Mental Health Care in the Pediatric Clinic

Treating Depression

Objectives

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

- Understand the role of medication and therapy in treatment of depression
- Understand how to start, continue and stop SSRIs for depression
- Note: we address suicide assessment and safety planning in a separate chapter.

AACAP Practice Parameter:

For **uncomplicated** or **brief** depression with mild impairment

- Psychoeducation - explaining what depression is and providing written or online references.
- If stressors at home or school can be addressed in a brief intervention, this can also help relieve symptoms of depression. For example, a depressed teen may find schoolwork piling up to the point that they feel they will never catch up. Writing a letter to the school recommending accommodations until depression resolves may help
- These elements may be sufficient.
- Expect improvement in 4-6 weeks.
- Remember, in community samples, most episodes of MDD are brief.

Brief interventions for depression

- Help identify activating behaviors and make a plan to use them. *"I can get out my paints 3 times this week and see what I feel like painting." "I have promised Emily that we will run to the lake and back on Tuesdays, Thursdays and Saturdays."*
- Open up communication. Many depressive thoughts are based on false assumptions, misunderstandings, and unmet interpersonal needs. *"I can't tell my mom my problems because she has too many of her own."*
- Parents can support their teens by listening, staying calm, encouraging routine sleep and activity
- Avoid leaving depressed teens home alone for long periods.
- Offer hope- depression is treatable
- Review sleep hygiene – regular bedtime, regular wake up
- Maintain contact. Schedule regular follow-up visits to see how things are going.
    - Clinician engagement alone has been shown to reduce suicidality.
    - Gives message that you care and want to see them again

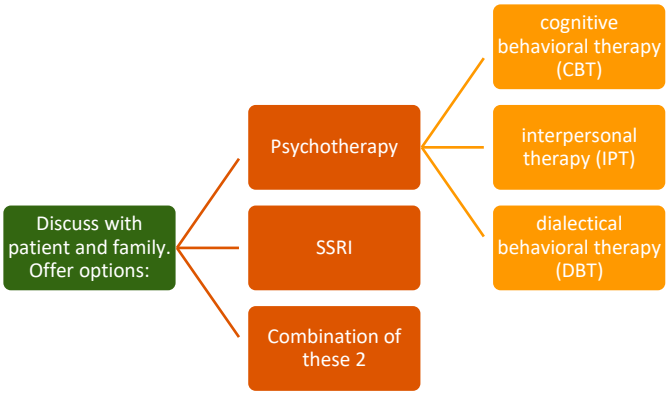
At follow-up visits:

- Check in on depression - use a rating scale to track progress
- Conduct safety assessment
- Escalate to medication and/or therapy if not improving

AACAP Practice Parameter: moderate to severe or prolonged depression

Therapy options with evidence base for treatment of depression in children and adolescents include:

- cognitive behavioral therapy (CBT)
- interpersonal therapy (IPT)
- dialectical behavioral therapy (DBT)



For moderate to severe depression, it is appropriate to consider **medication therapy, some form of formal psychotherapy, or both**. While cognitive behavioral therapy has been the modality of choice in the large medication combination studies, there is also an evidence base for other types of psychotherapy. Interpersonal therapy, or IPT, focuses on patterns of relationships and communication that are often central to emotional distress in adolescence. Dialectal behavioral therapy, or DBT, focuses on emotional regulation and distress tolerance, and can be very helpful for teens who engage in recurrent self-destructive behaviors

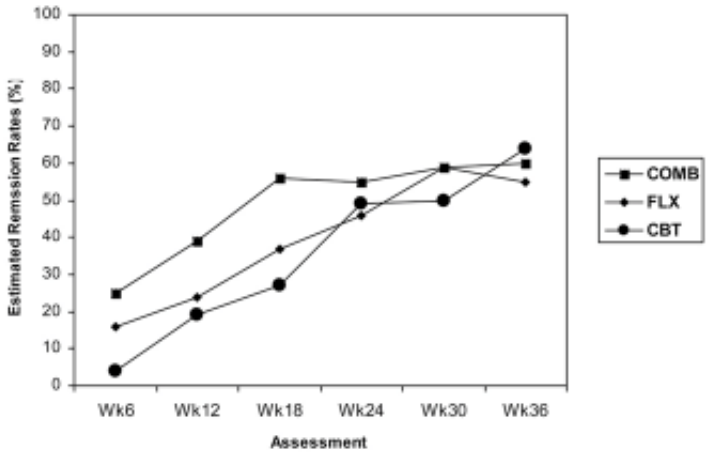
Evidence base: Treatment for Adolescents with Depression Study (TADS)

