Fitzgerald
Colibri Healthcare

Non-opioid Controlled Substances: Benzodiazepines, Sedative Hypnotics, and Psychostimulants

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1

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2

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Disclosure

- No real or potential conflict of interest to disclose.
- No off-label, experimental or investigational use of drugs or devices will be presented.

3

3

Objectives

At the conclusion of this lecture, the attendee will be able to:

1. Analyze indications for benzodiazepine therapy and minimize abuse potential.
2. Evaluate mechanisms and abuse potential of psychostimulants.
3. Compare and contrast controlled and non-controlled options for insomnia.

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4

Tips

- References
  - Listed throughout and at the end of the presentation
- To facilitate your learning
  - Specific tables/images can be viewed full page at the end of your handout.

5

5

Anxiety Disorders

Core Features – Worry and Anxiety

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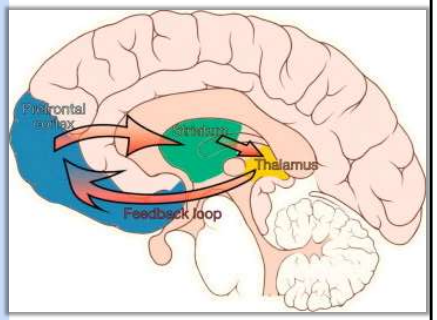
Worry – The CSTC Loop

- Apprehensive expectation
- Misery
- Catastrophic thinking
- Recurrent thought
  - E.g., obsession, rumination, delusions



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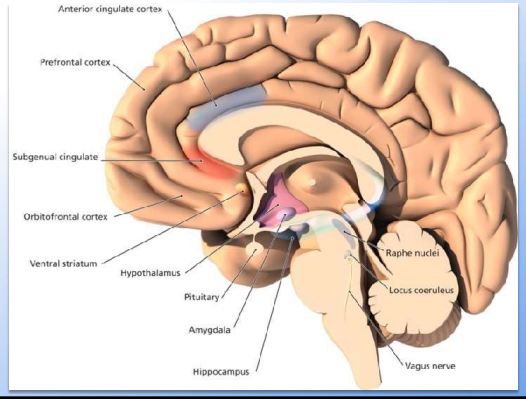
The Fear (Anxiety) Pathways: Perception, Processing and Motor



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Implicit Neurotransmitters

- Worry is a consequence of imbalances in gamma aminobutyric acid (GABA), 5-HT, norepinephrine (NE) and dopamine (DA).
  - Appears to be a genetic link to the availability of one of the enzymes of DA degradation
- Increased DA availability can predispose to worry in times of stress.

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Management of Anxiety

Acute vs. Chronic

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Management of Chronic Anxiety

- Most anxiety disorders do not require long-term management with benzodiazepines; however, there are those that do.
- Benzodiazepines are indicated primarily for acute anxiety and panic attacks.

11

11

Selective Serotonin Reuptake Inhibitors (SSRIs)

Serotonin is a key neurotransmitter innervating both the amygdala and cortico-striato-thalamo-cortical (CSTC) loop.

SSRIs can be effective in reducing both anxiety and worry in virtually all chronic anxiety disorders.

12

12

Selective Serotonin Reuptake Inhibitors (SSRIs) (continued)

- Mechanism of action is the blockade of serotonin reuptake in CSTC pathways.
- Most effective in managing the "worry" feature of anxiety disorders
- Serotonin not as integral to fear response
  - Logically, SSRIs are not as effective for the motor symptoms.

13

13

Selective Serotonin Reuptake Inhibitors (SSRIs) (continued)

Some SSRIs are more efficacious than others in the CSTC loop.

Most common agents for chronic anxiety

- Paroxetine
- Fluvoxamine
- Escitalopram
- Citalopram

14

14

Selective Serotonin Reuptake Inhibitors (SSRIs) (continued)

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- Primary advantages include both safety and limited risk of addiction.
  - SSRIs were designed for safety
  - Virtually no cardiovascular effect
  - Not characterized by physical dependency
  - Abrupt withdrawal may be unpleasant but not unsafe.

15

15

Selective Serotonin Reuptake Inhibitors (SSRIs) (continued)

- Paroxetine (Paxil®)
  - Among SSRIs, this one is almost never used when anxiety is not present.
  - Has some anticholinergic and norepinephrine inhibition functions that make it particularly suitable in controlling anxiety.
  - Also, some unique safety and adverse effect considerations.

16

16

Selective Serotonin Reuptake Inhibitors (SSRIs) (continued)

- Fluvoxamine (Luvox®)
  - First-line option for…
    - Obsessive-compulsive disorder
    - Social anxiety disorder
    - Panic disorder
  - Does not demonstrate the antidepressant discontinuation syndrome of other SSRIs
  - It inhibits most CYP450 isoenzymes.

17

17

Other SSRIs for Anxiety

- Escitalopram
  - Demonstrated efficacy in treating anxiety disorders
  - A good choice when drug interactions are a concern
    - Virtually no CYP450 inhibition

18

18

Other SSRIs for Anxiety (continued)

- Citalopram
  - A reasonable option for anxiety due to its antihistamine effect
  - Consider FDA warning about QT interval prolongation
    - Dose not to exceed 40 mg daily
    - Dose not to exceed 20 mg daily in the elderly

19

19

Norepinephrine and Anxiety

- Norepinephrine is a key neurotransmitter innervating both the amygdala and CSTC loop.
- The success of SNRIs in anxiety management is referred to as the "noradrenergic paradox" because there is strong evidence of norepinephrine stimulation with anxiety.

Source: Montoya, A., Bruins, R., Katzman, M. A., and Blier, P. (2016).

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20

20

Norepinephrine and Anxiety (continued)

- Despite this predictable and typically observed relationship, virtually every SNRI demonstrates clinical symptom improvement in anxiety states.
  - May be a transient increase in anxiety symptoms
  - With an appropriate therapeutic trial, all SNRIs demonstrate clinical efficacy.

Source: Montoya, A., Bruins, R., Katzman, M. A., and Blier, P. (2016).

21

21

Norepinephrine and Anxiety (continued)

- No clear, defining neurophysiologic rationale for this phenomenon
- Best theories cite the complexity of circuitry
  - Postulates that increasing noradrenergic activity results in downstream compensatory inhibitions

Source: Montoya, A., Bruins, R., Katzman, M. A., and Blier, P. (2016).

22

22

Other Options for Anxiety

- Buspirone (Buspar®)
  - A partial 5-HT_{1A} agonist
  - Effective only for GAD
    - Not indicated for anxiety subtypes
  - True MOA – Not well understood
  - Considered non-physically addicting
    - Originally designed as an alternative to benzodiazepines for GAD

23

23

Other Options for Anxiety (continued)

- Buspirone (Buspar®) (cont.)
  - Onset of action – Delayed
  - Not meant for acute anxiety management
  - Believed to work by way of adaptive events as opposed to acute occupancy of 5-HT_{1A} receptors
  - While it is a reasonable alternative to benzodiazepines in chronic management, it is not intended or effective for acute anxiety attacks

24

24

Other Options for Anxiety (continued)

- Alpha-2-delta ligands
  - Gabapentin and pregabalin
  - Blocks release of excitatory neurotransmitters
    - Decreases the release of…
      - Glutamate in amygdala to reduce fear
      - Glutamate in the CSTC loop to reduce worry
  - Effective for social anxiety and panic disorder

25

25

Management of Acute Anxiety

- Numerous agents are available for chronic anxiety disorders.
  - Most not effective for acute anxiety
- Benzodiazepines – Drug of choice for acute anxiety and panic
  - Extremely effective
  - Highly subject to abuse

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26

26

Benzodiazepines

- Function essentially as GABA agonists at post-synaptic receptors
  - Acutely attenuate/inhibit the motor responses triggered by the amygdala
- Functionally, they are CNS depressants

27

27

When to Use Benzodiazepines?

