Differential Diagnosis of ADHD and Bipolar Disorder

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Disclosure

• The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  – Dr. First will be discussing off-label use of medications in the presentation and will identify those issues.

• Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
• This activity has been independently reviewed for balance.
Differential Diagnosis

• “Determination of which one of two or more diseases with similar symptoms is the one from which the patient is suffering.”

—From Stedman’s Medical Dictionary
Diagnostic Challenge of ADHD/Bipolar Disorder

• Overlapping symptom profile complicates differential diagnosis

• High rates of ADHD/BD comorbidity

• Accurate diagnosis is important because of different recommended treatments for each condition:
  – Mood stabilizers for BD
  – Stimulants for ADHD

ADHD = attention-deficit/hyperactivity disorder; BD = bipolar disorder.
Diagnosis of ADHD

• Persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with academic or occupational functioning

• Onset of symptoms (but not impairment) by age 12

• Not better explained by another mental disorder

• Associated features:
  – Delays in motor or social development
  – Low frustration tolerance
  – Irritability
  – Mood lability

ADHD Developmental Issues

- In adults, hyperactivity-impulsivity decline with increasing age whereas inattention persists.

- Hyperactivity may change to inner tension or restlessness which can be confused with anxiety or depression.

- Typical trajectory of symptom type:
  - Hyperactive-impulsive type in infancy
  - Combined type during childhood
  - Inattentive type during young adulthood

Diagnosis of Bipolar Disorder

• Episodic condition with periods of normal mood

• Bipolar I Disorder: 1+ manic episodes, 0+ major depressive episodes

• Bipolar II Disorder: 1+ hypomanic episodes and 1+ major depressive episodes

Manic/Hypomanic Episodes

• Abnormally and persistently elevated, expansive or irritable mood, and increased goal-directed activity or energy

• 3 (or 4 if mood is only irritable):
  – Inflated self-esteem or grandiosity
  – Decreased need for sleep
  – More talkative than usual or pressure to keep talking
  – Flight of ideas or racing thoughts
  – Distractibility
  – Increase in goal-directed activity or psychomotor agitation
  – Involvement in activities with high potential for painful consequences

ADHD/Bipolar Disorder Symptom Criteria Overlap

ADHD

- **A.1.h:** Is often easily distracted by extraneous stimuli
- **A.2.a:** Often fidgets with or taps hands or feet or squirms in seat
- **A.2.f:** Often talks excessively

Bipolar Disorder

- **Manic B.5:** Distractibility (i.e., attention too easily drawn external stimuli)
- **Manic B.6/MDE A.5:** Psychomotor agitation
- **Manic B.3:** More talkative than usual or pressure to keep talking

## Overlapping and Nonoverlapping Symptoms

<table>
<thead>
<tr>
<th>Bipolar (manic phase)</th>
<th>ADHD</th>
<th>Degree of Overlap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distractibility</td>
<td>Easily distracted</td>
<td>High</td>
</tr>
<tr>
<td>Irritability</td>
<td>Irritability (associated feature)</td>
<td>High</td>
</tr>
<tr>
<td>More talkative</td>
<td>Talks excessively</td>
<td>Moderate</td>
</tr>
<tr>
<td>Psychomotor agitation</td>
<td>Hyperactivity</td>
<td>Moderate</td>
</tr>
<tr>
<td>Decreased need for sleep</td>
<td>Trouble going to sleep</td>
<td>Potentially confused</td>
</tr>
<tr>
<td>Elation, grandiosity, flight of ideas, increased goal-directed activity, involvement in activities with painful consequences</td>
<td></td>
<td>Little</td>
</tr>
</tbody>
</table>

