Comorbidity in ADHD: A Case-Based Approach

(page 27 in syllabus)

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Individual Disclosure Statement

Faculty Editor / Presenter

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Learning Objectives

• Identify and diagnose different types and presentations of ADHD

• Assess comorbid illnesses in ADHD patients in order to maximize treatment outcomes
Pre-Poll Question

On average, how many patients with ADHD do you see each week?

1. None
2. 1-2
3. 3-4
4. 5-6
5. 7-8
6. 9-10
7. 11-12
8. 13-15
9. More than 15
Comorbidities in Children

• Up to 87% of children with ADHD meet criteria for one other mental health disorder
Comorbidity Rates by ADHD Subtype (Children / Adolescents)

ADHD in general adult population: 4.4%
Substance Abuse in the ADHD Population

Sleep Disorders in the ADHD Population

80%

Restless Leg Syndrome in the ADHD Population

44%
Anxiety Disorders in the ADHD Population

47%

Mood Disorders in the ADHD Population

38%

Depressed (MDD) Population

One out of ten has ADHD

Bipolar Population

Two out of ten have ADHD


Consider:
Which is more impairing?
If disorders are independent or if one is secondary to the other (developmental course)

Common Sequence of Treatment

nicotine dependence
ADHD
anxiety disorders
mood disorders
alcohol / stimulant / substance abuse

ADULT
The Case: The anxious woman who misses appointments

The Dilemma: How to treat ADHD without making anxiety symptoms worse?
Pretest Question 1

Which treatment option is most likely to be effective for ADHD symptoms without worsening anxiety?

1. Modafinil
2. Amphetamine
3. Bupropion
4. Methylphenidate
Patient Intake

- 27-year-old woman
- Diagnosed with anxiety disorder 3 years ago
- She has not experienced sufficient symptom relief with several different SSRIs
  - She is currently taking 40 mg/day fluoxetine
- She is late to appointments and forgets important deadlines
- The patient presents with feelings of anxiety and low self-esteem
  - She attributes her low self-esteem to her mediocre grades in community college despite doubling her studying efforts
Psychiatric History

• The patient has a history of low grades throughout elementary, middle, and high school

• She reports that her poor performance at school was due to an inability to sit still during class, difficulty paying attention, and a tendency to lose her homework

• The patient recently completed the Brown Attention Deficit Disorder Scale for Adults (BADDs) and the Wender Utah Rating Scale (WURS)

• These rating scales reveal that the patient likely had undiagnosed ADHD as a child and that it has likely persisted into adulthood

• Based on the rating scale results, the patient is now diagnosed with ADHD
ADHD and Anxiety Disorders

Anxiety impairs working memory

Vicious Cycle Sets In

Leads to more anxiety

Worsens ADHD symptoms

Key Brain Regions in ADHD and Anxiety

Brain areas affected in ADHD
- dorsolateral prefrontal cortex
- prefrontal cortex
- orbital frontal cortex
- anterior cingulate cortex

Brain areas affected in anxiety
- amygdala
- hippocampus

ADHD and Anxiety: Considerations for Treatment Sequence

IF:

• ADHD symptoms preceded anxiety

• Anxiety is restricted to performance situations

• Anxiety and ADHD are independent and equally impairing

• Anxiety is greatly impairing

CONSIDER:

ADHD and Anxiety “Pharmacies”

ADHD pharmacy: adults

Modafinil, IR guanfacine, and bupropion are not approved in ADHD.

Only atomoxetine, OROS, d-MPH XR, d,l-AMPH XR, and lisdex are approved in adult ADHD.