- Benzodiazepines are meant primarily for acute episodes.
  - Patients acutely fearful
    - E.g., must get on an airplane
  - Patients who have panic attacks
    - Impending doom
    - Tachycardia/palpitations
    - Diaphoresis
    - SOB

28

28

Benzodiazepines (continued)

- Mechanism of action is potentiation of GABA receptors.
  - Functionally this class of medication is like ETOH.
- Not indicated for most anxiety disorders, but…
  - Are a first-line option for GAD and panic disorder when appropriate

29

29

Benzodiazepines (continued)

- How to use benzodiazepines?
  - Should you use them at all?
- How quickly does physiologic tolerance develop?
- Does the benefit ever outweigh the risk?

30

30

Benzodiazepines (continued)

- There is no clear evidence to support assertions about the time to physical dependence.
  - Studies range from 1 to 6 months.
  - One of the more detailed studies suggests >3 to 4 weeks.
  - Generally, evidence suggests that you may safely prescribe for 4 weeks.

31

31

Benzodiazepines (continued)

- When initiating therapy for chronic anxiety disorders
  - Benzodiazepines will provide immediate symptom relief in the patient at the start of care.
  - Patient education goes a long way in successful benzodiazepine use.
  - Clearly the goal is to not create a dependence.

32

32

Benzodiazepines (continued)

- When required long-term
  - Long-acting agents are preferred (unless the patient is elderly).
- Discontinuation regimens in the physically addicted require long-term titration.

33

33

Benzodiazepine Taper Regimens

- Several schools of thought exist.
  - Taper off the existing medication.
  - Convert to long-acting agent and taper.
  - Taper more rapidly using adjunctive medications.
- Consider that tapering benzodiazepines can produce SNS rebound.
  - Physiologic withdrawal may be dangerous.

34

34

Benzodiazepine Taper Regimens (continued)

- Reduce dose by 50% in the first four weeks.
  - Hold that dose for 4 weeks
  - Then reduce by 25% q2 weeks
- More complex clinical scenarios will require longer tapers.

35

35

Benzodiazepine Taper Regimens (continued)

- Example – Patient taking alprazolam 2 mg BID
  - Convert to diazepam 40 mg daily
  - Week 1 – 35 mg daily
  - Week 2 – 30 mg daily
  - Week 3 – 25 mg daily
  - Week 4 – 20 mg daily
  - Hold this dose through week 8

Source: https://www.mdcalc.com/benzodiazepine-conversion-calculator

36

36

Benzodiazepine Taper Regimens (continued)

- Example – Patient taking alprazolam 2 mg BID (cont.)
  - Weeks 9 and 10 – 15 mg daily
  - Weeks 11 and 12 – 10 mg daily
  - Weeks 13 and 14 – 5 mg daily
  - Week 15 – Discontinue

37

37

Alternatives to Benzodiazepines

- Other drugs that suppress the SNS
  - First-generation antihistamines
    - E.g., hydroxyzine
  - Antiadrenergic agonists (clonidine)
  - Beta-adrenergic antagonists (propranolol)
- Not as acutely effective as benzodiazepines
  - Preferred in those at risk for addictive behavior

38

38

Classifying Anxiety Disorders

Selection of Medications for Best Outcomes

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39

39

Symptoms of Anxiety

- Anxiety (fear) and worry are the cardinal features.
  - All anxiety disorders manifest these symptoms.
- Numerous subtypes of anxiety are identified.
  - Each have symptoms that predominate.

40

40

Additional Symptoms of Anxiety

- Difficulty concentrating
- Fatigue
- Arousal
- Panic attacks

- Compulsions
- Muscle tension
- Irritability
- Sleep disruption
- Phobic avoidance

41

41

Differentiating Among Anxiety Disorders

- The difference among types of anxiety disorders is not anatomic location of the malfunction or neurotransmitters involved.
- It is the nature and timing of the malfunction.

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42

Chronic Anxiety Disorders – GAD

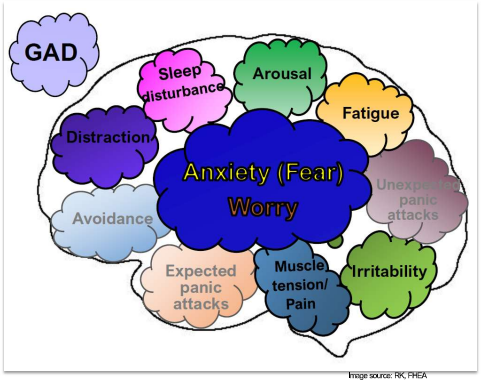

Image source: RK, FHEA

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Diagnostic Criteria for GAD

- Must have anxiety and worry **and** at least one other symptom.
- Symptoms have occurred most days for at least 6 months.
- There is social or occupational impairment as a result of symptoms.
- Very often onset in childhood.

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Chronic Anxiety Disorders – PTSD

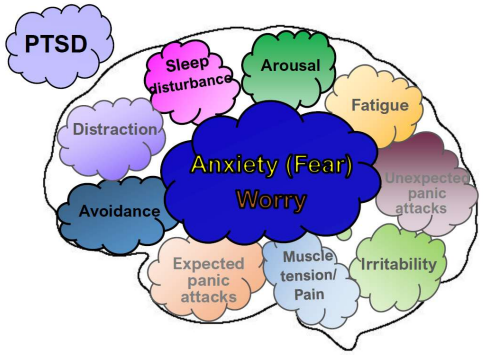

Image source: RK, FHEA

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Diagnostic Criteria for PTSD

- Anxiety and worry.
- Something truly awful has happened.
- Patients relive the events.
- Experience hyperarousal.
- Avoid those things that trigger re-experience.

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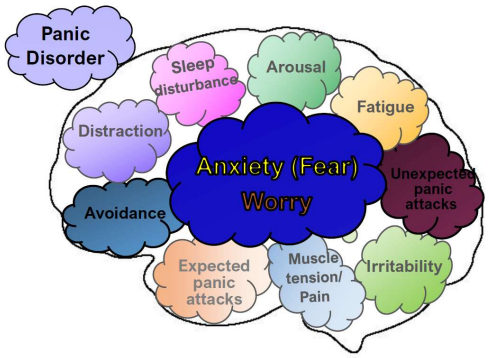
Chronic Anxiety Disorders – Panic Disorder



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Diagnostic Criteria for Panic Disorder

- Anxiety and worry.
- Patient experiences unexpected panic attacks.
- Lives in fear of repeat attacks.
- Frequently avoids places and activities that they associate with attacks.
- Occurred for at least one-month.
- Onset typically in early 20s.

48

48

Chronic Anxiety Disorders – Social Anxiety Disorder

Image source: RK, FHEA

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Diagnostic Criteria for Social Anxiety Disorder

- Anxiety and worry.
- Inordinate anxiety during circumstances in which they are observed by others.
- Duration of at least six months.
- Social or occupational dysfunction.

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As Always…Correct Dx!