### Overlapping and Nonoverlapping Symptoms (cont’d)

<table>
<thead>
<tr>
<th>Bipolar Depressed</th>
<th>ADHD</th>
<th>Degree of Overlap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>Difficulty falling asleep (not part of definition)</td>
<td>High</td>
</tr>
<tr>
<td>Irritability</td>
<td>Irritability (not part of definition)</td>
<td>High</td>
</tr>
<tr>
<td>Psychomotor agitation</td>
<td>Hyperactivity</td>
<td>Moderate</td>
</tr>
<tr>
<td>Fatigue or loss of energy</td>
<td>Loss of energy (not part of definition; associated with inattention)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>Low self-esteem (not part of definition)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Weight loss/gain, psychomotor retardation, loss of interest or pleasure, thoughts of death/suicidality</td>
<td></td>
<td>Little</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADHD</th>
<th>BD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood or early adolescent onset</td>
<td>Adolescent/adult onset</td>
</tr>
<tr>
<td>Persistent trait-like course; no change from premorbid state</td>
<td>Episodic course, change from premorbid state</td>
</tr>
<tr>
<td>May be excitable but not grandiose/elated</td>
<td>Grandiosity/elation</td>
</tr>
<tr>
<td>Distracted type of ceaseless mental activity and wandering mind</td>
<td>Racing thoughts</td>
</tr>
<tr>
<td>Reports being unable to function</td>
<td>Reports high level of functioning, not reflecting actual behavior</td>
</tr>
<tr>
<td>Chronic low self-esteem</td>
<td>Episodes of depression</td>
</tr>
<tr>
<td>Usually possesses insight</td>
<td>Tends to lack insight</td>
</tr>
<tr>
<td>Difficulty falling asleep</td>
<td>Reduced need for sleep</td>
</tr>
<tr>
<td>Complaints of being unable to concentrate/focus</td>
<td>Subjective sense of sharpened mental abilities</td>
</tr>
</tbody>
</table>

Comorbidity of Adult ADHD with Bipolar Disorder in Adults

National Comorbidity Survey Replication (N=3199)

- 21.2% Among Respondents With BPD
- 3.5% Among Respondents Without BPD
- 19.4% Among Respondents With ADHD
- 3.1% Among Respondents Without ADHD

BPD = bipolar disorder.
## Comorbidity of ADHD and Bipolar Disorder

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bird HR, et al. <em>Arch Gen Psychiatry</em>. 1988;45(12):1120-1126.</td>
<td>Children aged 4–16 (N=777)</td>
<td>17%</td>
</tr>
</tbody>
</table>

ADD = Attention Deficit Disorder.

Possible Explanatory Hypotheses

• Comorbidity due to chance phenomenon?
  – Prevalence of comorbid cases higher than expected if due to chance

• Comorbidity is an artifact of overlapping criteria
  – Subtracting symptoms common to both conditions still leaves 79% and 64% of ADHD/BD participants retaining their diagnosis

• ADHD is a developmental precursor of BD

• Comorbidity is due to a common diathesis
Age of Onset of Mood Disorder Earlier with Comorbid ADHD

The overall lifetime prevalence of comorbid ADHD in a cohort of 1000 patients enrolled in the STEP-BD was 9.5%.

N=1000; P=.0001.

STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder.

Duration of Wellness in the Last 2 Years in Bipolar Patients with and without Comorbid ADHD

The overall lifetime prevalence of comorbid ADHD in a cohort of 1000 patients enrolled in the STEP-BD was 9.5%.

N=1000; P=.013.
The overall lifetime prevalence of comorbid ADHD in a cohort of 1000 patients enrolled in the STEP-BD was 9.5%.
Comorbid ADHD/Bipolar Disorder vs Bipolar Disorder

• Earlier age at first onset of mania
  – 3–5 years earlier than patients with BD

• More severe course of BD
  – Greater number of episodes and shorter duration of wellness
  – Lower functional scores, lower education, fewer partnerships, more suicide attempts, more legal problems