ADHD + Anxiety: Response to Methylphenidate

• Amphetamines may be less effective in patients with comorbid anxiety disorders but are still viable treatment options
  – Stimulants might exacerbate anxiety symptoms, so use cautiously

• Methylphenidate may be less effective in patients with ADHD and comorbid anxiety

• Modafinil can target ADHD symptoms, indirectly alleviating anxiety symptoms

• Escitalopram targets anxiety symptoms but does not have proven efficacy for ADHD symptoms

• Bupropion might target symptoms of depression with comorbid ADHD but does not have evidence of efficacy for anxiety disorder

• Adjunct cognitive therapy can be very helpful
Case Outcome

- The patient is maintained on fluoxetine 40 mg/day
- Modafinil (200 mg/day) is added
- The patient reports improvement in ADHD symptoms but complains of headache and nausea
- Modafinil dose is lowered to 100 mg/day
- Headaches and nausea resolve
- The patient is enrolled in cognitive behavioral therapy
- Her ADHD symptoms (most notably, forgetfulness) continue to improve
- She recently completed her second semester of college with passing grades in all but one of her classes
The Case: The man with ADHD who damaged his liver

The Dilemma: How to treat ADHD in a patient with a long history of substance abuse?
Pretest Question 2

In a patient with ADHD, a history of substance abuse, and severe liver damage, which treatment option is best?

1. Amphetamine
2. Atomoxetine
3. Lisdexamfetamine
4. OROS methylphenidate
5. 1 or 2
6. 3 or 4
Patient Intake

- 33-year-old man with a childhood history of ADHD
- The patient also has a history of substance abuse
  - He abused stimulants in his early twenties during college and is a recovering alcoholic
- His medical history is significant for moderate liver damage
- He has not been treated for his ADHD since he was a teenager
- The patient is now having significant work impairment due to his symptoms and is in danger of losing his job at an aircraft assembly plant
ADHD and Substance Use in Adolescents

Adolescents with ADHD:
15%–30% have SUD

Adolescents with SUD:
40%–75% have ADHD

• ADHD is an independent risk factor for later SUD
• An adolescent with both disorders will likely have
  – Longer course of illness
  – Greater severity with more relapses
  – Greater difficulty remaining abstinent

ADHD and Substance Use in Adults

- Never-treated adults with ADHD have a 2X higher risk of developing SUD over their lifespan than normal adults.

- SUD in ADHD adults is probably more severe than in the absence of ADHD.


*12-month prevalence
Top Reasons for Illicit Stimulant Use in College Students

- Helps me concentrate: 60%
- Helps me study: 50%
- Increases my alertness: 40%
- Gives me a high: 30%
- Experimentation: 20%
- Helps me lose weight: 10%

n=382

Routes of Administration for Illicit Stimulant Use in College Students

- **Orally**: 100% lifetime users
- **Snorting**: 30% lifetime users
- **Smoking**: 5% lifetime users
- **Inhaling**: 0% lifetime users
- **Injecting**: 0% lifetime users
- **Other**: 0% lifetime users

Reinforcing vs Therapeutic Effects

- Therapeutic effects: steady state and stable DA increases
  - Tonic: maintains baseline steady state DA levels, sets responsiveness of DA system

- Reinforcing effects: abrupt and fast DA increases
  - Phasic: fast DA changes highlighting saliency of stimuli

- Rate of DA increase due to rate of entry of drug into brain
  - Smoking > injection > snorting > oral
  - Higher doses > lower doses

- Extractability is key

Progression of Stimulant Abuse

A  fun
“Where’s my dopamine?”

B  craving
“Where’s my dopamine?”

C  reverse tolerance/addicted
“brain-washed”

D  anhedonia/sleepiness
withdrawal

E  compulsive use
sex
paranoia
HIV
violence

F  enduring cognitive loss
“burnout”

Minimizing Abuse Potential for Patients With Substance Use Disorders

Typically first-line

Can be earned

*Not approved in ADHD

Only atomoxetine, OROS, d-MPH XR, d,l-AMPH XR, and lisdex are approved in adult ADHD.

ADHD pharmacy: adults

SUD pharmacy

Attending Physician’s Mental Notes

• Lisdexamfetamine might theoretically be the least likely stimulant to have abuse potential

• Stimulants generally do not require dose adjustment in patients with liver impairment

• Atomoxetine’s dose must be reduced for patients with liver damage (by half for moderate impairment)
  – Atomoxetine itself can rarely cause severe liver damage

• CBT could certainly be effective
  – Medication may provide faster benefit
Case Outcome