- Anxiety, hypomania and ADD can simultaneously occur.
- True anxiety is characterized primarily by pervasive anxiety and worry, usually about something ill-defined.
  - Medication regimens very similar to MDD.
- Listen to the patient's primary concerns that will often identify the right diagnosis.

51

51

First-line Therapies Similar…

- But not identical!
- Not all anxious patients will respond to SSRIs or SNRIs.
  - Desirable because they are easy and safe.
  - This only matters if they work!

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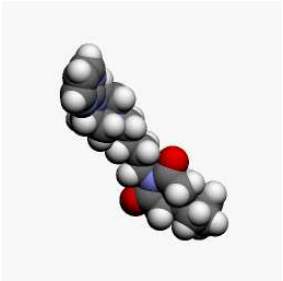
GAD First-line

- SSRI
- SNRI
- Buspirone
- Benzodiazepines
- Alpha-2-delta ligands



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https://commons.wikimedia.org/wiki/File:Pregabalin3D.gif

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Panic Disorder First-line

- SSRI
- SNRI
- Benzodiazepines
- Alpha-2-delta ligands

54

54

Social Anxiety First-Line

- SSRI
- SNRI
- Alpha-2-delta ligands
- **Beta blockers as an alternative option

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PTSD First-line

- SSRI
- SNRI
- Pharmacotherapy is typically <u>not</u> the preferred approach to PTSD management.

Image source: Public domain, https://commons.wikimedia.org/wiki/File:PTSD.png

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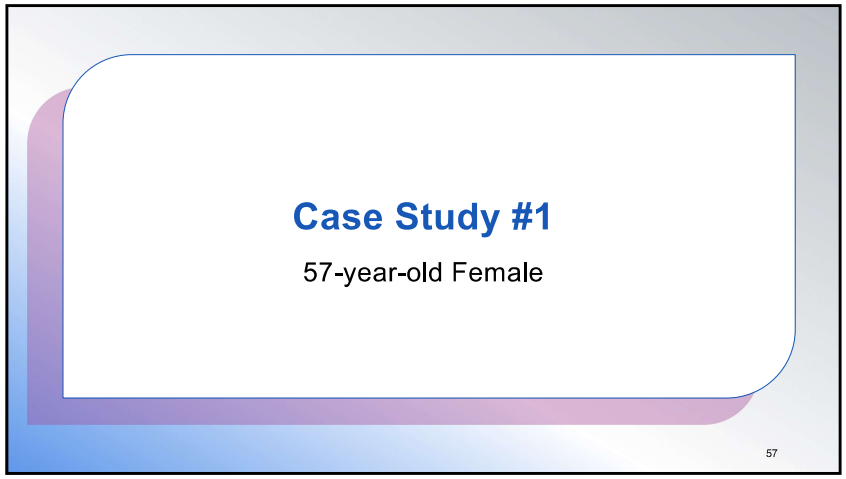

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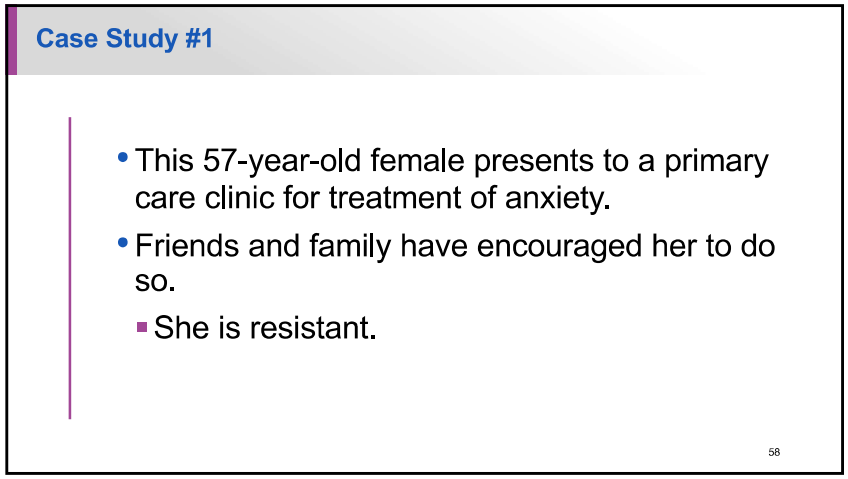

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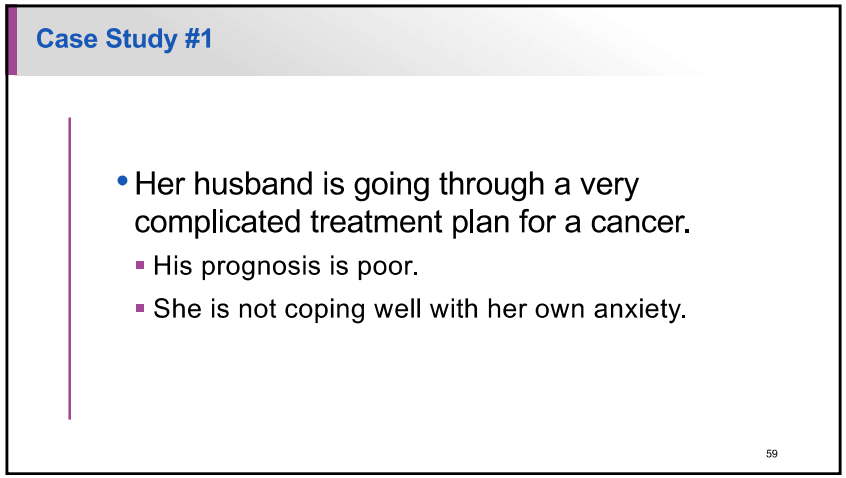

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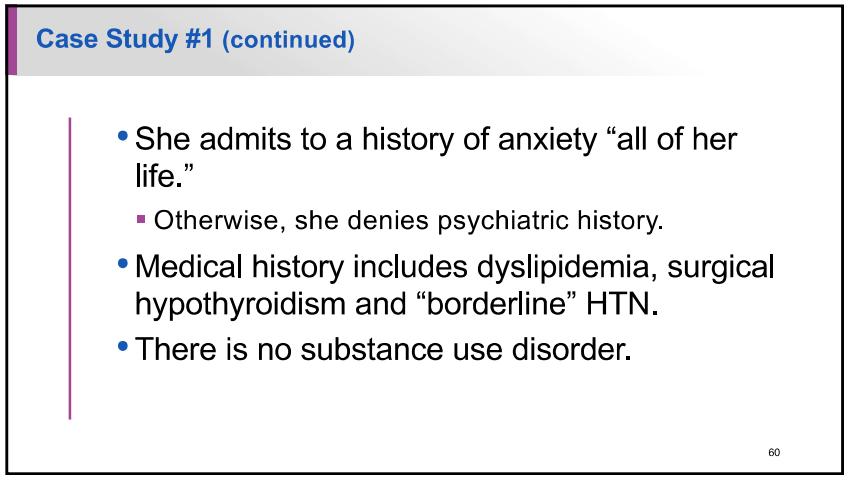

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Case Study #1 (continued)

- HPI – This patient reports that she has been anxious all her life.
  - In grade school, always "worried about something"
  - Admits to worrying about "everything"
    - Unable to identify specific sources of worry

61

61

Case Study #1 (continued)

- The patient denies panic attacks.
- Admits that she is in constant motion.
- Experiences episodes of getting "scared" with a racing heart and trouble breathing.
  - She "waits these out" and they resolve.

