Bipolar Disorder: Diagnosis & Treatment Options

Matthew Macaluso, D.O.
Director of Residency Training
Director of Clinical Trials Research
Potential Conflicts of Interest

• Dr. Macaluso received grant or research support from the following entities in the last 12 months:
  
  • Alkermes (schizophrenia)
  • Allergan (treatment resistant depression)
  • Eisai (Alzheimer disease)
  • Envivo/Forum (schizophrenia)
  • Janssen (depression/treatment resistant depression)
  • Kansas Biosciences Authority (bipolar disorder)
  • Naurex (treatment resistant depression)
  • National Institute of Mental Health—RAPID Network (depression)

All payments were made to the University of Kansas Medical Center Research Institute and Dr. Macaluso received no direct remuneration from these entities
Question 1

All of the following are FDA-approved for treating acute mania except:

a. Carbamazepine
b. Chlorpromazine
c. Clozapine
d. Divalproex
e. Aripiprazole
Question 2

Which of the following drugs has a recommended starting dose for acute mania of 25 mg/kg/day?

- a. Divalproex ER
- b. Carbamazepine ER
- c. Risperidone
- d. Lithium
- e. Quetiapine
Question 3

Which antidepressant appears to have the highest switch rate when used to treat bipolar depression?

a. Bupropion
b. Sertraline
c. Venlafaxine
Question 4

Which of the following medications is not FDA-approved for bipolar maintenance?

a. Lithium  
b. Divalproex  
c. Olanzapine  
d. Lamotrigine  
e. Aripiprazole
Question 5

Which of the following medications has the most convincing evidence for reducing suicidal behavior in bipolar patients?

a. Clozapine
b. Lamotrigine
c. Olanzapine
d. Divalproex
e. Lithium
Epidemiology of BAD

1) Lifetime prevalence of BAD I & II in general population is 3.7%-3.9%

2) Prevalence in patients presenting with Depression is
   - 21%-26% in PCP office
   - 28%-49% in Psychiatric clinics

3) No difference for gender, ethnicity or socioeconomic classes
Etiology of BAD

- Unknown
- Kindling phenomenon
- Clear genetic component for BAD-I, similar to Schizophrenia
- Medical/Physiologic factors
- Genetic-Environmental Interaction
Medical causes of Mania:

- **Medications & drugs:**
  - Antidepressants
  - Dopamine agonist
  - Steroids
  - Isoniazid
  - AZT
  - Cocaine
  - Amphetamine
  - PCP

- **Medical Disorders:**
  - Hyperthyroidism
  - Multiple Sclerosis
  - HIV infection
  - Epilepsy
  - Brain tumor/infection
  - Stroke
  - Sleep deprivation
  - Open heart surgery
Age of onset for BAD

• Peak period of onset is between 15 and 19 years of age
• 16% have onset at the age of 30 years or beyond
• 9% of patients >60 years develop affective disorders
DSM-5 Criteria for Manic Episode:

• A distinct period of abnormally & persistently elevated, expansive, or irritable mood, lasting at least 1 wk. (or any duration if hospitalization is necessary)
• During the period of mood disturbances, 3 (or more) of the following sx. Have persisted (four if the mood is only irritable) and have been present to a significant degree:
  1) inflated self-esteem or grandiosity
  2) decreased need for sleep
  3) more talkative than usual or pressure to keep talking
  4) flight of ideas or subjective experience that thoughts are racing
  5) easy distractibility
  6) increase in goal directed activity or psychomotor agitation
  7) excessive involvement in pleasurable activities that have a high potential for painful consequences e.g. shopping sprees, sexual indiscretions etc.
Bipolar II Disorder

• Presence (or history) of one or more major depressive episodes

• Presence (or history) of at least one hypomanic episode characterized by
  - persistently elevated, expansive, or irritable mood for at least 4 days with
  3 or more of the criteria used for manic episodes
Mixed Features

• Three criteria for major depression are present in addition to meeting the full criteria for mania
BAD, frequently misdiagnosed

• 1 in 5 patients with BAD is correctly diagnosed
• Those incorrectly diagnosed are likely to be more impaired, female, and poorer
• 1 in 3 is misdiagnosed as having unipolar depression, perhaps due to the prevalence of the depressive phase of the illness
Difficult to diagnose in children & adolescents, why?

- Not under consideration
- If mild, was seen as “moodiness”
- If severe, was seen as “adjustment disorder”
- Lack of longitudinal history
- ETOH/Drug abuse may confuse the picture
Differential Diagnosis

- ADHD
- Conduct disorder
- ODD
- Anxiety disorders
- Substance abuse
- MDD
- Personality disorders
BAD vs ADHD

- BAD
  - Change from usual behavior
  - Sudden worsening of symptoms
  - Hyperactivity is episodic
  - More aggressive and antisocial behavior
  - Presence of grandiosity, flight of ideas, racing thoughts, pressured speech and euphoria

- ADHD
  - Typical pattern of behavior
  - Low self esteem
  - Continuous hyperactive behavior
  - Less aggressive and antisocial
  - No flight of ideas, racing thoughts, grandiosity, pressured speech & euphoria
“A 23 year old female with recurrent major depressive episodes treated with Prozac develops over a 2-week period greatly increased energy and libido and the ability to feel refreshed after only 2-3 hours of sleep at night. She is in unusually good spirits and has started a number of projects, including teaching herself classical Greek, and repainting her house inside and out. She states that this is the best she has felt in years. Her husband insisted that she need a medical evaluation when she wanted to invest her family`s life savings of over $400,000 in a suspicious copper mining business”
Antidepressant-induced Mania

