Mental Health Care in the Pediatric Clinic

Treating Anxiety

By the end of this chapter you will be able to:

- Explain the role of SSRIs in treating anxiety
- Describe how to start, titrate, and switch SSRIs
- Outline the role of structured psychotherapy in the treatment of anxiety

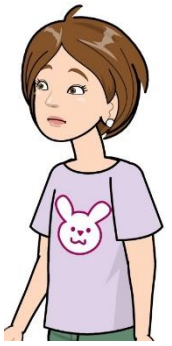
Anxiety and Treatment: major points

If anxiety is mild to moderate or of recent onset, Cognitive Behavioral Therapy (CBT) is first line treatment.

If anxiety is moderate to severe, combined treatment with CBT with a selective serotonin reuptake inhibitor (SSRI) is superior to either treatment alone.

The goal of treatment is **remission**, when the child experiences no or few anxiety symptoms.

Case: Emily, with Generalized Anxiety Disorder



Emily is a 12 year girl who presents with frequent stomachaches and nausea. These have gotten worse as she approaches her high school entrance exams. Emily worries about how she will do on the tests, and she worries about her homework, and assumes that if she does poorly she will fail out of school and her parents will be disappointed in her. She lies in bed at night rehashing the day and worries that she has offended others by what she said or did, and berates herself for not doing better. She is increasingly irritable and tense, and sleeps poorly.

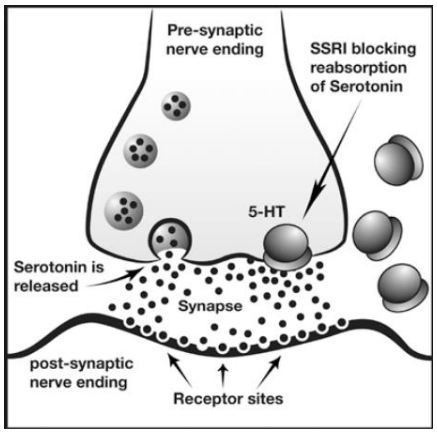
Emily's anxiety interferes with her functioning in that she spends excessive time trying to perfect on school work and she has somatic symptoms causing distress. She is still able to attend school with good grades and can engage socially.

You ask Emily to complete a GAD-7, on which she has a score of 18, above the cut-off level of 10. You think about the severity of Emily's anxiety. She has a fairly high symptom burden in terms of her own distress, but she is able to perform functionally at a normal to high level, so you categorize her anxiety as moderate.

Pharmacotherapy for anxiety in children and adolescents

Selective Serotonin Reuptake Inhibitors

The class of medications called the Selective Serotonin Reuptake Inhibitors (SSRIs) came onto the market in 1987 with fluoxetine. This represented a new strategy for treating depression and anxiety. The SSRI's were simpler to use than older antidepressant medications and did not have the risk of cardiac toxicity and fatality in overdose that the older medications have. SSRI's work by blocking the reuptake of serotonin in the pre-synaptic nerve ending, thus increasing the available serotonin in the synaptic cleft.



Mixed Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

A related class of medications is the mixed serotonin-norepinepherine reuptake inhibitors, or SNRIs. There are 3 drugs in this group: venlafaxine, duloxetine and desvenlafaxine. The SSRIs and SNRIs together are sometimes referred to as SRIs, or serotonin reuptake inhibitors. As a class, the SNRIs are slightly less effective and less rapidly effective in the treatment of pediatric anxiety than are the SSRIs, but venlafaxine and duloxetine have been found to be effective in randomized controlled trials for the treatment of both pediatric depression and anxiety.

Serotonin Reuptake Inhibitors: FDA Approvals

Approved for OCD

- fluvoxamine ≥ 8 years of age
- sertraline ≥ 6 years of age
- fluoxetine ≥ 7 years of age

Approved for Depression

- fluoxetine ≥ 8 years of age
- escitalopram ≥ 12 years of age

Approved for Non-OCD Anxiety

- duloxetine ≥ 7 years of age for Generalized Anxiety Disorder (GAD)

SRI Efficacy for Non-OCD Anxiety Disorders

Separation Anxiety, GAD and Social Anxiety

- fluvoxamine – RUPP, 2001
- fluoxetine – Birmaher et al, 2003
- sertraline - Walkup et al, 2008
- escitalopram - Strawn et al, 2020

Social Anxiety

- paroxetine - Wagner et al, 2004
- fluoxetine - Beidel et al 2007
- venlafaxine - March et al, 2007

GAD

- sertraline - Rynn et al., 2001
- venlafaxine - Rynn et al., 2007
- duloxetine - Strawn et al 2015

FDA approval for serotonin reuptake inhibitors in children and adolescents has been primarily for treatment of OCD and depression. There are no SSRIs with an FDA indication for non-OCD anxiety. Duloxetine, an SNRI, has FDA approval for treatment of GAD in children aged 7 and up.