Funded by National Institute of Mental Health in 1999
439 adolescents with depression
3 stages:

- Acute: 12 weeks
- Longer duration: 36 weeks
- Durability: 1 year naturalistic f/u after completion of treatment

Randomized into 4 arms:

- Fluoxetine alone
- Fluoxetine plus CBT
- CBT alone
- placebo



Results: The combination of the SSRI with CBT was superior to either alone in achieving remission until about week 24 when the active treatments converged. The fluoxetine and combination groups had lower depression scores by treatment week 6 than did CBT and placebo. The patients who received placebo had significant improvement in the first 6 weeks. This high placebo response rate is common in studies of adolescent depression. It may be related to way depression is assessed, to relatively low severity of depression among trial participants, or to a beneficial effect on depression of participating in a study.

TORDIA: Treatment of SSRI-Resistant Depression in Adolescents

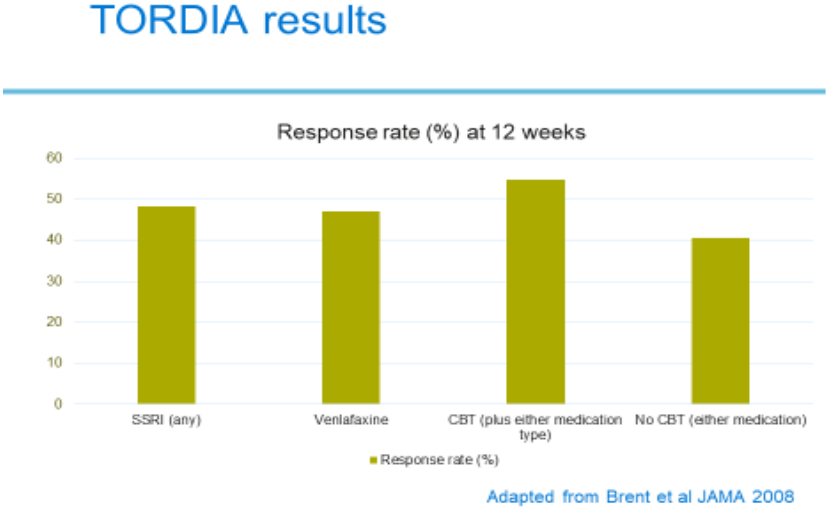
As noted above, the remission rate in the TADS was about 60%. This means that a significant number of adolescents will not respond to initial treatment with an SSRI. The TORDIA study addressed the question of appropriate next steps in a teen whose depression has not remitted with an initial SSRI. It compared another SSRI (fluoxetine, sertraline, paroxetine) with venlafaxine, which is an SNRI, and with either class combined with CBT.

TORDIA randomized 334 adolescents with DSM-IV defined MDD initially resistant to SSRI treatment to treatment with 12 weeks of:

- Another SSRI
- Venlafaxine (Effexor)
- Another SSRI + CBT
- Venlafaxine + CBT

Responders at 12 weeks continued on treatment to 24 weeks, followed naturalistically through 72 weeks.

Similar to the TADS, the combination of a medication switch plus CBT was superior to a medication switch alone. Venlafaxine was not superior to the SSRIs, and venlafaxine was less well tolerated due to side effects.



Adapted from Brent et al JAMA 2008

An important result of TORDIA was that those patients who were going to have remission separated out from those who would not by week 6. This suggests that if you are not getting a response to a treatment plan by week 6, it may be necessary to identify an alternate plan.

Risk factors for not remitting included more severe depression, more family problems, and alcohol or drug use at the study start.

