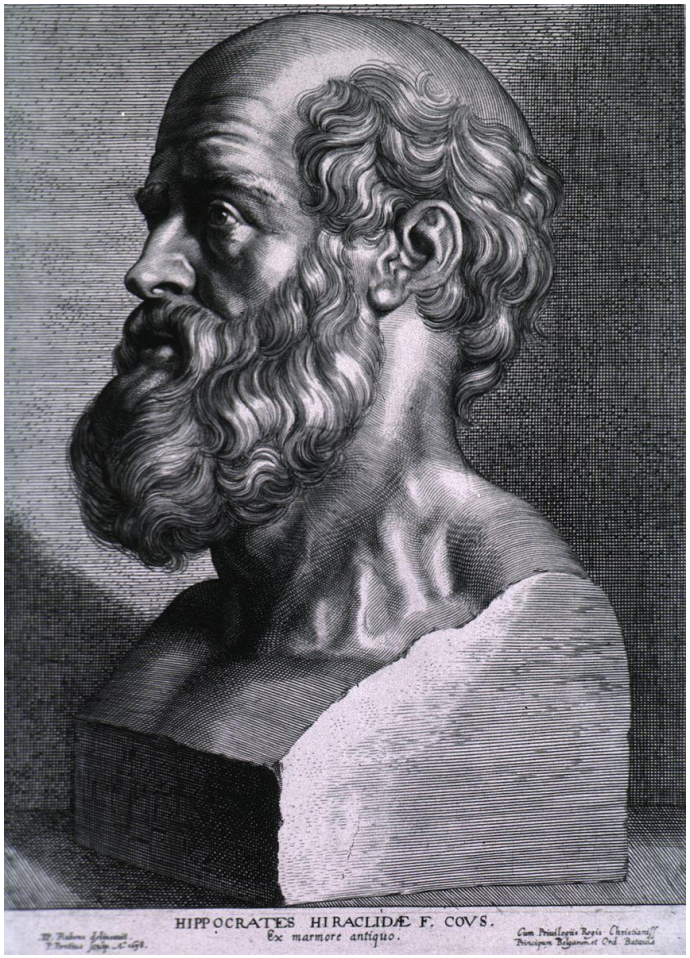
Disclosures

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.

Historical perspectives

- Hippocrates Description of Melancholia (Fourth Century BCE)
  - Aversion to food
  - Despondency
  - Sleeplessness
  - Irritability
  - Restlessness
  - Caused by an excess of black bile



Aristotle

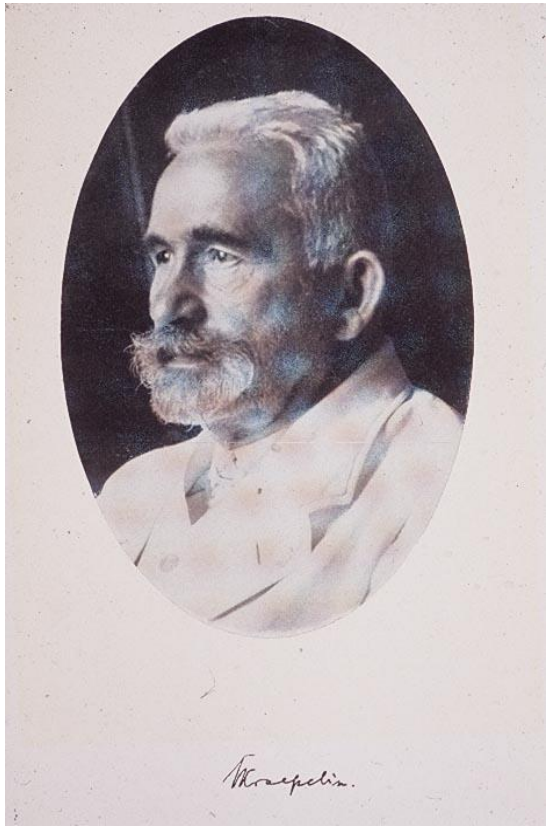
- Notices the frequent occurrence of melancholia in philosophers, artists and statesmen.
- Gives the example of Plato and Socrates.