- The patient is initiated on lisdexamfetamine 30 mg/day
- He continues to perform poorly at work, forgetting deadlines and overlooking important protocols
- Lisdexamfetamine dose is increased to 50 mg/day
- The patient is fired from his job following a near miss safety incident due to continued negligence
- Lisdexamfetamine dose is increased to 70 mg/day
- The patient reports significant improvement in his ADHD symptoms
- He reluctantly agrees to start cognitive behavioral therapy and continues to show improvement
- He is now enrolled in a job assistance program and is actively seeking employment
The Case: The boy with ADHD who beat up his teacher

The Dilemma: How to prevent a life of criminal activity?
Pretest Question 3

Compared to patients with ADHD only, patients with ADHD + oppositional defiant disorder (ODD) + conduct disorder (CD) have an increased risk for:

1. Smoking
2. School suspension
3. Being fired
4. All of the above
Patient Intake

• 12-year-old boy
• Diagnosed with ADHD at age 7 and oppositional defiant disorder (ODD) at age 8
• History of aggression toward peers
• Expelled from school last month after attacking his teacher
  – “He kept bugging me about not doing my homework. So I punched him in the stomach and kicked his shin.”
• Recently diagnosed with conduct disorder (CD)
• The patient has also developed a facial tic that “makes [him] look like a freak”
Current Medications

- Extended-release d,l-amphetamine (Adderall XR) 40 mg/day
- Previous trials of lisdexamfetamine dimesylate, atomoxetine, and immediate-release d,l-methylphenidate (Ritalin) were unsuccessful
Oppositional Defiant Disorder

- Persistent stubbornness and refusal to comply with instructions or unwillingness to compromise with adults or peers
- Deliberate and persistent testing of the limits
- Failing to accept responsibility for one's own actions and blaming others for one's own mistakes
- Deliberately annoying others
- Frequently losing one's temper

Conduct Disorder

- Repetitive and persistent pattern of behavior that violates
  - Basic rights of others
  - Age-appropriate social norms or rules
- Aggression toward people and animals
- Destruction of property
- Deceitfulness or theft
- Shares characteristics with ODD (disobedience and opposition to authority)

### Long-Term Outcomes for ADHD and Behavioral Comorbidities

<table>
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Yellow font: vs ADHD
Red fill: vs ADHD + ODD

Delinquency Is Greatest in Patients With ADHD + CD

COMT Val/Val Genotype + Low Birth Weight = ADHD + ODD / CD?

ADHD / ODD Pharmacy for Children

**First-line**
- Atomoxetine
  - Stimulant, long-acting

**Second-line**
- Risperidone
  - Stimulant, short-acting
- Guanfacine
  - Psychosocial, group parent training

**Third-line**
- TCA
- Clonidine
  - ER

Note: no agent is approved for comorbid ADHD/ODD. Risperidone, TCA, IR guanfacine, and IR clonidene are not approved for ADHD.

Turgay. CNS Drugs 2009;23:1-17;
Multimodal Treatment Is Most Effective for ADHD + ODD

ADHD and Tics

Patients with ADHD+CD are at an increased risk for severe delinquency; early intervention is key.

Many patients will have ODD symptoms all the way through bedtime, thus making it important to choose an agent that can be effective late in the day without inducing insomnia.

ADHD+ODD may require a higher dose than ADHD alone.

ADHD+ODD+tic or anxiety disorder: consider atomoxetine before stimulants.

Both atomoxetine and $\alpha_2$ agonists (e.g., guanfacine and clonidine) have shown efficacy for reducing tics and are first-line treatments for ADHD+ODD.

A multimodal treatment approach, including various psychosocial interventions, may be most effective for patients with ADHD and comorbid ODD or CD.

Case Outcome

- The patient is initiated on guanfacine XR (1 mg/day) while slowly tapering d,l-amphetamine
- Guanfacine dose is increased by 1 mg/week to achieve 4 mg/day
- The patient is enrolled in an intensive 8-wk summer treatment program that includes a token system, social skills training, sports skills training, and weekly group-based parent training
- The patient’s parents notice a marked improvement in their son’s behavior
  - Although the patient still has aggressive outbursts, they are less frequent and less severe
- The patient’s facial tics improve and bother him much less
- In the fall, the patient begins a new school with a specialized classroom behavioral management program
- He is also planning to try out for a local baseball team with a friend he met at the summer treatment program
The Case: The night owl with ADHD

The Dilemma: How to improve sleep quantity and quality in patients with ADHD?
Pretest Question 4

In a patient with delayed sleep phase syndrome and a dim light melatonin onset (DLMO) occurring at 22:00 hrs (10 PM), when should exogenous melatonin be administered in order to advance the patient’s sleep phase?