Longer term observations in the TORDIA study included significant residual symptoms, particularly irritability and low self-esteem, among both remitters and non-remitters, and a relapse rate of about 25% in the year after remission.

The Rest of the Evidence Base for Pharmacologic Treatment of Pediatric Depression

The TADS study and one smaller RCT of fluoxetine vs placebo are the only non-industry funded studies of SSRIs in adolescent depression to date. In both studies, the placebo response rate was fairly high, (35% and 33% respectively), but the fluoxetine response was significantly higher (61% and 56%, respectively).

In 1997, a law known as the pediatric exclusivity provision provided marketing incentives to manufacturers who would conduct studies of drugs in children. This law had a limited duration and spurred many manufacturers to run antidepressant trials in pediatric depression.

Sponsor, Authors, Year,	Medication	Duration (weeks)	Active Medication Group (%)	Placebo Group (%)	Sites (N)	Participants (N)
NIMH						
Emslie et al., 1997	Fluoxetine	8	56	33	1	96
March, 2004	Fluoxetine	12	61	35	13	439[c]
Industry						
Emslie et al., 2002	Fluoxetine	8	65	53	15	219
Keller et al., 2001	Paroxetine	8	66	48	12	275[c]
Berard et al., 2006	Paroxetine	12	69	57	33	286
Emslie et al., 2006	Paroxetine	8	49	46	40	206
Wagner et al., 2003	Sertraline	10	69	59	53	376
Wagner et al., 2004	Citalopram	8	47	45	21	178
von Knorring et al., 2006	Citalopram	12	60	61	31	244
Wagner et al., 2006	Escitalopram	8	63	62	25	264
Emslie et al., 2009	Escitalopram	8	64	53	40	312
Emslie et al., 2007	Venlafaxine XR	8	61	52	50	367
Atkinson et al., 2014	Duloxetine	10	67	63	65	337
Emslie et al., 2014	Duloxetine	10	69	60	60	463

This table illustrates the outcome of the pediatric exclusivity provision in pediatric depression trials. The first 2 rows are the NIMH trials and the rest are industry-funded trials. Take a look at 2 things – the placebo response rate and the number of sites. The industry-funded trials all had high placebo response rates – ranging from 46 to 63%. These placebo response rates were associated with fairly low baseline severity scores – in other words, they recruited subjects whose depression was not very severe to begin with, so more got better with the passage of time, and so medication was no better than placebo. In addition, the large number of sites – up to 65 sites per study, may have resulted in heterogeneity in adherence to study protocols.

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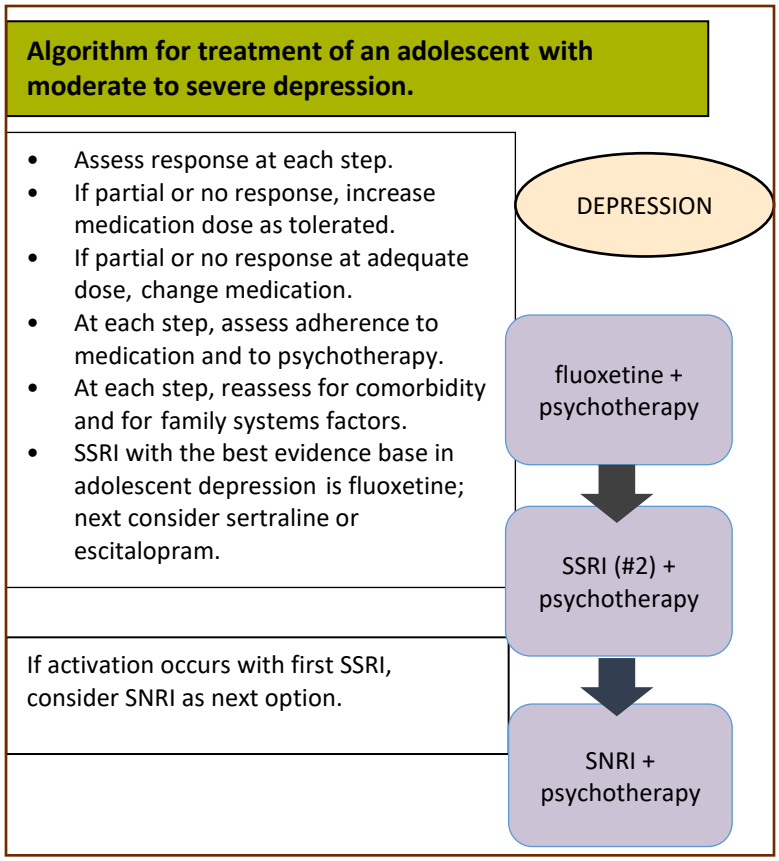
The upshot of this is that meta-analyses of all RCTs done for pediatric depression show that medication is no better than placebo because the negative industry trials wash out the 2 significant NIMH-funded trials. Most child and adolescent psychiatry experts argue that the industry-funded trials cannot be considered negative trials; they should be considered failed trials and not included in meta-analyses.

