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Case 1: Wearing down a diagnosis

The Question: What are the similarities and differences between anxiety and autism spectrum disorder (ASD) in children? How does it affect treatment and prognosis?

The Psychopharmacological Dilemma: Does this patient have an anxiety disorder, which can be treated effectively with a simple regimen that has a good prognosis, or does she have an ASD, which would require a more extensive regimen and possible lifelong treatment?

Karen Clarey, Stephanie Wong, and Takesha Cooper



Pretest self-assessment question (answer at the end of the case)

Which evidence-based treatment is recommended for severe anxiety in the pediatric population?

- A. Low-dose benzodiazepines as needed for anxiety attacks
- B. Selective serotonin reuptake inhibitor (SSRI) alone
- C. Cognitive behavioral therapy (CBT) alone
- D. Combination of SSRI with low-dose benzodiazepines as needed
- E. Combination of SSRI with CBT



Patient evaluation on intake

- A 7-year-old female with prior diagnoses of unspecified anxiety, obsessive-compulsive disorder (OCD), and Asperger's disorder who is brought in by her mother for treatment and clarification of her previous diagnoses



Psychiatric history

- The patient has been anxious for 3–4 years; she was first diagnosed 2 years prior to the initial visit
 - She worries that her neighbors will hurt others, that her dog is hiding under her bed and will bite her, that she will contaminate others when she is ill, that she will get words wrong while reading, etc.
 - She is afraid of the dark and cannot go to the restroom or walk down the hallway alone
- She has panic attacks with hyperventilation leading to syncope
- She has struggled with sleep since birth
 - She is anxious and activated at sleep time
 - Ultimately, she cannot fall asleep unless making physical contact with her mother
- She demonstrates some compulsive behaviors
 - She arranges or rewrites excessively until things are “just right”

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- She throws papers away if mistakes are made or erases the paper until small holes appear
- She lines toys up
- She insists on changing clothes when mildly dirty
- Chips cannot touch the sandwich on a plate, otherwise she will throw a tantrum
- She is hypersensitive to sensory stimuli
 - She complains to teacher when class is too loud, which leads to switch in classroom
 - She does not like tags on shirts and must wear soft clothing
 - She prefers soft food such as mashed potatoes or cooked carrots



Social and personal history

- She attends elementary school (2nd grade), has a 1st grade reading level, and has no special education
- She lives with three sisters, a cousin, and her mother
- Her parents divorced when she was 3 years old
- Her parents have joint legal custody; her mother has physical custody and her father sees her one weekend a month
- She has a normal developmental history



Medical history

- She has astigmatism and wears glasses
- There is no history of head injury, loss of consciousness, seizures, or cardiac problems



Family history

- Mother and father have a history of depression treated with paroxetine (Paxil)
- Maternal side
 - Depression with substance use disorder in aunt and uncle (heroin and methamphetamine, respectively)
 - Bipolar disorder in aunt and uncle
 - Thyroid disorder in grandfather and cousin
- Paternal side
 - Anxiety in grandmother
 - Substance use disorder in grandfather (substance unknown)



Medication history

- Clonidine (Catapres) 0.1 mg at bedtime for insomnia
- Previously used melatonin, dose unknown, but was not effective

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Psychotherapy history

- There is no psychotherapy history to report



Patient evaluation on initial visit

- The patient has reported symptoms of anxiety pertaining to various aspects of her life – school, family, safety, and health
- She appears restless with baseline anxious affect worsened when challenged to do something she is uncomfortable with (e.g. she bangs her head on a book when struggling to read)
- She is preoccupied with structure and is rigid and inflexible in her routine
- She is obsessive about organization of objects, writing, and self
- She shows hypersensitivity to various sensory stimuli with poor coping
- It is reported that patient has had poor sleep due to overactivation since she was an infant
- There is no history of psychotherapy or special education
- She is compliant with clonidine (Catapres) for sleep with little improvement; no other medication trials
- The provider decided to start sertraline (Zoloft) 12.5 mg daily for anxiety
- Continue clonidine 0.1 mg at bedtime for insomnia



Question

Does this choice of medication make sense?