62

62

Case Study #1 (continued)

- She admits to…
  - Lifelong trouble sleeping
    - Worse now due to husband being very ill
  - Daily fatigue
  - Often irritable and quick to get angry
  - Difficulty concentrating
- She denies muscle pain.

63

63

Case Study #1 (continued)

- The patient reports that years ago an attempt at SSRI therapy produced homicidal ideation (HI).
- The medication was immediately stopped.
  - She was advised never to take an SSRI again.

64

64

Case Study #1 (continued)

- At this time, the patient is afraid to take any medication for anxiety due to risk of HI.
- Refuses to consider benzodiazepines for fear of becoming addicted.

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Case Study #1 (continued)

- Admits to only making this appointment because her husband and friends insisted.
- She has no way to relieve anxiety.
  - Used to smoke but had to stop due to husband's cancer.

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Analysis of HPI

Image source: Kay Jayno, photographer

- Worry +
- Anxiety +
- Sleep disturbance +
- Fatigue +
- Irritability +
- Difficulty concentrating +
- Muscle tension –

67

67

Case Study #1 (continued)

- Physical exam
  - Appropriately dressed and groomed
  - Attends to hygiene
  - Good eye contact
  - Coherent thought
  - Voice well modulated

68

68

Case Study #1 (continued)

- Physical exam (cont.)
  - Affect is anxious.
  - BMI of 17.3 kg/m2
  - Vital WNL; pulse was 94 bpm, BP 138/82 mm Hg
  - Otherwise, PE normal

69

69

Case Study #1 (continued)

- What's your diagnostic impression?
  - First, we rule out supraphysiologic thyroid hormone replacement.
  - TSH was 5.2 mIU/L; FT_4 15 pmol/L.
- Once we rule out physiologic cause, which anxiety disorder is most likely?
  - Generalized anxiety disorder

70

70

GAD First-line

- SSRI
- SNRI
- Benzodiazepines
- Buspirone
- Alpha-2-delta ligands

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Consider the Options

- SSRI and SNRI are contraindicated given the history of homicidal ideation.

Benzodiazepines are appropriate for GAD when other options are ineffective or inappropriate.

- Buspirone is a serotonin agonist.
  - Are there coincident concerns about the homicidal ideation?

72

72

Consider the Options (continued)

- Alpha-2-delta ligands
  - Very different mechanism of action as compared to the serotonin-mediated options
  - Not typically used first-line but rather as an add-on for partial responders to SSRI/SNRI/benzodiazepines

73

73

What did we do?

- We made an aggressive attempt to convince her to take a benzodiazepine.
- She refused, which left us with buspirone and alpha-2-delta ligands.

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Image source: Olya Kobruseva, photographer, https://www.pexels.com/photo/2-white-and-brown-heart-shaped-decors-5428836/

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Shared Decision Making

- We discussed the pros and cons of each of the remaining two choices.
- Despite the patient's trepidation, we started buspirone 7.5 mg BID.
- Follow-up in one week to ensure that she was not homicidal.

76

76

One-Week Follow-up

- She was not homicidal; tolerating well
- No effects, but no adverse effects
- Dose was increased to 10 mg BID; advised to follow up in 1 week.

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Second One-Week Follow-up

- On therapy for 2 weeks total and 10 mg BID × 1 week
  - She felt like things were starting to improve.
- She was very excited that her husband even commented on the fact that she seemed a little better.
- Dose was increased to 15 mg BID; advised to follow up in 2 weeks.

78

78

Follow-up 1 Month After Start of Rx

- One month after starting buspirone and 2 weeks at 15 mg BID, the patient was ecstatic.
- She was sleeping; she was eating and had gained 4 lb (1.8 kg) since her first office visit.
- Her husband accompanied her to reinforce how well she was doing.

79

79

Chronic Maintenance

- She remains on 15 mg BID.
- Her husband has since died, but she maintains that the buspirone has changed her life.
- While the subsequent events of her husband's cancer were very difficult, she has maintained control of her anxiety.

80

80

Case Study #2

10-year-old Female

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Case Study #2

- A 10-year-old female presents with her mother for evaluation and treatment of anxiety.
- The patient is not particularly talkative; most history comes from the mother.

82

82

Case Study #2 (continued)

- The mother says they are here because today her daughter would not leave the classroom at school during recess.
- The patient insisted that they call her mother.

83

83

Case Study #2 (continued)

- What do you do with a new patient?
  - The social history is unremarkable.
    - Patient lives with her mother, father and older brother.
    - She does not have a substance use disorder.
    - She attends elementary school; the school year has been in session for approximately one month.

84

84

Case Study #2 (continued)

- What do you do…(cont.)
  - The social history is unremarkable. (cont.)
    - The patient has friends at school.
    - She expressly denies any bullying or difficulty with teachers.
    - This is the first year that her brother has gone to a different school.
    - Otherwise, the school environment is noncontributory.

85

85

Case Study #2 (continued)

- HPI – This otherwise healthy 10-year-old female presents for evaluation.
- As described, at school today she abruptly insisted upon mother's presence.

86

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Case Study #2 (continued)

- The school staff could not resolve the situation.
  - The mother was called.
- Mother denies:
  - History of separation anxiety
  - Stranger event
  - School-related problems

87

87

Case Study #2 (continued)

The patient denies anxiety or worry (after being asked in age-appropriate language).

Denies rapid heart rate, SOB, diaphoresis.

The patient cannot articulate any associated thoughts or feelings; she just wanted her mother there.

88

88

Case Study #2 (continued)

- When Mom arrived at the school, the school counselor was in the classroom talking with the child.
- The counselor offered no concrete ideas as to the nature of the event.
  - School staff ascertained no physical symptoms.
  - Otherwise, everyone was confounded.

89

89

Case Study #2 (continued)

- Mom took the child home.
  - Child appeared fine.
    - Offered no real explanation of events.
- Mom could not find a counselor; patient was brought to the psychiatric practice.

90

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Case Study #2 (continued)

- The patient denies
  - Headache
  - Vertigo
  - Lightheadedness
  - Abdominal discomfort or n/v/d/c
  - Visual changes
  - Hallucinations or delusions
  - Dissociation

91

91

Analysis of HPI

- The patient separated herself from activities and focused on seeing mother immediately.
- A symptom assessment was noncontributory.
- Patient normalized when mother appeared.
- This was a first event.

92

92

Analysis of HPI (continued)

- Repeated, thorough, age-appropriate questioning indicated that there were no fears related to the school environment and no physical problems.

93

93

Case Study #2 (continued)

- Complete ROS was benign, excepting the event that precipitated this office visit.

94

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Case Study #2 (continued)

- Physical exam
  - Quiet 10-year-old female
  - Sits on mother's lap during the first part of the visit
    - She eventually shifted to her own chair.
  - She was not fidgety or restless.
  - When asked questions, she gave very brief answers.

95

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Case Study #2 (continued)

- Physical exam (cont.)
  - Voice was quiet but appropriate given the circumstances.
  - She would make eye contact when spoken to.
  - Overall, the PE was noncontributory.

96

96

Case Study #2 (continued)

- What's your diagnostic impression?
- Consider the differentials
  - Generalized anxiety disorder
  - Social anxiety disorder
  - PTSD
  - Separation anxiety disorder
    - Typically, the reluctance is to leave the parent.
    - Several month's duration

97

97

Case Study #2 (continued)

- When you can't figure it out, some piece of information is missing.
  - The patient became acutely fixated on seeing the mother immediately.
  - As soon as she saw her mother, she calmed down.
  - During the office visit she is with her mother.