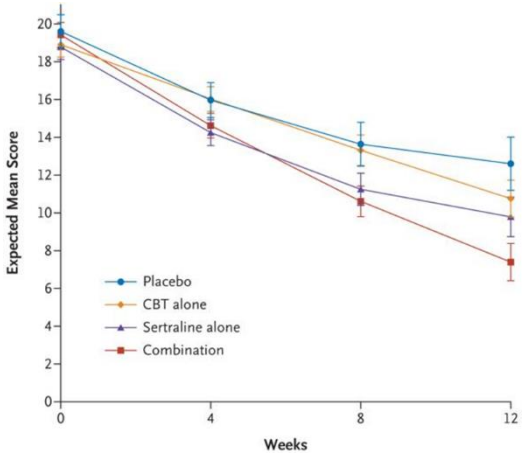
Lack of FDA approval does not mean lack of evidence for efficacy of SRIs in children and adolescents. The studies listed here are all randomized controlled trials indicating efficacy superior to placebo of the indicated medication.

Child/Adolescent Anxiety Multimodal Study (CAMS)

The NIMH-funded Child-Adolescent Anxiety Multimodal Study (CAMS) (Walkup et al NEJM 2008) randomized 488 children between the ages of 7 and 17 years who had a primary diagnosis of separation anxiety disorder, generalized anxiety disorder, or social phobia to receive 14 sessions of cognitive behavioral therapy, sertraline (at a dose of up to 200 mg per day), a combination of sertraline and cognitive behavioral therapy, or a placebo drug for 12 weeks. The CAMS found combination sertraline plus CBT to be most effective, better than either treatment alone, and superior to placebo. Sertraline alone and CBT alone were also superior to placebo.

CAMS Study Arm	CBT	Sertraline	CBT + sertraline	placebo
Response rate (%) at 12 weeks	59.7	54.9	80.7	23.7

Scores on the Pediatric Anxiety Rating Scale during the 12-Week CAMS Study



Here is a figure showing how the anxiety rating scales for the participants changed over the 12 weeks of the study. The arms with sertraline only and sertraline plus CBT separated out from the CBT only and placebo arms at 8 weeks. This and similar studies form the basis of current strategies to use either an SSRI, CBT, or both in the treatment of anxiety in children and adolescents.

First line SSRI medications for use in primary care					
generic name	Dosage forms & strengths	Starting dose - max dose	Typical effective dose	Half life (hrs)	CYP450 interactions
fluoxetine	10, 20, 40 & 60 mg capsule 20 mg/5ml liquid	10 mg - 60 mg	20-40 mg	48-72; active metabolite up to 2 weeks	Inhibits 2D6 and 3A4
sertraline	25, 50, & 100 mg tablets 20 mg/ml liquid	25 mg -200 mg	50-100 mg	22-36	Weakly inhibits 2D6 and 3A4
escitalopram	5, 10 & 20 mg tablets 1 mg/ml liquid	5 mg – 20 mg	10-15 mg	27-36	No significant interactions

For the purposes of this educational series, we are going into detail on just 3 of the SSRI medications, and neither of the SNRIs. The three medications listed here, sertraline, fluoxetine, and escitalopram, are all appropriate first-line choices for children and adolescents with anxiety or depression. Side effects of these 3 medications are essentially the same and will be addressed below.

Emily: next steps
You discuss treatment options with Emily and her mother.
They are concerned about her level of distress. Emily's mother has a history of anxiety and takes sertraline. They would like to begin with combined therapy, and have already identified a CBT therapist.

After discussing benefits, risks, and side effects of sertraline with Emily and her mother, you write a prescription for sertraline 50 tablet with instructions to take ½ tablet daily for 2 weeks then increase to the full tablet.

SSRI side effects: preface
Kids with anxiety and/or depression tend to have somatic symptoms that overlap with the common side effects of SSRIs.

Despite high reported rates of side effects with SSRIs in randomized controlled trials, discontinuation rates are low.

Most common side effects decrease by the 3rd month of treatment or sooner.

Common adverse effects of SSRIs and how to address them

Symptom	Possible solutions
GI distress: nausea, vomiting, abdominal pain, diarrhea	Take with food, take at night, wait it out, should improve with time
Headache	Take at night, wait it out, should improve with time
Sleep disturbance: too sleepy, or can't sleep	Change the dose time, wait it out, should improve with time
Sweating, flushing, flu-like symptoms, dry mouth	Wait it out, should improve with time

While side effects to SSRIs are common, they are generally mild, improve with time, and are rarely felt to be intolerable. They can sometimes be addressed by changing the timing of the dose relative to food and sleep. The SSRIs discussed in this series are all generally taken in the morning, but there is no difference in efficacy if taken later in the day or at bedtime.