- Yes
- No



Attending physician's mental notes: initial evaluation

- The child exhibits constant worry, restlessness, and somatic symptoms, and thus best meets the criteria for generalized anxiety disorder (GAD). It is reasonable to rule out OCD
- Autism is not likely given that social emotional reciprocity is intact, she is able to maintain peer friendships, plays imaginatively, uses and understands non-verbal gestures appropriately, and has good eye contact consistently
- The overlap between symptoms of autism spectrum disorder (ASD) and anxiety includes repetitive motor movements (lining toys up, rocking), insistence on sameness/inflexibility, and fixated interests, yet given her lack of impairment socially, the above symptoms are better explained by GAD
- She would benefit from CBT and an SSRI

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Case outcome: first interim follow-up visit at 4 weeks

- The patient still has anxiety-driven outbursts but these are less intense and less frequent
- She is still sleeping in her mother's bed
- She is open to more clothing options
- Her teacher reported an improvement in reading
- She has good medication adherence
- She denies side effects
- Therapy is pending due to insurance issues
- She continues with clonidine (Catapres) 0.1 mg at bedtime for insomnia



Question

What would be your next step?

- Increase sertraline (Zoloft) to 25 mg
- Maintain sertraline dose and wait for a further response



Attending physician's mental notes: first interim follow-up visit at 4 weeks

- The child is on a very low dose of sertraline (Zoloft) with continued significant symptoms of anxiety; thus, a dose increase is indicated. The mother is agreeable to increasing sertraline to 25 mg daily for further improvement of symptoms
- She would benefit from CBT, but the insurance is pending
- Psychoeducation provided on anxiety and how thoughts impact feelings and behaviors
- Also practiced abdominal breathing with the patient and parent, with homework to practice for 1–2 minutes each day

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Case outcome: interim follow-up visit at 9 months

- Sertraline (Zoloft) has been steadily increased and she has been taking 100 mg daily for about 1 month
- The patient still has some anxiety, but described it as mild and only occurring with reasonable triggers
- She is still sleeping in her mother's bed
- She has received various awards in school, including reading awards
- The patient was reading at pre-K level 1 year ago and is now at 3rd grade level
- Overall, the most improvement seen since the initial evaluation
- The therapy referral is still in progress
- Continue sertraline at 100 mg for now; continue clonidine (Catapres) 0.1 mg at bedtime for sleep
- The mother reports the primary care physician (PCP) also started diphenhydramine (Benadryl) 25 mg at bedtime for sleep

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Question

Is diphenhydramine (Benadryl) a reasonable choice for insomnia in children?

- Yes, for a short-term daily use
- Yes, for long-term daily use
- Yes, but only as needed
- No



Attending physician's mental notes: first interim follow-up visit at 9 months

- The patient is tolerating sertraline (Zoloft) well with significant improvements in functioning from prior to medication
- As therapy referral is still pending, the parent is working with the child using a structured CBT manual, which appears to help
- Addition of diphenhydramine (Benadryl) by the PCP is helping, and the parent wishes to continue
- Diphenhydramine is a reasonable short-term option for pediatric insomnia. An alternative would be increasing dose of clonidine (Catapres) or initiating melatonin (Table 1.1)
- Will consider taper off of clonidine to avoid polypharmacy if sleep improves alone with diphenhydramine

Table 1.1 Sleep medications used in the pediatric population

Medication class	Examples	Take-home point
Non-prescription medications		
Antihistamine	Diphenhydramine, hydroxyzine, chlorpheniramine	Short-term use in younger children, especially those with atopy
Melatonin	Several over-the-counter preparations available	Best for circadian rhythm phase delay or sleep-onset insomnia
Prescribed medication		
Benzodiazepine	Lorazepam, temazepam, etc.	Limit use in children as can be habit forming. Anxiolytic properties can be useful short term (<1 week)
Non-benzodiazepine receptor agonists	Zaleplon, zolpidem, eszopiclone	Sleep-related behavioral side effects limit utility in pediatric population
Off-label medication		
Antidepressants	Atypical antidepressants: trazodone, mirtazapine Sedating SSRIs: fluvoxamine, citalopram Tricyclic antidepressants: imipramine, amitriptyline	Most useful with comorbid mood/anxiety disorders
α-Agonists	Clonidine, guanfacine	Often used for pediatric insomnia. Generally safe and effective despite little data to support their use. Can lead to hypotension

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Case outcome: interim follow-up visit at 2.5 years