98

98

Case Study #2 (continued)

- The discussion with the mother and patient became focused on the mother.
  - Why was the patient acutely fixated on, and comforted by, her mother's presence?

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Case Study #2 (continued)

- Mother commented that she was a stay-at-home mom.
  - Had never even been away from the patient overnight except for when she had the car accident.

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Case Study #2 (continued)

Almost exactly one year ago to the day the mother had been in a very serious car accident and hospitalized for several days.

The mother had no idea that it had made any meaningful impact on the patient as the family had minimized the event in conversation.

102

102

What's the diagnosis?

- The most likely diagnosis is PTSD.
- That event was clearly more catastrophic to the child than anyone appreciated.
  - Likely just having her mom out of the house for several days was traumatic.
- She was unable to consciously identify or articulate the awful event.

103

103

PTSD First-line Therapies

- SSRI
- SNRI
- Pharmacotherapy typically not the preferred approach to PTSD management.

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104

PTSD Best Practices

- The patient needs to be referred to a therapist who specializes in children who have experienced trauma.
- Pharmacotherapy is likely not going to be the answer for her.

105

105

What did we do?

- Pending the therapy referral, we still had a 10-year-old girl who needed to go to school.
- She said that she was not worried about going to school; she likes it.
- Mother is worried about similar events, appropriately so.

106

106

Image source: Olya Kobruseva, photographer, https://www.pexels.com/photo/2-white-and-brown-heart-shaped-decors-5428836/

107

107

Shared Decision Making

- We discussed options for acute anxiety in a 10-year-old.
- Ultimately, we agreed on hydroxyzine 25 mg up to TID PRN.
- Mom felt better having it available.
- No harm to the patient and might help.

108

108

One-Week Follow-up

- The patient had one similar episode in school 2 days later, so Mom started giving her the hydroxyzine before school.
- Patient took it for a couple of days but then didn't like it.
- In the interim, Mom had connected with an appropriate therapist.
  - We did not see them again.

109

109

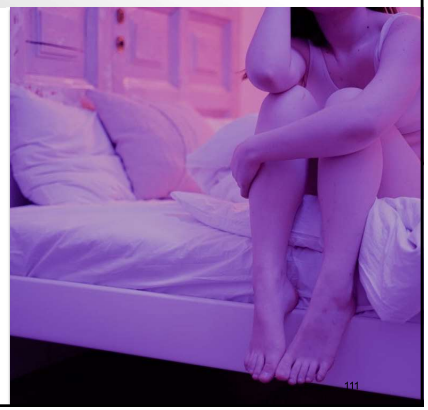
Pharmacologic Management of Sleep

110

110

Insomnia: Diagnosis or Symptom?

- Insomnia defined
  - Difficulty falling asleep
  - Difficulty remaining asleep
  - Early morning awakening
  - Nonrestorative sleep
- Very often undertreated



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111

Insomnia as a Diagnosis

Primary insomnia	Non-24 circadian rhythm disorder
• Occurs independent of other factors • Maybe related to general psychophysiologic arousal	• Generally recognized in blind patients • Occurs in those with normal vision

112

112

Insomnia as a Symptom

- Represents traditional view of insomnia
- Can occur as a consequence of…
  - Medical disorders
  - Psychiatric disorders
  - Medication adverse effect
  - Substance use disorder

113

113

Insomnia as a Treatment Target

- Whether a symptom or diagnosis, insomnia often undertreated.
- Identification of underlying causes should be primary focus of HPI.
  - Treat any underlying comorbidities
  - May need treatment of insomnia while contributing disorders are managed

114

114

Physiologic Mechanisms of Insomnia

115

115

Pathophysiology of Insomnia

- Hyperarousal as a primary theme
  - Can involve
    - Cortical nervous system
    - Autonomic nervous system
    - Cognitive arousal
    - Affective arousal

116

116

Pathophysiology of Insomnia (continued)

- Molecular mechanisms
  - Wake promoting/sleep suppressing
    - Catecholamines
    - Orexin
    - Histamine
  - Sleep promoting/wake suppressing
    - Adenosine
    - Serotonin
    - Melatonin

117

117

Pathophysiology of Insomnia (continued)

- Neurocognitive model (NREM instability)
  - Perpetuated by maladaptive behavioral coping strategies
  - Consequence of conditioned arousal
  - Association of wakefulness with sleep-related cues
  - Cortical arousal as underlying mechanism

118

118

Pathophysiology of Insomnia (continued)

- Rapid eye movement (REM) instability
  - Consequence of decreased REM sleep
  - Fragmented REM sleep promotes the perception of increased wakefulness and nonrestorative sleep.
  - Characterized by subjective-objective sleep discrepancies

119

119

Pathophysiology of Insomnia (continued)

- Behavioral and cognitive contributors
  - Diathesis-stress model
  - Stimulus control model
  - Cognitive model

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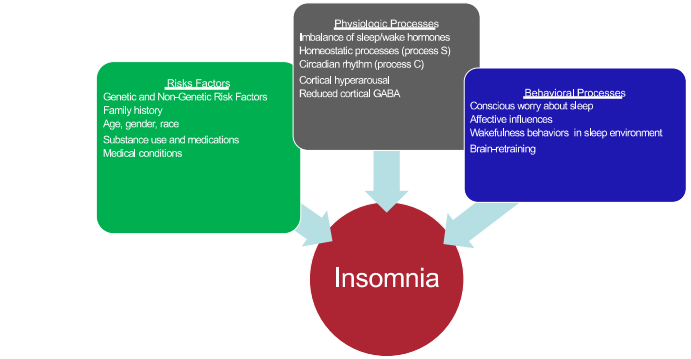
120

Pathophysiologic mechanisms of insomnia



Adapted from Levenson, J. C., Kay, D. B., & Buysse, D. J. (2015). The pathophysiology of insomnia. *Chest, 147*(4), 1179–1192. https://doi.org/10.1378/chest.14-1617

121

Classification of Insomnia

- Acute
  - Readily identifiable trigger
  - The patient has not had insomnia before.
  - Does not last longer than 4 months
  - Treatment target is the insomnia itself.

122

122

Classification of Insomnia (continued)

- Primary chronic
  - Caused by predisposing factors
    - Circadian rhythm disorders
    - Physiologic or psychological stress
    - Often multifactorial etiology
  - Insomnia is the primary treatment target.
  - Greater than 4 months duration

123

123

Classification of Insomnia (continued)

- Associated insomnia
  - Typically related to underlying mood disorder
    - Depression
    - Dysthymia
    - Bipolar
    - Schizophrenia
    - Poor sleep hygiene
    - Substance use disorder

124

124

Pharmacologic Management

- Recommended sequence of agents
  - Short- or intermediate-acting benzodiazepine receptor agonists (BzRAs) or melatonin agonist
  - Alternative short- or intermediate-acting BzRAs
  - Sedating antidepressants

125

125

Pharmacologic Management (continued)

- Recommended sequence of agents (cont.)
  - A combination of BzRA or melatonin agonist with antidepressant
  - Antiepileptic medications
  - Second-generation antipsychotics

126

126

Benzodiazepine Receptor Agonists

- Primary difference among agents
  - Duration of action
- None intended for long-term use
  - Triazolam
  - Estazolam
  - Temazepam
  - Flurazepam