Avicenna (980-1087 CE) Describes Melancholia and Mania in his Canon of Medicine

- Mania
  - Anger
  - Hostility and aggressive behavior
  - Anxiety
  - Agitation
  - Meaningless play
  - Increased activity and agitation
  - More common in spring and summer
  - Closely related to melancholia
  - Suggests various herbal medicines for both mania and melancholia

Emil Kraepelin (1856-1926)

- In late 19th century classifies the major psychotic disorders into manic-depressive insanity and dementia praecox.
- Manic-depression is associated with episodic symptoms and better outcomes.



Lifetime and 12-Month Prevalence and Age at Onset of DSM-IV/CIDI Bipolar Disorder in the 9282 Respondents

Prevalence Meean (SD)		Any Bipolar disorder		Bipolar I
Lifetime		4.4 (24.3)		1.0 (13.2)
12 month		2.8 (18.9)		0.6 (9.2)
Age of onset (years)				
Mean (SE)		20.8 (11.8)		18.2 (11.6)

Merikangas, K. R. et al. Arch Gen Psychiatry 2007;64:543-552.

ARCHIVES OF GENERAL PSYCHIATRY

Diagnosis

- At lease a week of abnormal and persistently elevated, expansive or irritable mood and abnormally and persistently goal-directed behavior or energy, associated with 3-4 of the following.
  - Inflated self esteem or grandiosity.
  - Decreased need for sleep.
  - Pressured speech.
  - Flight of ideas.
  - Distractibility.
  - Increased goal directed activity or agitation.
  - Excessive involvement in activities with a high potential for painful consequences.
- The mood changes are severe enough to cause marked impairment in social or occupational functioning (Not just transient changes).
- Evaluate for secondary causes of the mood disorder such as medical disorders, prescription medications or substances.

Diagnostic and Treatment challenges:

- Full blown mania is rarely missed in clinical settings, however, hypomania is more difficult to identify
- Some reasons for misdiagnosis include
  - Limited insight of patients into mania/hypomania
  - Lack of systematic assessment of mania by clinicians
  - Stigma
  - Variability of age of onset and presentation
  - Misdiagnosis as unipolar depression
  - Psychiatric and medical comorbidities
  - Comorbid substance use disorders
  - Symptom overlap with other psychiatric conditions

Smith, Daniel, Nassir Ghaemi, and Mark Zimmerman. "Is underdiagnosis the main pitfall when diagnosing bipolar disorder?." *BMJ. British medical journal* 340.7748 (2010): 686-687.
Thomas P. *J Affect Disord.* 2004;79(suppl 1):S3-S8.
Berk M, et al. *Med J Aust.* 2006;184:459-462.

Psychosis

- More than half of manic episodes are associated with psychosis
  - Hallucinations
  - Delusions
  - Disorganization in speech and thought
  - Catatonic behaviors

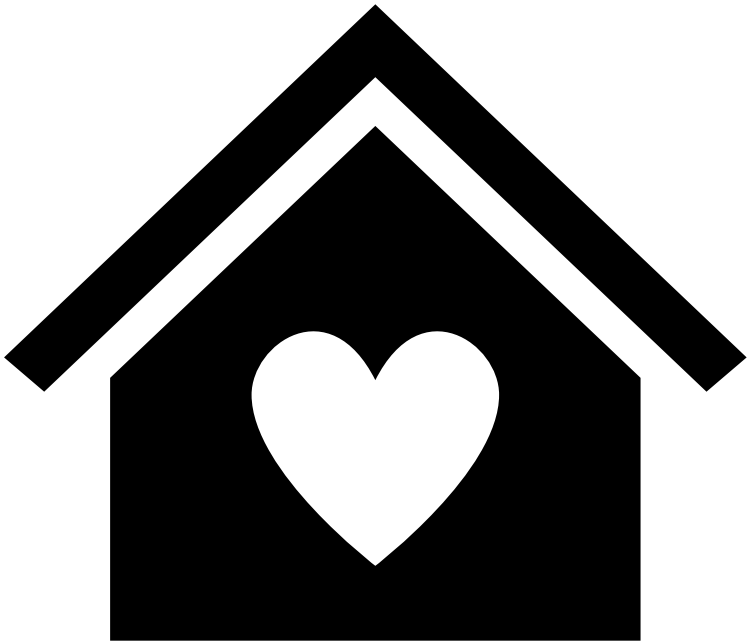
Dunayevich E, Keck PE Jr. Prevalence and description of psychotic features in bipolar mania. Curr Psychiatry Rep. 2000 Aug;2(4):286-90.