- 1/4 to 1/3 of BAD patients using A/D may be susceptible to medication induced mania with:
  - previous antidepressant manias
  - strong family history of BAD
  - illness began in adolescence
  - exposure to multiple antidepressant trials
Treatment options for BAD:

- Mood Stabilizers
- Mood Stabilizer plus Antipsychotic
- Mood Stabilizer plus Benzodiazepine
- Mood Stabilizer plus Antidepressant
- ECT
- Medication Plus Psychotherapy
Mood Stabilizers:

- Lithium Carbonate (lithium)
- Divalproex Sodium (Depakote)
- Carbamazepine (Tegretol)
- Oxcarbazepine (Trileptal)
- Lamotrigine (Lamictal)
- Topiramate (Topamax)
Atypical Antipsychotics:

- Olanzapine (Zyprexa)
- Risperidone (Risperdal)
- Quetiapine (Seroquel)
- Aripiprazole (Abilify)
- Ziprasidone (Geodon)
- Clozapine (Clozaril)
- Lurasidone (Latuda)
- Symbyax (Olanzapine + Fluoxetine)
APA Guideline for Rapid Cycling:

- Initial intervention is to identify any organic cause or substance abuse.
- Treat with Lithium or Valproate or Lamotrigine.
- Antidepressant particularly contribute to Rapid Cycling so should be tapered if possible.
Labs before Lithium administration:

- CBC with Differential
- T4 & TSH
- BUN
- U/A
- 24 hr urine for Creatinine clearance & Protein excretion
- Serum Creatinine
- Serum Electrolytes
- EKG if > 40 years old
- Pregnancy test in CBP female
Drugs that alter Lithium level:

• *Increase Lithium:*
  - Thiazide diuretics
  - Indomethacin and NSAIDs
  - Erythromycin
  - Spironolactone
  - Enalapril
  - Tetracycline
  - Metronidazole
  - Triamterene

• *Decrease Lithium:*
  - Theophylline
  - Acetazolamide
  - Aminophylline
  - Mannitol
  - Urea
Lithium Toxicity:

Lithium toxicity can be from decreased clearance or acute overdose.

Treatment of Lithium toxicity includes,

a) Serum measurement of Lithium, creatinine, electrolytes, and plasma osmolality
b) Gastric lavage
c) Monitoring of fluid intake & output
d) Neuro checks
Side Effects of Lithium:

• Headaches, confusion, hand tremor
• Polyuria & Polydipsia in 50% of patients
• 30% patients develop GI symptoms
• Leukocytosis is common & persistent, but reversible
• Weight gain in 10% of patients
• T wave flattening or inversion
• Hypothyroidism in 10% of patients with chronic use.
• Worsening of Acne and Psoriasis
Side Effects from Lithium:

Narrow therapeutic index. Therapeutic level is 0.6-1.2 mEq/L.

- Tremor, impaired coordination, dysarthria, thirst, anorexia, and GI distress at 0.8 –1.5 mEq/L
- Nausea, vomiting, slurred speech, diarrhea, coarse tremors, severe ataxia, confusion, delirium, seizures, coma, death from 2.0-4.5 mEq/L
Labs before starting Valproate:

- CBC with differential
- Platelet count
- Liver function tests
- Coagulation parameters (PT and PTT)
- Pregnancy test if not sure about method of contraception
Side effects of Valproate:

- GI upset
- Sedation
- Weight gain
- Transient alopecia
- Edema
- Rash
- Allergic dermatitis

- Elevated LDH, SGOT, SGPT
- Hepatotoxicity (1/40,000)
- Pancreatitis
- Thrombocytopenia
Carbamazepine

- Therapeutic range is 3-14 mcg/mL
- Signs of toxicity includes vertical nystagmus and ataxia
- Boxed warnings for aplastic anemia & agranulocytosis
- Serious dermatological conditions includes 1. Toxic epidermal necrolysis (Lyell’s synd) 2. Steven-Johnson syndrome
Drugs that alter Carbamazepine:

**Increased Levels:**
- erythromycin
- Cimetidine
- Fluoxetine
- Ca channel blockers
- Isoniazid
- Propoxyphene

**Decreased Levels:**
- Phenobarbital
- Phenytoin
Drugs level decreased by Carbamazepine:

- Oral contraceptives
- Warfarin
- Theophylline
- TCAs
- Valproate
- Haloperidol
Lamotrigine

- Side effects: Rash (steven johnson syndrome) is most serious side effect affecting 1% pediatric, age < 16 years, and 0.3% of adult population
- Risk of rash increased
  - If administered with valproate formulations
  - With higher initial doses
  - Faster titration than recommended
Topiramate

- 4th line agent
- 1.5% risk of renal stones due to its carbonic anhydrase inhibition which increases urinary pH and reduce urinary citrate excretion
- Its use with other carbonic anhydrase inhibitors or in pts. On ketogenic diet increased risk of renal stones
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The End.
Thank You.