127

127

Benzodiazepine Receptor Agonists

- The “Z” drugs
  - Zolpidem
  - Zaleplon
  - Eszopiclone
- Developed to minimize
  - Adverse effects
  - Abuse potential
- Greatest efficacy in higher doses

128

128

Pharmacologic Management

- Zolpidem
  - Recommended initial dose
    - Immediate release forms
      - 5 mg for women
      - 5 to 10 mg for men
    - Sustained release forms
      - 6.25 mg for women
      - 6.25 to 12.5 mg for men

129

129

Pharmacologic Management (continued)

- Zolpidem (cont.)
  - Treatment emergent adverse effects should be considered.
    - Higher doses can lead to next day driving impairment.
  - Can produce anterograde amnesia
  - Consider CYP3A4 implications

130

130

Pharmacologic Management (continued)

- Zaleplon
  - Rapid onset/short half-life
  - Morning grogginess not an issue
    - Completely metabolized before morning
  - Usual dose 10 mg
    - 5 mg for patients with inhibited metabolism
  - Effective for middle-of-the-night awakenings
  - No significant CYP3A4 issues

131

131

Pharmacologic Management (continued)

- Eszopiclone
  - Longer half-life than other agents
  - Extensively metabolized by CYP3A4
  - Next day impairment – Concern

132

132

Pharmacologic Management (continued)

- Melatonin agonist – Ramelteon
  - Indicated for difficulty falling asleep
  - Not associated with fall risk or w1cognitive impairment
  - Avoid with CYP1A2 and 3A4 inhibitors

133

133

Pharmacologic Management (continued)

Melatonin agonist – Tasimelteon

- Mechanism of action similar to ramelteon
- Indicated for non-24 Circadian rhythm disorder
- Theorized to synchronize melatonin and cortisol levels.

134

134

Pharmacologic Management (continued)

- Tricyclic antidepressants (TCAs)
  - Doxepin approved for insomnia
  - Many other TCAs used off-label
  - Low doses
    - Very effective
    - Associated with minimal adverse effects
  - Should not take with food
    - Markedly delays absorption and effective plasma concentrations

135

135

Pharmacologic Management (continued)

- Orexin receptor antagonist – Suvorexant
  - Targets the hormone orexin
    - Regulates wakefulness and sleep
  - Improves total sleep time and sleep onset
  - Should not be given <7 hours before planned awakening
  - Potential for abuse lower than other agents discussed

136

136

Pharmacologic Management (continued)

Orexin receptor antagonist (lemborexant)

- Many of the same considerations as suvorexant.
- Greater CYP3A4 substrate concerns.
- In comparative studies reportedly was better at inducing sleep than suvorexant.
- Reported incidence of hypnogogic hallucinations, cataplexy.

137

137

Pharmacologic Management (continued)

Orexin receptor antagonist (daridorexant)

- Functions as an orexin antagonist in the general sense
- Different from other orexin antagonists in its selectivity
  - Decreases the wake drive without altering sleep stages.

138

138

Pharmacologic Management (continued)

- Off-label medications
  - Trazodone
  - Mirtazapine
  - Quetiapine
  - Olanzapine
  - Risperidone
- Options capitalize on adverse effects.

139

139

Pharmacologic Management (continued)

- Over-the-counter medications (OTC)
  - Antihistamines
    - Commonly used in OTC sleep medications
    - Consider anticholinergic effects
  - Melatonin
    - Capitalize on the natural diurnal melatonin cycle
  - Herbal options
    - Valerian and kava

140

140

Pharmacologic Management (continued)

- All prescription sleep medications have warnings about strange behavior.
  - Some patients report driving, eating or talking with no memory afterward.
  - ETOH and other hypnotics potentiate these adverse effects.

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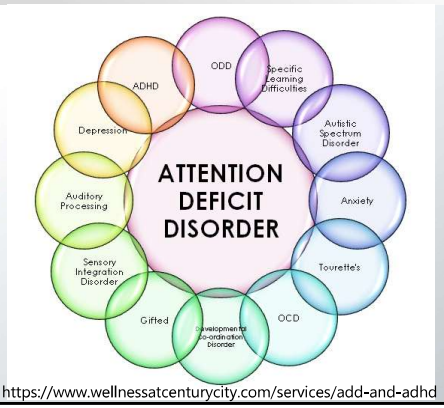
141

Pathophysiology of ADD



https://www.wellnessatcenturycity.com/services/add-and-adhd

142

142

Pathophysiology of ADD

- There are several postulated pathophysiologic mechanisms that involve abnormalities of both anatomy and physiology.
- Drug therapy targets abnormalities of two physiologic mechanisms.
  - Dopamine
  - Norepinephrine

143

143

Pathophysiology of ADD (continued)

- Prefrontal cortex figures prominently
- Frontal and temporal regions theorized to develop more slowly in children
- Critical to memory and behavior

144

144

Pathophysiology of ADD (continued)

- Neurochemical deficits include
  - Dopamine dysregulation
  - Norepinephrine dysregulation
- Deduced based upon
  - Response to drug therapy
  - Molecular genetics
  - Maldistribution of neurotransmitters in the brain of affected patients

145

145

Dopamine

- Responsible for a wide variety of neural processes
  - Maintains motivation/reward
  - Critical in the ability to attend
    - Enhances focus on a particular task
  - Facilitates joy/pleasure
    - Positive emotions
  - Features prominently in motor movement

146

146

Norepinephrine

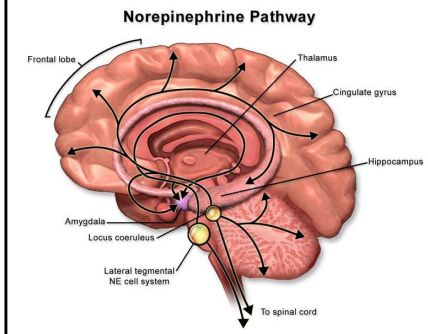


Image source: BruceBlaus, author; CC BY-SA 4.0

- Enhances prefrontal cortex network connections
- Frontal cortex helps dampen background noise.

147

147

Pathophysiology of ADHD

- Core symptoms of ADD
  - Inattention
  - Impulsivity
- Core symptom of ADHD
  - Hyperactivity
- Directly linked to imbalances of dopamine and/or norepinephrine in relevant neurological pathways

148

148

Pathophysiology of ADHD (continued)

- Under normal or healthy circumstances
  - Pyramidal neurons in the prefrontal cortex maintain a baseline "tonic" or slow synaptic firing of these neurotransmitters.
  - Additionally, these neurons can produce "phasic" or bursts of synaptic activity.

149

149

Pathophysiology of ADHD (continued)

- In a healthy patient with well-developed anatomy…
  - Neurotransmitters maintain appropriate balance of communication.
- With respect to memory, attention, and concentration these neurotransmitters have specific roles.

150

150

Pathophysiology of ADHD (continued)

- Dopamine and norepinephrine work together to tune the pyramidal neurons in the prefrontal cortex.
- When these neurotransmitters are out of balance, a collection of symptoms can occur that produces the clinical syndrome ADD.