• Less adherent to treatment

Real World Impact of Comorbid ADHD and BD

- Earlier Age of Onset (BD) = More Virulent
- Shorter Well Intervals
- Greater Propensity to Depression
- More Depressive Episodes
- Higher Rates of Comorbidity (Anxiety/SUDs)
- Hx of Aggression & Violence
- Poorer Prognosis

SUD = substance use disorder.
Comorbid ADHD/Bipolar Disorder Management

• Treat the most severe condition first (almost always BD)

• Treatment of ADHD should be considered when ADHD symptoms persist following mood stabilization and have moderate to severe impact on functioning and quality of life

• It may be safe to use stimulants if BD symptoms respond well to mood stabilizers

Staged Management

- When there are clear diagnoses of comorbid ADHD and BD, treat the most serious condition first (most often BD)

- **Stage 1** – If BD is the most serious:
  - Treat with mood stabilization (eg, lithium, anticonvulsants, atypical antipsychotics)
  - May yield adequate outcomes with low levels of residual impairment

- **Stage 2** – If significant residual ADHD symptoms in between episodes:
  - Treat with stimulants or atomoxetine

Atomoxetine is not FDA approved for the treatment of BD.
Staged Management (cont’d)

• If clear diagnosis of ADHD is made and BD is only suspected, then ADHD can be treated first with stimulants or atomoxetine
  – Monitor potential worsening of BD symptoms as stimulants may exacerbate subthreshold mania, especially in absence of mood stabilizer—can occur acutely or after several months of effective treatment for ADHD
  – If BD emerges, stop ADHD treatment and use mood stabilizer until BD has stabilized
  – Review Dx of ADHD before considering further treatment

Illustrative Cases
Case of “Jenny”

• Jenny, a 33-year-old woman, presents with complaints of difficulty paying attention, poor organization, losing things, being forgetful, and being fidgety. No prior treatment.

• Family history of relatives with cycling mood disorders:
  – Brother with schizoaffective disorder, bipolar type
  – Father with alcohol dependence and bipolar II disorder
  – Paternal aunt with bipolar II disorder
  – Paternal great-grandmother with periods of “moodiness and breakdowns” with irritability who reportedly for no reason “picked fights and threw dishes”

Case of “Jenny” (cont’d)

• Son diagnosed with ADHD 3 years ago but on methylphenidate 5 mg became profoundly euphoric and sleepless with worse hyperactivity

• Low dose of sertraline made him totally sleepless, more irritable, and non-functional at school and at home

• Subsequently, off all medications, he had periods of inappropriate euphoria, hypersexuality, and decreased need for sleep (4 hours less than standard for his age)

• His best behavior so far has come from therapeutic levels of lithium

Case of “Jenny” (cont’d)

• When asked, Jenny says she had never experienced manic symptoms

• From clinical interview, she met full criteria for ADHD with a lifelong history of
  – Careless mistakes (A.1.a)
  – Difficulty sustaining attention to tasks (A.1.b)
  – Poor follow-through (A.1.d)
  – Poor organization (A.1.e)
  – Regularly losing things (A.1.g)
  – Easily distracted (A.1.h)
  – Constantly being forgetful in her daily activities (A.1.i)
  – Being fidgety (A.2.a)
  – Talking slightly excessively (A.2.f)

Case of “Jenny” (cont’d)

• Jenny was also diagnosed with MDD (BDI score of 30 [high end of moderate depression]) with significant anxiety component (BAI of 25 [moderate anxiety])

• Treated with 30 mg paroxetine which caused a significant decrease in her depression and 0.375 mg of clonazepam with improvement of anxiety

Case of “Jenny” (cont’d)

- Jenny continued to be forgetful, scattered, and troubled, with procrastination as well as being very distractible
- Prescribed dexedrine 15 mg in AM and 12.5 mg at noon; caused her to be focused for 2 weeks
- Then became more energized with:
  - Elevated mood (A)
  - Increased self-esteem (B.1)
  - Needed only 3 hours of sleep (B.2)
  - Became more talkative (B.3)
  - Had racing thoughts (B.4)
  - Spent hours housecleaning and calling on friends (B.6)