The bottom line is that if you are treating an adolescent with depression only – no anxiety, consider starting with fluoxetine first because it has the best evidence base. Sertraline and escitalopram are good second line choices for depression, and if the patient has anxiety as well, you are fine with any of these 3 medications.

This algorithm suggests a plan for treatment choices and strategies in adolescent depression. The algorithm does not include recommendations for children with depression only and no anxiety – there is a very limited evidence base for children in this category.

For adolescent depression, start with fluoxetine, increase as tolerated to an adequate dose which is generally going to be 40 mg. If your patient does not achieve symptom response or approach remission on an adequate dose, re-evaluate the diagnosis and assess for comorbidities that may be impeding response, like a trauma history or ongoing stressors.

While the algorithm recommends that the SSRI be combined with psychotherapy at each step, you do not need to wait for your patient to start psychotherapy to start a medication. Remember that in the NIMH-funded studies of SSRIs, fluoxetine alone was close to fluoxetine plus CBT in getting kids to remission.



First line SSRI medications for use in primary care

Trade / generic name	FDA approval status	Dosage forms & strengths	Starting dose - max dose	Typical effective dose	Half life (hrs)	CYP450 interactions
Prozac / fluoxetine	OCD in ages >= 7 years; depression in ages >= 8 years	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
Zoloft / sertraline	OCD in ages >= 6 years	25, 50, & 100 mg tablets 20 mg/ml liquid	25 mg -200 mg	50-100 mg	22-36	Weakly inhibits 2D6 and 3A4
Lexapro / escitalopram	Depression in ages >= 12 years	5, 10 & 20 mg tablets 1 mg/ml liquid	5 mg – 20 mg	10-15 mg	27-36	No significant interactions

Suggested SSRI titration in people aged 7-17 years

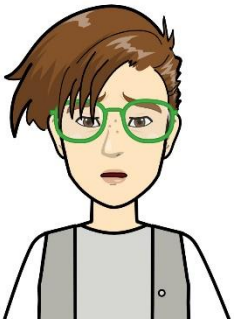
Here is a suggested titration schedule for SSRIs in pediatric patients. *It is not meant to be followed exactly in every patient but is simply a guide.* We used to say about SSRI titration "start low and go slow". The problem with that strategy is that prescribers would leave kids on subtherapeutic doses 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. 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.

	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

SSRI side effects

We covered SSRI side effects, including the boxed warning on suicidality, in the chapter on treating anxiety. If you would like to review these, please refer to the pdf for that chapter or to the RAMP website.

Ben



Let's return to our patient, Ben, who we met in the last chapter. You gave Ben and his mom some online resources and had them return in a few days when you could block some time for a longer appointment. When Ben comes back you speak with him alone and ask him to complete a PHQ-9. PHQ-9 score of 17, with a "1" for question 9 (thoughts of hurting yourself or would be better off dead). When you ask about this, Ben says he thinks sometimes that there is no point to his life but denies any thoughts of wanting to hurt himself in any way.

Ben says he has been depressed for about 1 month. Junior year has been hard: "I just don't feel like I can live up to what I'm supposed to be. I feel like a failure." He tries to get to sleep at night but gets locked into negative thoughts that keep him awake until 1-2 am.