Insight and Accepting Treatment

- Insight may be diminished during acute phases of mania and psychosis
- Lack of insight can become an obstacle to accepting treatment and treatment non-adherence

Yatham, Lakshmi N., et al. "Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: *Bipolar disorders* **2018** Mar;20(2):97-170

The role of the family



- Provide support for healthy behaviors.
- Listen to the individuals concerns.
- Remember that stigma is a serious obstacle to getting treatment.
- Keep an open line of communications with the clinicians treating the family member.
- Don’t hesitate to ask questions from the treatment team.
- Education, support, and advocacy for patients and families
  - DBSA (Depression and Bipolar Support Alliance) dbsalliance.org
  - NAMI (National Alliance on Mental Illness) nami.org

Treatment Options

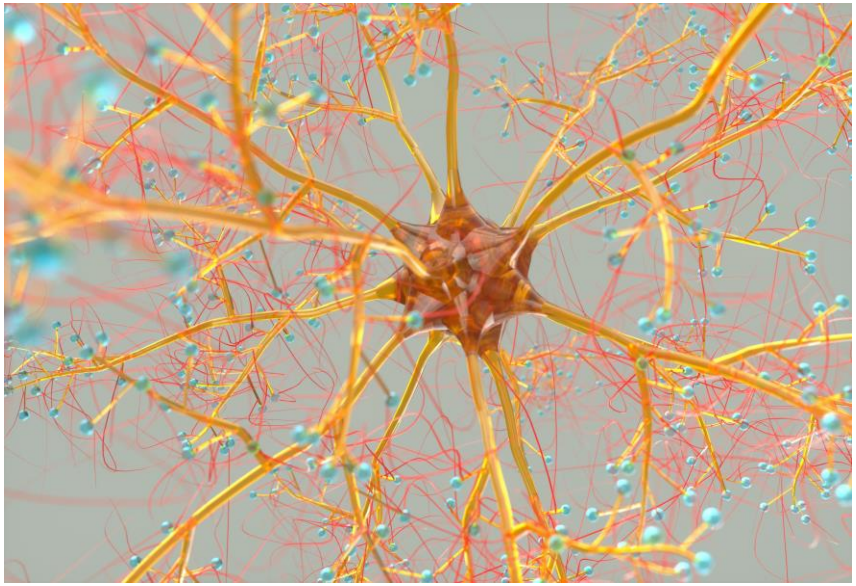
- As mania/psychosis develop, the first question for the treatment team is safety
- Is the patient in need of hospitalization/partial hospitalization or can the condition be managed with regular clinic visits?
- Does the patient need to come in more frequently to see their clinician?

FDA approved treatments for acute mania

- Atypical Antipsychotics
  - Aripiprazole
  - Asenapine
  - Cariprazine
  - Olanzapine
  - Risperidone
  - Quetiapine
  - Ziprasidone
- Mood Stabilizers
  - Lithium
  - Divalproex
  - Carbamazepine

Butler M, Urosevic S, Desai P, et al. Treatment for Bipolar Disorder in Adults: A Systematic Review [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018 Aug. (Comparative Effectiveness Review, No. 208.) Chapter 4, Drug Treatments for Acute Mania.Available from: https://www.ncbi.nlm.nih.gov/books/NBK532191/

Treatment Options



- Lithium is the only agent that was developed specifically for bipolar disorder.
- All other treatments were initially developed for other conditions, then studied for effectiveness in bipolar disorder
  - Antipsychotics (Schizophrenia)
  - Mood stabilizers (Anti-epileptics)
  - Benzodiazepines (sedatives)
  - Antidepressants (MDD)

First line for treatment of mania

- Monotherapy:
  - Lithium
  - Quetiapine
  - Divalproex
  - Asenapine
  - Aripiprazole
  - Paliperidone
  - Risperidone
  - Cariprazine