- The patient has been followed every 1–2 months
- Sertraline (Zoloft) has been gradually increased and is now at 150 mg; she has been on this dose for about 1 year and 8 months
- Clonidine (Catapres) was tapered off and discontinued approximately 1 year ago, as it was no longer helping with sleep
- She is still taking diphenhydramine (Benadryl) at bedtime for sleep as of 3 months earlier, and was sleeping alone in her own bed most nights; however, recently anxiety due to sleeping alone has returned
- The patient began therapy 1.5 years ago and went for approximately 8 months; however, her mother felt it was ineffective and quit
- She is more adventurous in her choice of clothing and foods
- She has more restlessness and irritability
- She has more complaints about loud noises to the point of leaving the classroom in the middle of lessons
- Bullying at school might explain the spike in anxiety



Question

What would you do next?



Attending physician's mental notes: interim follow-up visit at 2.5 years

- There has been exacerbation of symptoms with continued impairing anxiety
- Her mother is agreeable to raising sertraline (Zoloft) to 175 mg due to the spike in anxiety and resulting poor sleep
- In order to augment the increased SSRI dose, she is encouraged to return for booster CBT sessions
- The parent will talk with the school about bullying and assist the patient with coping skills

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Case outcome: interim follow-up visit at 3.5 years

- 1 year ago, the patient began a sertraline (Zoloft) taper due to ongoing improvement in anxiety symptoms
- It was tapered by decrements of 25–50 mg every 1–2 months; she is currently on 25 mg daily
- The patient has not returned for therapy
- She has been sleeping in her own bed with no problems for 3 months
- Her sensory issues have diminished and she is enjoying different textures, food, and environments
- She is functioning well both at home and at school

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- The patient was challenged to have a playdate at a friend's house to challenge her anxiety and this was successful
- She continues to use diphenhydramine (Benadryl) for sleep



Question

What would you do next?



Attending physician's mental notes: interim follow-up visit at 3.5 years

- The patient has responded well to sertraline (Zoloft) over the past 3.5 years from titration to 175 mg to gradual taper completely off medication
- Although the patient would have benefited from consistent CBT from a trained provider, this was not available in the locale. Nonetheless, the patient and parent were able to implement some CBT techniques and the parent's willingness to work with the patient on a manualized treatment, while not ideal, was helpful
- After more than 3 years of treatment, the patient has gained confidence in her ability to manage her anxiety and use her cognitive skills to reduce thinking errors, and has increased willingness to face her fears



Case debrief

- Our patient was initially diagnosed with unspecified anxiety, OCD, and Asperger's disorder by multiple physicians
 - A proper diagnosis guides proper treatment. Adequate treatment was not started in this case due to an unclear diagnosis. Also, patients with multiple diagnoses often experience polypharmacy, and thus diagnostic clarity is key
 - The patient was started on clonidine (Catapres) to target sleep problems and this was likely to address other behaviors, such as outbursts. If sleep problems were secondary to the underlying anxiety disorder, it is possible the sertraline (Zoloft) alone would have resolved the sleep difficulties
- After a full history review of all symptoms, the patient appeared to more closely fit into a diagnosis of GAD
 - The treatment became more simplified and targeted, and there was hope for remission of her symptoms
- The SSRI sertraline, which is FDA approved for OCD in children, is widely used off label for GAD in children. It has been shown to reduce somatic symptoms of anxiety in children with GAD,

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including a reduction in the Hamilton Anxiety Rating Scale in a double-blind, placebo-controlled trial of children aged 5–17 years

- CBT was recommended but, unfortunately, access was limited
- Sertraline, along with clonidine for sleep, was used and slowly titrated to alleviate symptoms
- There were frequent follow-ups at 1–2-month intervals, and the patient began to show significant improvement in her symptoms
- Diphenhydramine (Benadryl) was initiated by her PCP for further augmentation for insomnia
 - Due to the risk of unnecessary polypharmacy, clonidine was eventually discontinued
- There were instances of deterioration, which were effectively managed by increasing the dose of sertraline
 - A benefit of sertraline is the wide dosage range, which was essential in this case
- At her peak dose, the patient improved quickly and tolerated a slow taper to ultimately completely discontinue medication and achieve symptom remission