1. 12:00 hrs (12 PM)
2. 17:00 hrs (5 PM)
3. 19:00 hrs (7 PM)
4. Immediately before desired bedtime
Patient Intake

- 8-year-old male patient newly diagnosed with ADHD
- The patient’s grades are suffering, primarily due to careless mistakes on his schoolwork
- He does not seem to be able to complete any of his chores at home
- He is continuously being disciplined at school for talking and running around the classroom at inappropriate times (e.g., quiet reading time)
- He is moderately overweight (BMI 27.2) and admits to a diet consisting mainly of macaroni and cheese, chips, and candy
Patient Intake

- The patient’s parents have difficulty getting him to bed at night
  - He is often awake until midnight or later
- Even if his parents force him to stay in bed, he fidgets for hours before falling asleep
- Results from a polysomnogram indicate that the patient has delayed sleep phase syndrome and restless leg syndrome
- The patient’s family history is positive for a maternal uncle with RLS who became dependent on zolpidem
Delayed Sleep Phase Syndrome

• Habitual sleep-wake times that are delayed (usually more than two hours) relative to conventionally or socially accepted norms
• A typical patient has difficulty initiating sleep and prefers late wake-up times

Clinical features
• Once asleep, sleep quality normal
• Morning “sleep drunkenness”
• Often starts in adolescence
• May be associated with schizoid, avoidant features

Pathophysiology
• Endogenous circadian rhythm delayed
• May have difficulty entraining to usual environmental cues
• Polymorphisms of clock genes

Treatments
• Education
• Timed bright light
• Phase delay behavioral therapy
• Melatonin
• Hypnotics, stimulants, or modafinil (?)
Treating Delayed Sleep Phase Syndrome

- good sleep hygiene
- CBT
- melatonin
- quetiapine
- diphenhydramine
- zaleplon
- zolpidem
- ramelteon
- trazodone
- flurazepam
- temazepam
- estazolam
- triazolam
- quazepam
- zolpidem CR
- eszopiclone

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1st-line sleep onset:
- zolpidem CR
- eszopiclone

2nd-line:
- zaleplon
- zolpidem
- ramelteon
- trazodone
- flurazepam
- temazepam
- estazolam
- triazolam
- quazepam

2nd-line nonstimulants:
- atomoxetine
- clonidine
- guanfacine ER

1st-line stimulants:
- MPH
- d-MPH
- d-amph
- dl-MAS

1st-line stimulants (sleep onset and sleep maintenance):
- OROS-MPH
- LA MPH
- d-MPH-XR
- transdermal MPH

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adjunctive/combos:
- SDA
- DPA
- behavioral therapy

3rd-line nonstimulants:
- NDRI
- SNRI
- TCA

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Sleep-Wake Hygiene

**Sleep Time**
- No stimulants before bed
- Dark room
- Cool environment
- No disturbances

**Wake Time**
- Activity
Restless Leg Syndrome

- Urge to move limbs usually associated with paresthesias or dysesthesias
- Symptoms start or become worse with rest
- Physical activity often provides some relief
- Symptoms worsen at night
- Associated with dopamine or iron deficiency
- Treatments include
  - Dopamine agonists (ropinirole, pramipexole)
  - Iron replacement
  - Gabapentin/pregabalin
  - Low potency opiates
  - Benzos

Case Outcome

• The patient is initiated on clonidine XR (0.1 mg at bedtime)

• His hyperactivity symptoms improve moderately, and both his parents and his teacher notice some improvement in the patient’s ability to complete tasks

• He is still often inattentive, and his school performance continues to suffer due to careless mistakes

• The patient and his parents are educated about proper sleep hygiene

• Despite efforts to improve the patient’s sleep hygiene, he is still experiencing delayed sleep onset and restless leg symptoms

• The patient’s parents are concerned about putting their son on any medication to specifically target his sleep issues
Melatonin