151

151

Pathophysiology of ADHD (continued)

- Norepinephrine stimulates alpha$_{2A}$ receptors.
  - The result is increased connectivity in the relevant pathways.
    - This results in increased strength of the incoming signal as background noise is minimized.
      - Sustained attention
      - Alertness
      - Response to stimuli

152

152

Pathophysiology of ADHD (continued)

- Dopamine activates D_1 receptors.
  - This results in enhanced focus.
  - Prevents inappropriate connections from occurring
    - Working memory
    - Behavior
    - Motivation

153

153

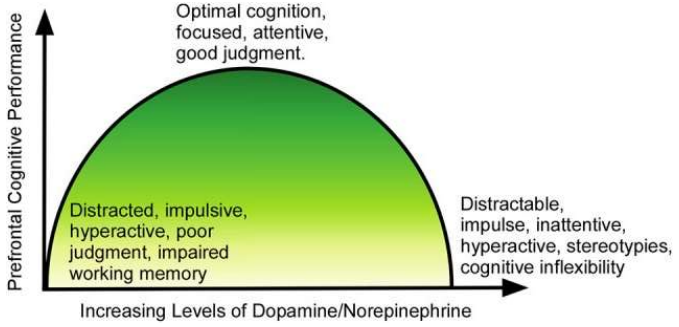
Pathophysiology of ADHD (continued)

- A steady state balance of both dopamine and norepinephrine is the desired state.
- Extremes on either end can result in a collection of ADD symptoms.

154

154

Pathophysiology of ADHD (continued)



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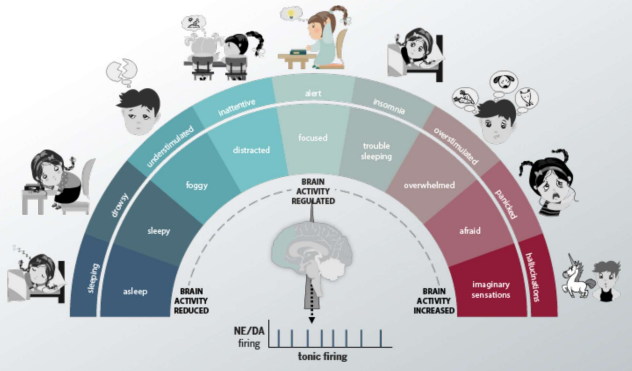
Pathophysiology of ADHD (continued)



156

156

Pharmacotherapy

- First consider and treat any comorbidities.
  - Substance use disorder
  - Mood disorders
    - Bipolar
    - Depression
    - Anxiety
- Remember nonpharmacologic therapy

157

157

Psychostimulants

- Mainstay of ADD therapy
  - Achieves on average 70% symptom reduction
- These medications **modulate** amount of DA and NE.
  - Effectiveness determined by symptom control vs. functional outcomes

158

158

Psychostimulants (continued)

- Exist in two broad categories
  - Methylphenidates
  - Amphetamine salts
- Very similar in most ways
  - Symptom control
  - Dose formulations
  - Adverse effect profile
  - Abuse potential

159

159

Psychostimulants (continued)

- Adverse effects rare when used properly
- Appetite suppression occurs early in therapy.
  - Weight should be monitored.

160

160

Psychostimulants (continued)

- Growth restriction can occur.
  - Final adult height may be shortened by 1" (2.54 cm).
- No documented relationship to cardiovascular events **when used properly**

161

161

Stimulants

- Dosing
  - Numerous long-acting and short-acting forms exist.
  - Long-acting forms provide better "tonic phase" control leading to…
    - More consistent symptom control
    - More convenient dosing
    - Minimization of postdose euphoria

162

162

Stimulants (continued)

- Methylphenidates (Ritalin®, Concerta®)
  - Blocks dopamine and norepinephrine reuptake
  - Have the most rapid onset and shortest duration
    - Several long-acting forms available, including the methylphenidate transdermal system (Daytrana® patch)

163

163

Stimulants (continued)

- Methylphenidates…(cont.)
  - Methylphenidate extended-release orally disintegrating tablets (Cotempla XR-ODT®) for once-daily dosing
  - Dexmethylphenidate (Focalin®) twice as potent as others in class

164

164

Stimulants (continued)

- Amphetamine salts (Adderall®, Dexedrine®, Vyvanse®)
  - Mechanism of action very similar to methylphenidates
  - Modulation of tonic NE and DA is goal.
  - Speculation abuse potential is higher than methylphenidate.

165

165

Stimulants (continued)

- Short-acting forms have highest potential for abuse.
  - Crushing, snorting, chewing – More consistent with abuse delivery

166

166

Stimulants (continued)

- Dextroamphetamine-amphetamine (Mydayis®)
  - Extended-release only
  - Taken once daily upon awakening
    - Clinical efficacy up to 16 hours
- Amphetamine extended-release orally disintegrating tablets (Adzenys XR-ODT®) also once daily

167

167

Non-Stimulants

- A variety exist
  - Abuse potential – Limited
  - Efficacy approximately 40%
  - Typically used when stimulants not indicated
    - Abuse potential
    - Intolerable adverse effects
    - Patient preference

168

168

Atomoxetine (Strattera®)

- Norepinephrine reuptake inhibitor
  - Purely norepinephrine reuptake inhibitor
  - No impact on dopamine
  - Typically well tolerated
  - No abuse potential
  - Response rate – Less impressive

169

169

Alpha$_{2A}$ Receptor Agonists

- Subgroup includes guanfacine and clonidine
  - Guanfacine (Tenex®, Intuniv®)
  - Clonidine (Catapres®, Kapvay®) (off-label)
- Both of these drugs directly activate antiadrenergic responses.

170

170

Alpha$_{2A}$ Receptor Agonists (continued)

- Mechanism of action
  - Very different than other ADHD drugs
- Primary symptom utility for
  - Hyperactivity
  - Impulsivity
- Does not increase attention as well as other options

171

171

Bupropion

- Not indicated for ADHD
  - Primary actions related to dopamine and norepinephrine reuptake
- Consider as an option for someone with depression and mild ADHD symptoms

172

172

Modafinil and Armodafinil

- Wakefulness agents
  - MOA – Not clear
  - Not approved at this time for ADHD, but are used off-label for this purpose
- These drugs produce prolonged wakefulness and attention.
  - Adverse effect profile – Minimal

173

173

Case Study #3

42-year-old Male

174

174

Case Study #3

- A 42-year-old male presents for evaluation.
  - He has been seeing a therapist for bipolar disorder and anxiety for several months.
- He really thinks he has ADD.
  - He was reading about it online.

175

175

Case Study #3 (continued)

- He reports trouble staying focused at work and at home.
- Shares custody of his daughter
  - He knows he does not pay attention.
  - He tries to be engaged but cannot focus.

176

176

Case Study #3 (continued)

- The patient has been on bipolar meds for years.
- He can't get much done at work.
  - Produces anxiety
  - Becomes an insomniac
- He is not following through on things at work.
  - Decreases productivity

177

177

Case Study #3 (continued)

- He acknowledges not paying attention to his daughter.
  - She says, "You never listen."
- The patient has never been diagnosed with ADD.
  - He searched online ADD and thinks that is the problem.