- Adjunctive therapy with Lithium or Divalproex:
  - Quetiapine
  - Aripiprazole
  - Risperidone
  - Asenapine

Yatham, Lakshmi N., et al. "Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: *Bipolar disorders* **2018** Mar;20(2):97-170
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Second line for treatment of mania

- Olanzapine
- Carbamazepine
- Olanzapine + (Lithium/Divalproex)
- Lithium + Divalproex
- Ziprasidone
- Haldol
- ECT

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Third line for treatment of mania

- Carbamazepine/Oxcarbazepine + Lithium/Divalproex
- Chlorpromazine
- Clonazepam
- Clozapine
- Haloperidol + Lithium/Divalproex
- rTMS
- Tamoxifen
- Tamoxifen + Lithium/Divalproex

Yatham, Lakshmi N., et al. "Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: *Bipolar disorders* **2018** Mar;20(2):97-170

Long-acting antipsychotics

- Administered in an injectable form once every 2 weeks, up to once every three months
- Not indicated for acute treatment of manic episodes
- Helps with improving medication adherence and preventing recurrence of episodes
- Aripiprazole, Fluphenazine, Haloperidol, Paliperidone, Risperidone.

Common Medication Side Effects (Lithium)

Common, mostly early on in treatment

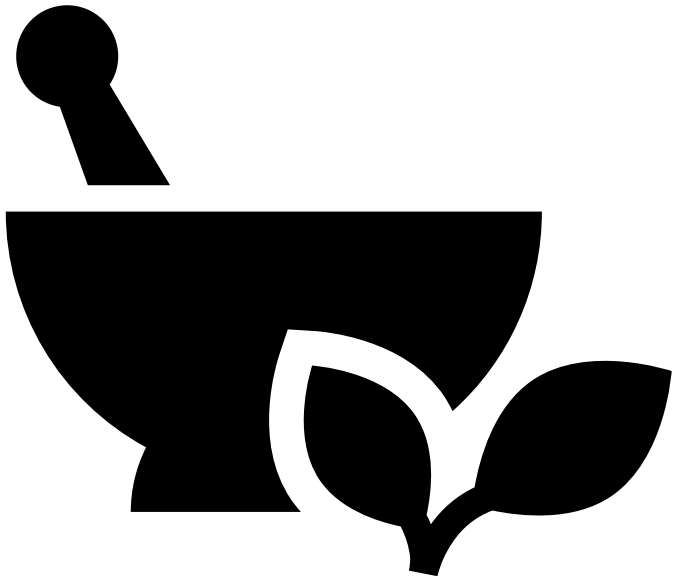
- Sedation
- Weight gain
- Thirst/Urinating more frequently
- Nausea, loose stools, constipation
- Tremors

Adverse events from longer term treatment

- Thyroid and parathyroid dysfunction
- Kidney dysfunction
- Dermatological conditions (acne, psoriasis, hair loss)

Lithium Toxicity

- Drug interactions
- Dehydration
- Drug over dosage



Ng F, Mammen OK, Wilting I, et al. The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. Bipolar Disord. 2009;11:559-95.

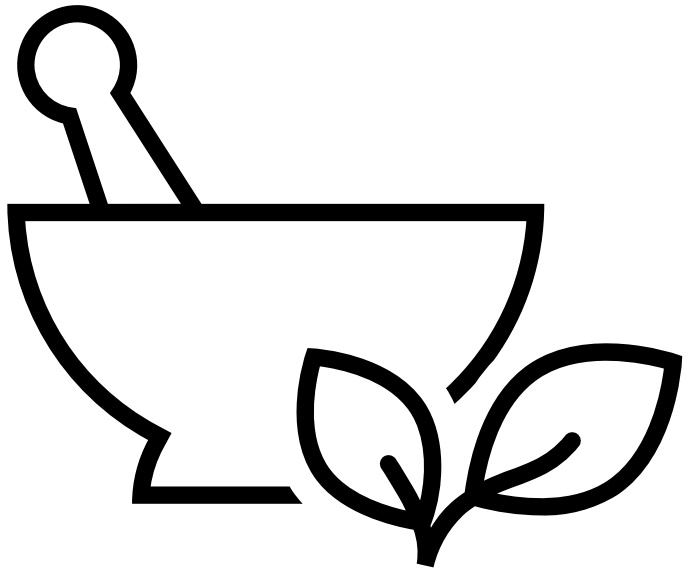
Common Medication Side Effects

Antipsychotics

- Sedation
- Weight gain and metabolic abnormalities
- Motor abnormalities

Anticonvulsants (Valproate, Carbamazepine)