Adverse Effects of SSRIs and how to address them: sexual side effects
As many as 50% of adults have sexual side effects with SSRI treatment.
These include decreased libido, arousal, duration of orgasm, and intensity of orgasm.
We tend to not ask adolescents about baseline sexual symptoms, the impact of anxiety or depression on sexuality, or sexual side effects of treatment.

If we don't ask, teens may discontinue an effective treatment without explaining why.
Options include lowering the dose or using a non-SSRI medication. Ask your consulting psychiatrist.

Adverse Effects of SSRIs and how to address them: hematologic
Easy bruising, bloody noses
Due to serotonin receptors on platelets – does not affect platelet count
Rarely clinically significant
May be a problem if taking another medication that promotes bleeding, such as chronic NSAID use

Adverse Effects of SSRIs and how to address them: activation
What is activation?

- irritability, agitation, restlessness, hostility, aggression, disinhibition, emotional lability
- Generally presents in the first 2-3 weeks of treatment with an SSRI
- More common in children< adolescents< adults
- May be associated with suicidality
- Is not the same thing as a manic episode and does not indicate risk of bipolar disorder

What to do about activation?

- Decrease the dose and monitor symptoms – they should resolve at about the same rate they came on
- Consider switch to a second SSRI or an SNRI
- Or discuss with your consultant psychiatrist

SSRIs and the FDA Boxed Warning on Suicidal Ideation Suicidality: Boxed Warning

- In 2004, the FDA issued a boxed warning following a review of 24 clinical trials involving 4,400 children and adolescents who had been prescribed an antidepressant for major depression, anxiety or OCD. About 4/100 children taking medication spontaneously reported suicidal thoughts and/or behaviors compared to 2/100 taking placebo.
- A second analysis, based on data from 27 RCTs (>5,300 children), found a statistically significant risk difference of 0.7%.
- A third analysis of 35 RCTs (<6,000 patients), found a non-significant risk difference of 0.9%.
- A fourth meta-analysis in children and adolescents with generalized, separation and social anxiety disorders also failed to link suicidality and antidepressant treatment.

Talking about the boxed warning: language you can use
Everybody develops their own style in discussing the boxed warning on suicidal ideation. The goal is to be complete but concise, letting patients and families know that the risk is real but rare, refers to thoughts and behaviors but not suicides, and that you are bringing the patient and family in on a plan to manage these symptoms should they arise. The verbiage below is one model for discussing the boxed warning**.**
"Every medication used to treat depression has a warning from the FDA that says that in rare cases, a child or teenager who starts the medication may feel worse instead of better, and have thoughts of hurting or killing themselves."
"This occurs rarely, and usually in the first few weeks of treatment. In studies of antidepressants, it occurred more commonly in patients who were taking the medication than in those who were taking a placebo pill. No patients in the studies actually committed suicide."

"I don't expect that this will happen to you as we start treatment for your anxiety. But it's very important that you understand that as you start taking the medication, if you don't feel right, especially if you have thoughts about death or wanting to hurt yourself, that you let somebody know right away and let me know as soon as possible."
"Who is the person you will be able to talk to if you have any feelings that are scary or uncomfortable, especially about hurting yourself, over the next several weeks?"

Emily: first follow up visit
You see Emily back 4 weeks later.
"I don't really see any change. Maybe a tiny bit less anxious? I like my therapist, but have just had 2 visits."
GAD-7 score = 16
Side effects:

- *Stomach upset for 6 days, now improved*
- *Trouble sleeping, still, no more than baseline*
- *Denies headache or easy bleeding*
- *Denies agitation*
- *Denies suicidal ideation or thoughts of self-harm*

Emily is tolerating the current dose of sertraline 50 mg, has just started therapy, and sees some subjective improvement but is still quite symptomatic. It has only been 4 weeks. It would not be wrong to continue another 3-4 weeks at this dose, but an increase now to sertraline 100 mg would be more likely to move Emily more quickly to response and remission.

You tell Emily to use the remaining 50 mg tablets and take 1 ½ tablets daily until gone, then start sertraline 100 mg daily.