Case of “Jenny” (cont’d)

• Paroxetine and dexedrine discontinued but symptoms persisted for a week

• Started on valproic acid sprinkles 500 mg a day with level of 72. Symptoms remitted after an additional week

• 1 month later Jenny became depressed again. Bupropion 150 mg bid was added to the valproic acid which ameliorated her depression and did not cause recurrence of her manic symptoms

Case of “Jenny” (cont’d)

• At this point, Jenny recalled times prior to the manic episode where she had periods of “a week or weeks” in which she felt “increased energy” and had a mild decrease in sleep, felt unusually good about herself, felt slightly high, was a bit more talkative, had more distractibility than was typical for her, and have an increase in “stupid mistakes”

• Example of how recall of past hypomania sometimes occurs only after a more dramatic and severe episode

Case of “Jenny” (cont’d)

• Over next 9 months, her mood was stable but her functioning continued to be impaired with symptoms of ADHD

• Jenny was given dexedrine 5 mg in AM, 5 mg at noon, and 2.5 mg late day. The dexedrine increased her productivity strikingly, and made her cognitively sharper with better impulse control and less distractibility

Case of “Evan”

• Evan, a 25-year-old, single, white man who has been employed full time as a waiter at a restaurant for 9 months, is referred after dropping out of college subsequent to being arrested for making fake college IDs. In addition to this, his parents report that he has taken money from them for college when, in fact, he was not attending classes.

• Evan moved back home with his parents 1 year ago; since then, he has had angry outbursts and has destroyed some household property. His parents report that he has written bad checks, a history of chronic lying, years of substance abuse, and severe mood swings with violent outbursts.

• The psychiatrist interviews Evan privately, and then speaks with his mother for historical confirmation. His father is interviewed at a later session for corroborating information.

Initial Differential Diagnosis?

• Substance Use Disorder
  – “Years of substance abuse”
• Intermittent Explosive Disorder
  – Angry outbursts and destroyed property
• Personality Disorder (Antisocial/Borderline Personality Disorder)
  – Arrested for making fake college IDs; chronic lying; taking money from parents for college while not attending
• Bipolar Disorder
  – Mood swings with violent outbursts

Developmental History and Family Background

• No drug exposure during pregnancy or delivery complications

• According to parents, reached normal developmental milestones

• Mother employed as supervisor of middle school teachers, has master’s degree; Father, retired middle school principal, also has master’s degree

• No history of physical abuse

Childhood History

- Restless in class but not disruptive
- Daydreamer
- Took longer to finish assignments in class
- Procrastinated with homework, typically handing it in late
- Moved by teacher to front of classroom because inattentive and impulsive
- Mother reported as a child he was inattentive at home and required oversight much of the time
- Fidgety and distractible during conversations
- Disorganized; taking more time to finish tasks
- Impulsive but not reckless

ADHD Diagnosis and Treatment

• Diagnosed at age 11 with ADHD by pediatrician
• Treated with methylphenidate “for years” with improved academic and social performance
• Recalls being less restless, calmer, and better focused in class with greater ability to sustain attention
• Became irritable when methylphenidate wore off
• By age 17 stopped taking methylphenidate because of increasing alcohol and drug abuse and because leaving for college

Drug Abuse History

- Started at age 15 with alcohol on weekends
- At age 16, taken to Emergency Department for alcohol intoxication
- By age 22, drinking 5 days/week and smoking marijuana 4 x/day
- Reports “experience with all the drugs” except intravenous use

Substance Use and ADHD

• According to NCS-R, those with ADHD are 3 × more likely to have an SUD and 7.9 × more likely to be drug dependent than those without ADHD

• Prevalence of SUD was 15.2% for those with ADHD and 5.6% for those without ADHD
Prior History Mood Disorder Treatment