- Dim light melatonin onset (DLMO)
  - Evening increase in endogenous melatonin
  - Defined as the time at which 3 pg/mL of melatonin is found in saliva
  - Delayed in patients with delayed sleep phase syndrome
  - Circadian rhythm disorders may be partially due to a polymorphism in the circadian locomotor output cycles kaput (CLOCK) gene – associated with both “eveningness” and ADHD

- Exogenous melatonin treatment given 5 hrs before DLMO is effective for advancing sleep onset

- Melatonin treatment has been shown to be safe and effective in both short- and long-term studies in children with ADHD and comorbid sleep disorders

Van der Heijden et al. Chronobiol Int 2005;22(3):559-70;
Suprachiasmatic Nucleus (SCN)

Retinohypothalamic Tract
Suprachiasmatic Nucleus (SCN)

Retinohypothalamic Tract
Suprachiasmatic Nucleus (SCN)

Pineal Gland

Retinohypothalamic Tract

melatonin
Suprachiasmatic Nucleus (SCN)

Pineal Gland

melatonin

Retinohypothalamic Tract

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Parents’ Opinions of Melatonin Treatment

- Melatonin is an effective therapy for the sleep onset problems of my child
- Melatonin improved the daytime behavior of my child
- Melatonin improved the mood of my child

Iron Supplementation

- Iron is a cofactor for tyrosine hydroxylase, which is needed for the synthesis of dopamine
- Iron deficiency has been associated with both RLS and ADHD
- 84% of children with ADHD have serum ferritin levels < 30 ng/mL

Iron Supplementation Improves ADHD Symptoms

- Iron supplementation also improved restless leg syndrome
  - Number of children with RLS decreased from 75% at baseline to 10.5% following treatment

Poor Diet May Exacerbate ADHD Physical and Sleep Symptoms

An elimination diet improves physical and sleep complaints in children with ADHD

* p<0.05 comparing diet and control groups

Patients with ADHD commonly suffer from sleep problems (most notably, delayed sleep onset, difficulty initiating and maintaining sleep, and restless leg syndrome).

1/3 of children with ADHD who are NOT on medication suffer from chronic insomnia.
- Stimulant use may cause or exacerbate insomnia in some children.

ADHD and sleep disorders can present with similar symptoms, including inattention, hyperactivity, and impulsivity; it is therefore important to evaluate sleep problems during the initial ADHD assessment.

There are numerous pharmacological (e.g., melatonin) and nonpharmacological (e.g., sleep hygiene) practices that can improve the sleep disturbances that are common in patients with ADHD.

Case Outcome

• Lab results for DLMO confirm the diagnosis of delayed sleep onset syndrome as well as iron deficiency

• Melatonin (2.5 mg taken 5 hours before determined DLMO) is initiated

• The patient begins going to bed earlier and is more attentive; he still experiences symptoms of RLS in the evenings

• His school performance improves but is not quite at the level of his peers
Case Outcome

- The patient’s parents make a conscious effort to improve the patient’s diet; they begin including iron-rich foods, such as dark, leafy greens, raisins, beans, and egg yolks, into most of their son’s meals; to his parents’ surprise, the patient develops a taste for spinach salad and artichokes.
- The patient loses 7 lbs within the first 2 months of the diet change.
- His ADHD symptoms further improve, and his academic performance is within the normal range for his grade level (albeit at the lower end of the range).
- The patient’s RLS symptoms also improve shortly after initiating the iron-rich diet.
Summary

• Attention deficit/hyperactivity disorder (ADHD) is a chronic and impairing disorder that not only can persist into adulthood but in many cases remains undiagnosed until adulthood.

• Most patients with ADHD have comorbid psychiatric disorders, which can obscure diagnosis and may also have an important impact on treatment selection.

• As patients age, ADHD symptom manifestations can evolve from “externalized” (hyperactivity) to “internalized” (inattention, internal restlessness), and changing symptoms and life demands may necessitate treatment modifications.

• There are many treatment options for ADHD, including several new medication formulations being tested and integrated into the market.
Post-Poll Question

On average, how many patients with ADHD do you see each week?

1. None
2. 1-2
3. 3-4
4. 5-6
5. 7-8
6. 9-10
7. 11-12
8. 13-15
9. More than 15