Take-home points

- Anxiety disorders and ASD have multiple overlapping symptoms, which can make diagnosis difficult
- Distinguishing between the two can be done by assessing all symptoms exhibited by the child and obtaining a thorough history to find key symptoms missing for a certain diagnosis
 - In this case, persistent deficits in social impairment and communication that are classic in ASD were missing
 - Objective assessments such as the Autism Diagnostic Observation Scale are often used to make an ASD diagnosis, but are not widely available
- It is also important to assess the underlying motivation for symptoms
 - For example, refusal to separate from the caregiver, as in our patient, can be seen both in anxiety disorders and ASD
 - In anxiety, the refusal to separate is driven by fear of what might occur to the caregiver or to the patient if they are separated
 - In autism, refusal to separate is more likely a result of unwillingness to change routine without any overt “fear” involved
- The correct diagnosis leads to proper treatment, better understanding of the disorder by caregivers, and a decrease in overmedication/undermedication in children

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- SSRI/serotonin-norepinephrine reuptake inhibitor (SNRI) in combination with CBT is the gold standard for treatment of GAD in children
 - They may benefit from the addition of other medications to target symptoms not addressed by an SSRI alone, such as insomnia
- To taper sertraline (Zoloft), reduce by 25–50 mg weekly to avoid discontinuation symptoms
- If the patient does respond to sertraline, a trial of another SSRI would be recommended. After failure of two SSRIs, an SNRI would be indicated
 - Duloxetine (Cymbalta) is FDA approved in children with GAD
- Benzodiazepines have a limited role in pediatric anxiety but can cautiously be used transiently while waiting for an SSRI to begin working
- Clinical trials have found mixed results for tricyclic antidepressants in pediatric anxiety disorder. Side effects limit their usefulness in this population



Performance in practice: confessions of a psychopharmacologist

What could have been done better here?

- As mentioned previously, CBT is an important part in the treatment of pediatric GAD. For mild to moderate GAD, CBT alone is preferred but for severe GAD, a combination approach is indicated
- CBT offers tools such as cognitive reframing and self-monitoring to help patients gain control over their symptoms
- CBT access to this patient was very limited and could have hindered her eventual remission
- While some elements of CBT were presented to the patient during psychiatric follow-ups and at home, she would have benefited from increased access to CBT done in a structured and focused setting
- Earlier and longer access may have led to earlier control of her symptoms and thus decreased the need for psychopharmacological management

What are possible action items for improvement in practice?

- Become familiar with cognitive behavioral principles to teach your patients during their medication follow-up visits or, better yet, become a CBT-trained provider to avoid split treatment
- Research and better understand the pediatric options for sleep, including sleep hygiene and other behavioral interventions in addition to medication options

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Tips and pearls

- Diagnosis guides treatment, and thus it is imperative to perform a thorough assessment to ensure you are treating the proper condition
- For children, it is generally recommended to start low and go slow with medication
- Children often require the full doses used in adults due to more rapid drug metabolism at younger ages
- When medicines are indicated for pediatric anxiety, SSRIs are first line
- The goal of treatment with sertraline (Zoloft) is complete remission of current symptoms and prevention of future relapses
- The more anxious the patient appears, the lower the starting dose of sertraline should be and the slower the titration upward
 - This is due to possible activating effects of the medication when first started
- If sertraline seems to wear off before the end of the day, sometimes giving it twice per day can help
- Sertraline must be tapered to avoid withdrawal effects
- It is important to taper clonidine (Catapres) to prevent rebound hypertension that may occur with abrupt discontinuation, especially in children who are more sensitive to the hypertensive effects
- Remember to warn parents and children of the black box warning for all SSRIs warning of increased risk of suicidal ideation and behavior



Two-minute tutorial

Recognition and management of pediatric anxiety disorders

- Anxiety disorders are one of the most common psychiatric conditions seen in the pediatric population
- Screening for the presence and severity of anxiety symptoms along with comorbid psychiatric and medical conditions is recommended when evaluating all pediatric patients
- Recognition and management of these disorders is critical in preventing the development of other psychiatric disorders, such as depression and substance use disorders in adulthood
- Various brain structures have been implicated in anxiety disorders
 - The amygdala plays a prominent role in an individual's fear response
 - Hyperactivity of this structure is seen in functional magnetic resonance imaging (fMRI) studies in anxiety disorders