Here is a suggested titration schedule for SSRIs in pediatric patients. It is not meant to be followed exactly in every patient but is simply a guide. We used to say about SSRI titration "start low and go slow". The problem with that strategy is that prescribers would leave kids on subtherapeutic doses of SSRIs for months, and the kids wouldn't get better. We know from large RCTs that if pediatric patients are going to respond to a dose of an SSRI, the first signs of response are present at 2 weeks and clear response is present at 6 weeks. So if you see no improvement at all on a particular dose, and the patient is tolerating the dose, you should titrate up with the goal of achieving symptom remission. Your goal is to get kids to the point where they no longer meet criteria for their anxiety or depressive disorder and they have returned to full functioning.

Suggested SSRI titration in people aged 7-17 years

	escitalopram	sertraline	fluoxetine
Initial	5 mg	25 mg	10 mg
Week 2	10 mg	50 mg	20 mg
Week 4	10 mg	50 mg	20 mg
Week 6	10 mg	100 mg	20 mg
Optional Increases			
Week 8	15 mg	150 mg	40 mg
Further optional increases in ages 12-17 years			
Week 10	20 mg	200 mg	60 mg

Start low and titrate assertively to achieve symptom remission.

Goal of treatment: remission

Response : No symptoms or significant reduction in anxiety symptoms for at least 2 weeks
Remission : Absence of significant symptoms of anxiety for ≥2 weeks
Relapse : A *DSM* episode of anxiety during the period of remission

Assessing response is only meaningful if the medication is taken daily.

"How many days out of the week do you take your SSRI?"

"What makes it hard for you to take your SSRI every day?"

"How many days out the week do you miss a dose of your SSRI?"

Most kids won't tell you if you don't ask.

SSRIs are effective only if taken daily.

Emily: continuation of treatment

At 8 week visit, GAD-7 score is 8, Emily is working on exposures in CBT therapy, and is pleased with her progress. No dose change.

In March, Emily reports increased anxiety that she cannot control with her new coping skills. This is related to academic and family stressors. GAD-7 score is 13. ***You increase sertraline to 150 mg daily.***

In May, Emily reports relief from symptoms she had in March. GAD-7 score is 6.

In July: Emily is having a good summer. GAD-7 score = 4

In early October: return to school ok, some anxiety. GAD-7 score = 8. Has graduated from CBT.

In January, still doing well in school. Wonders how long she needs to on her medication. She has an out-of-state academic competition coming up. GAD-7 score = 5.

If remission, then what?

Plan for a maintenance period on medication of about 9 - 12 months.
This period may include ongoing psychotherapy.
Periodic med checks should include rating scales to assess for symptom burden, and identification of strengths and stressors.
Plan to discontinue medication should be made with patient and family input.
Plan to discontinue medication at a time of low stress.

Stopping an SSRI

Taper off:
25% of dose/week taper is usually tolerated.
Discontinuation symptoms may include
dizziness, nausea, vomiting, tiredness, headache, gait and sleep disturbance

If these occur, taper by 25% of dose every 2-3 weeks or slower
Fluoxetine up to 40 mg can be stopped at once due to long half-life of metabolite: it "auto-tapers."
Discuss recognition and prevention of a relapse.
Recognition:
"How would you know if your anxiety were starting to come back? What would you notice?"
Prevention:
"What are things that you can do to keep your anxiety under control if you start to notice these things?"

Emily: discontinuation plan
In April, Emily reports she got through the trip and competition just fine. GAD-7 score = 4. You discuss discontinuation. She feels ready.

Taper off medication:
- *Have Emily drop to 1 tablet of the 100 mg dose for a week.*
- *Write prescription for sertraline 50 mg*
  - *1.5 tablets (75 mg) daily for 1 week*
  - *1 tablet (50 mg) daily for 1 week*
  - *0.5 tablet (25 mg) daily for 1 week, then stop*

Any discomfort with this plan, go back to previous dose for another week, then try drop again. Call if more pills needed or unable to tolerate the decreased dose after the longer step.

Relapse recognition:
"How would you know if your anxiety were starting to come back? What would you notice?"
Emily: "I would find myself doubting myself more often, and spending more time worrying about getting things right."

Relapse prevention:
"What are things that you can do to keep your anxiety under control if you start to notice these things?"
Emily: "I will remind myself that I can learn from mistakes, and that I can check my perceptions with my mom to see if I'm overreacting."

A word about benzodiazepines: No
There is no evidence base for benzodiazepines in outpatient pediatric anxiety. A few small RCTs have been negative.
In children, benzodiazepines may cause paradoxical agitation.
In adolescents, benzodiazepines are often misused and diverted.
Benzodiazepines are associated with high risk for dependency and addiction.

Summary

- For mild to moderate anxiety, start with cognitive behavioral therapy, emphasizing exposure and mastery.
- For moderate to severe anxiety, combination therapy of an SSRI with CBT is superior.