- Sedation
- Weight and appetite changes
- Tremors, dizziness
- Effects on liver functioning
- Effects on blood cells (easy bruising, drop in white blood cells)
- Drop in blood sodium (Carbamazepine)
- Interactions with other medications (Carbamazepine)



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Medication Monitoring

While on Antipsychotics,

- Check weight, monthly the first three months, then every three months
- check fasting blood sugar (or HgA1c), BP every three months for a year, then annually.
- Check lipids after three months, then annually
- ECG and Prolactin, if clinically indicated

While on Lithium

- Serum levels every 3-6 months (or after dose changes)
- Kidney function every 3-6 months
- Weight, thyroid function and calcium after 6 months, then annually

While on Valproate or Carbamazepine

- Weight, blood count, liver functioning, electrolytes at least annually once on stable dose.
- Medication serum levels when clinically indicated

Ng F, Mammen OK, Wilting I, et al. The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. Bipolar Disord. 2009;11:559-95.

ECT treatment for bipolar disorder

- ECT has been in use since the 40's
- Initially treatment was administered without anesthesia and with higher doses of electricity
- Modern treatments are administered with muscle relaxants and anesthesia
- 522 medication resistant bipolar patients (depressed, mixed, manic and catatonic)
- Almost 70% responded to ECT. Highest response rate was for catatonia (80.8%) and lowest for depression (68.1%)

Perugi G et al."The Role of Electroconvulsive Therapy (ECT) in Bipolar Disorder: Effectiveness in 522 patients with bipolar depression, mixed-state, mania and catatonic features." Curr Neuropharmacol. 2016 Oct 17.[Epub ahead of print]

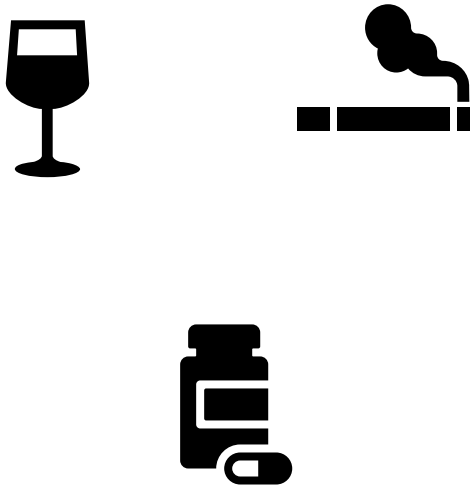
Sleep and Mania

- It is well established that sleep loss can trigger mood episodes in bipolar disorder
- Specifically, sleep loss can trigger manic episodes in individuals with Bipolar type I disorder or female gender
- Sleep hygiene and regular sleep are an important part of recovery from mania

Lewis KS, Gordon-Smith K, Forty L, et al. Sleep loss as a trigger of mood episodes in bipolar disorder: individual differences based on diagnostic subtype and gender. *Br J Psychiatry*. 2017;211(3):169–174.

Bipolar Disorder and Substance Use

- Up to 45% of patients with bipolar disorder may struggle with comorbid substance use.
- It leads to reduced rates of remission and increased risk of hospitalization and suicide.
- Treatment must occur simultaneously for bipolar disorder and substance use



Hunt GE, Malhi GS, Cleary M, Lai HM, Sitharthan T. Prevalence of comorbid bipolar and substance use disorders in clinical settings, 1990-2015: systematic review and meta-analysis. *J Affect Disord*. 2016;206:331-49.

Psychotherapies

- Most helpful in depressive and maintenance phases of the illness
- During mania/hypomania the therapist will help with adherence to treatments and medications, developing daily routine and regular sleep patterns

Thanks for your attention!

Looking forward to your questions and comments.