178

178

Case Study #3 (continued)

- So, what do you do with a new patient?
  - Complete medical history
    - Bipolar
    - Anxiety
  - Complete surgical history
  - Complete medication history
    - Lamotrigine (Lamictal®) 100 mg BID

179

179

Case Study #3 (continued)

- Complete ROS
  - Chronic anxiety about work
  - Sleep is generally not good.
    - Difficulty falling asleep (DFA)
    - Nocturnal awakenings
  - Occasional palpitations
  - Remainder of ROS – Negative

180

180

Case Study #3 (continued)

- HPI
  - Persistent sense of difficulty attending to important things
  - Often misses important details at work
    - Loses focus
    - Not productive at work

181

181

Case Study #3 (continued)

- HPI (cont.)
  - Inattentive to daughter and fiancée
  - Worries about…
    - Personal relationships
    - Work
    - Things he cannot define
  - Denies panic attacks but gets agitated

182

182

Case Study #3 (continued)

- HPI (cont.)
  - Diagnosed with BPD as an adolescent
  - Has been on numerous medications including lithium
  - Currently controlled with lamotrigine 100 mg BID
  - Denies mood swings
  - Admits to being “a little obsessive”

183

183

Case Study #3 (continued)

- HPI
  - Persistent sense of difficulty attending to important things
  - Often misses important details at work
    - Loses focus
    - Not productive at work

184

184

Diagnostic Criteria for Anxiety

- Excessive anxiety and worry occurring more days than not for at least 6 months about several activities or events such as work or school performance.
  - The worry is difficult to control.

185

185

Diagnostic Criteria for ADD

- Six or more of the following…
  - Fails to give close attention to details or makes careless mistakes in work or other activities
  - Has difficulty sustaining attention in tasks
  - Does not seem to listen when spoken to directly

186

186

Diagnostic Criteria for ADD (continued)

- Six or more of the following… (cont.)
  - Does not follow through on instructions and fails to finish schoolwork, chores or duties in the workplace
  - Has difficulty organizing tasks and activities
  - Avoids, dislikes or reluctant to engage in tasks that require sustained mental effort

187

187

Diagnostic Criteria for ADD (continued)

- Six or more of the following… (cont.)
  - Loses things necessary for tasks or activities
  - Easily distracted by extraneous stimuli
  - Forgetful in daily activities

188

188

Analysis of HPI

He's got criteria for both anxiety and ADD.

- Anxiety
  - Excessive worry/ anxiety which is difficult to control
  - Irritability
  - Concentrating difficulty
  - Sleep problems
- ADD
  - Fails to give close attention
  - Difficulty sustaining attention
  - Doesn't listen
  - Doesn't follow through
  - Avoids tasks that require sustained mental effort
  - Easily distracted

189

189

Case Study #3 (continued)

- Physical exam
  - Normal
  - Well groomed
  - Attends to hygiene
  - Good eye contact
  - Voice well modulated
  - Conversation – Mildly distracted

190

190

Case Study #3 (continued)

- What's your diagnostic impression?
  - Inattentiveness is a common symptom of anxiety.
  - Anxiety is less likely a symptom of ADD.
- Adults with ADD often have a childhood history although it's not required.
- Is this uncontrolled anxiety? ADD? Hypomania?

191

191

Diagnosis and Management

- He was diagnosed with anxiety and started on escitalopram.
  - His lamotrigine was continued.
- Advised to continue working with a therapist
  - Follow-up in 4 weeks

192

192

4-Week Follow-Up

- He reports no response to escitalopram.
  - Escitalopram is discontinued.
- Amphetamine salts (short-acting) -10 mg each morning is ordered.
- Follow-up in 4 weeks

193

193

Next Follow-Up 4-Weeks

- The patient reports marked improvement in symptoms.
  - Much more productive at work
- His fiancée tells him he is less distracted.
  - Requests additional dose at noon

194

194

Case Study #4

14-year-old Male

195

195

Case Study #4

- A 14-year-old male is encouraged to care by his mother.
  - Mom reports that during all his childhood he has been more difficult than siblings.
- He is in junior high school.
  - His inattentiveness is producing failing grades.

196

196

Case Study #4 (continued)

- During the office visit the adolescent sits quietly while his mother talks.
- Mother appears very frustrated.
  - Patient just does not remember to do school assignments or home chores.
  - He just wants to play videogames all day.

197

197

Case Study #4 (continued)

- So, what do you do with a new patient?
  - Complete medical history
    - None to report
    - Mom reports normal developmental progression.
    - No childhood diseases
    - Vaccines UTD

198

198

Case Study #4 (continued)

- So, what do you do with a new patient? (cont.)
  - No surgical history
  - No medications
  - Social history
    - Denies cigarettes, ETOH, substance use disorder
    - Has friends at school and a best friend
    - No concerns about bullying

199

199

Case Study #4 (continued)

- So, what do you do with a new patient? (cont.)
  - Social history (cont.)
    - No interest in girls
    - Per Mom, teachers deny behavioral problems at school.

200

200

Case Study #4 (continued)

- Complete ROS
- Denies any physical complaints
- Describes good appetite
- No anxiety, depression, SI
- Denies visual or hearing problems

201

201

Case Study #4 (continued)

- HPI
  - Mom describes a clear pattern of inability to focus on multiple-step instructions.
  - If given tasks individually, he will complete them.
  - Punishment is not helping.
    - Patient loses video game privileges when homework or chores are not done.

202

202

Case Study #4 (continued)

- HPI (cont.)
  - The patient concentrates in school and is studying Mandarin.
    - He maintains an “A” in this class.
    - He appears to do better in classes that do not have a large self-study component.

203

203

Case Study #4 (continued)

- HPI (cont.)
  - The patient admits that he forgets things when he must be self-directed.
    - He can pay attention in school when there is consistent direct video and audio reinforcement.
    - He remains focused on video games for the same reason.

204

204

Case Study #4 (continued)

- HPI (cont.)
  - Both Mom and patient describe persistent episodes of losing things.
    - Cell phone
    - Video games
    - School assignments

205

205

Case Study #4 (continued)

- HPI (cont.)
  - Mom states that the patient is urinating on the bedroom rug.
    - Patient admits this. He says he gets so focused on video games that he forgets to go to the bathroom.
    - There is no bedwetting, incontinence at school.

206

206

Case Study #4 (continued)

- HPI (cont.)
  - The patient specifically denies anxiety; maintains he just forgets.
  - Otherwise, both Mom and patient deny extremes of anger, moodiness, hallucinations, delusions, learning disability or defiance.

207

207

Case Study #4 (continued)

- Physical exam
  - Obese 14-year-old male
    - Estimate Tanner stage 2
  - Grooming/hygiene appropriate
  - Fair eye contact
  - Voice well modulated; speech appropriate
  - Good insight and judgment
  - Persistent left leg tapping during exam

208

208

Diagnostic Criteria for ADD

- Six or more of the following…
  - Fails to give close attention to details or makes careless mistakes in work or other activities
  - Difficulty sustaining attention in tasks
  - Does not seem to listen when spoken to directly

209

209

Diagnostic Criteria for ADD (continued)

- Six or more of the following…(cont.)
  - Does not follow through on instructions and fails to finish schoolwork, chores or duties in the workplace
  - Difficulty organizing tasks and activities
  - Avoids, dislikes or is reluctant to engage in tasks that require sustained mental effort

210

210

Diagnostic Criteria for ADD (continued)

- Six or more of the following…(cont.)
  - Loses things necessary for tasks or activities
  - Easily distracted by extraneous stimuli
  - Forgetful in daily activities

211

211

Diagnosis and Management

- The patient was started on amphetamine salts 10 mg at noon.
- Two-week follow-up
  - Mom and patient reported significant improvement.
- Patient continued regimen.
  - Mom and patient were encouraged to therapy.

212

212

End of Presentation
Thank you for your time and attention.

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213

213

Resources

Centers for Disease Control and Prevention (CDC). (2019). "CDC Guidelines for prescribing opioids for chronic pain."

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214

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221

221

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222

222

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223

223

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224

224

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225