• Seen by a psychologist at age 18 with “clinical depression” and treated for 2 years with sertraline

• Evan reported that his mood swings were less intense, but was left in a chronic dysthymic mood, feeling “just blah all the time”

• While in treatment for depression during his first year of college, his academic performance declined severely and the psychiatrist prescribed mixed amphetamine salts for ADHD

• Although this helped with cognition, it caused him to feel irritable and he stopped it

• He continued to abuse illicit substances and alcohol during this time without informing the treating psychiatrist

Prior History Mood Disorder Treatment (cont’d)

• At age 20, Evan was seen by a psychiatrist who suggested that he had BD, because of episodes lasting days to weeks consisting of depressed mood, quiet and withdrawn disposition, amotivation, apathy, hopelessness, passive suicide ideation, sensitivity to remarks, tearfulness, self-critical outlook, more easily reactive temperament, irritability, agitation, and angry outbursts.

• Evan also reported episodes that started after puberty during which his mood was expansive, overconfident, and more impulsive, with clarity of thought, accelerated mentation rate, rapid speech, and spending more money. He experiences this mood as qualitatively different from being happy. These episodes occurred less frequently and lasted a shorter duration of time (days) than the depressed state.

• He was treated with valproate for 1 year, which helped appreciably reduce his mood swings.

Family Psychiatric History

- Mother with depression treated with antidepressants
- Maternal grandmother described as alcoholic and depressed
- Maternal aunt with alcoholism/SUD, mood swings, and a psychiatric admission—diagnosis unknown
- 4 maternal cousins who are recovering alcoholics

Medical History

• Significant for migraine headaches
• Denies thyroid disease, stroke, loss of consciousness, myocardial infarction, fainting, chest pain, cardiac murmur, seizure, major surgery, or hospitalization

Treatment at Time of Evaluation

- At the time of the evaluation, taking fluoxetine 30 mg once daily in the morning for the past 8 months
- Denies taking any over-the-counter medications or supplements
- In alcohol recovery for 3 months before this evaluation but admitted to still using marijuana “a few times a week”

Treatment

• Because of the uncontrolled mood swings of his BD, the psychiatrist prescribed valproate and quetiapine for mood stabilization and continues fluoxetine.

• Evan’s agitation, irritability, and dysphoric mood quickly respond to valproate 750 mg daily and fluoxetine 30 mg daily.

Follow-Up

• 4 weeks after initiating mood stabilizers and now with stable mood, Evan says that his ADHD cognitive symptoms persist unchanged

• His initial ADHD-RS score when mood was unstable was 31; after mood stabilization and before ADHD treatment, the score was 28
  – The ADHD-RS consists of the 18 symptoms from the *DSM-IV*, each rated on a 0- to 3-point scale. Maximum score is 54; inclusion criteria for adult ADHD trials is usually 24

• The psychiatrist prescribed lisdexamfetamine and titrates it to 50 mg each morning. On this dose of ADHD-RS score drops to 13 in 3 weeks

ADHD-RS = ADHD Rating Scale.
Follow-Up (cont’d)

• Because of some residual fluctuating mood symptoms, the valproate was increased to 1000 mg daily, achieving a blood level of 35 mg/L (therapeutic range, 50–100 mg/L). Although the valproate blood level was subtherapeutic, given the patient’s mood stability, the dose remained unchanged.

• 3 months after starting treatment, Evan’s ADHD-RS score declined to 7 and, with greater confidence, he enrolled in 3 college courses. During this time, he stopped all marijuana use. Evan also noticed that he no longer suffered with migraine headaches, likely a benefit of the valproate.
Summary

• ADHD and BD have overlapping symptom presentations

• ADHD and BD are frequently comorbid and typically have worse functioning

• Accurate diagnosis is necessary for appropriate treatment

• Differentiate by paying attention to onset and course and identifying the core symptom clusters

• Use stepped approach when treating comorbid ADHD and BD