You ask Ben what he wants, and he says he just wants to feel better.
You discuss options with Ben and his parents.
They would like to proceed with combination therapy.
Ben's father is going to see if another therapist in the clinic where he goes for therapy can see Ben.
You concur with that plan, and then discuss medication treatment for depression for Ben.

Because fluoxetine is the first line choice for adolescent depression, you recommend fluoxetine for Ben.
You prescribe the 10 mg capsule, with instructions to take 1 capsule daily for a week then increase to 2 capsules daily.

Ben returns in 4 weeks.
He has started therapy and finds it helpful so far.

He is able to challenge his thoughts of not being "good enough".
PHQ-9 score today is 12, with a "0" for question 9, concerning suicidality.
No GI side effects.
You consolidate the dose to fluoxetine 20 mg daily.

Ben returns at week 8.
He continues in therapy and finds it helpful but lacks motivation to work on techniques he is learning.
He continues to have intrusive negative thoughts.
PHQ-9 score today is 15, with a "0" for question 9, concerning suicidality.
You increase the dose to fluoxetine 40 mg daily.

Ben, week 12
His mood is improved; he feels excited about end of junior year activities and summer plans.
Ben is pleased with therapy. He is working on communicating with parents about their expectations for him.
PHQ-9 score: 4

Ben's mood and functioning are now significantly improved. He is moving from the acute to the continuation phase of therapy for depression.

In the acute phase of depression treatment, the focus is on ensuring safety, educating the patient and family about depression, addressing factors at home, school, or socially that may mitigate the impact of depression, getting started in therapy and/or medication. The acute phase ends when depression symptoms have responded to treatment. During the continuation phase, medication and or therapy continue. Therapy may become less frequent as the patient learns to employ coping skills on his or her own. The maintenance phase is an extended period of treatment that may be maybe needed for patients who are at high risk for relapse.

Ben- 2 months later
Ben's mood is good. His PHQ-9 score is 3. His therapist has dropped him to every other week visits.

Acute (6-8 weeks):

- psychoeducation
- family and school accommodations
- establish in therapy
- start medication
- monitor medication response, medication side effects
- ongoing safety assessment.

Continuation (6-12 months)

- Psychoeducation
- Continue medication
- Monitor medication side effects
- Develop coping skills, improve communication
- Prepare for medication stop/relapse prevention

Maintenance (1 year or longer)

- Ongoing treatment for patients at high risk for relapse

How long to treat

- Similar to treating anxiety, treat depression with an SSRI for 6 to 12 months past remission
- Stop at time when things are going well, with no anticipated major challenges or difficulties- late spring/early summer is often a good time
- Discuss relapse recognition and prevention
- Some patients may need to continue treatment indefinitely:
  - those with 3 or more episodes of MDD

  - those with history of chronic, lifelong depression
- But almost every child or teen patient should have a trial off after remission of an initial episode.

Maintenance dose of an SSRI

- Whatever dose was required to achieve symptom remission is the maintenance dose.
- There is no indication that dropping to a lower dose after achieving symptom remission will result in continued symptom control.
- There is no evidence of benefit in trying to achieve maintenance at a lower dose.

Differences in doses needed to achieve remission may vary between individuals based on symptom severity, but also genetically-based drug metabolism. Faster metabolizers may require higher doses to achieve modest overall drug levels.

Discontinuing antidepressants

SSRIs (other than fluoxetine) taper off:

- 25% of dose/week taper is usually tolerated.

Discontinuation symptoms may include dizziness, nausea, vomiting, tiredness, headache, and sleep disturbance, although these are not common in young patients. If these occur, taper by 25% of dose q 2-3 weeks or slower. Fluoxetine can be stopped at once due to long half-life of metabolite: it "auto-tapers."

Ben, continued

You see Ben every 3 months until he has been in treatment for 13 months. It is January of his senior year. All his college applications are complete. He is feeling hopeful about the future. He is seeing his therapist for monthly check-ins. He wants to know if he can stop his medication.

You agree that he will discontinue his fluoxetine 40 mg and see you and plan for one more check in before he goes to college.

You discuss relapse recognition:

How will you know if your depression is coming back?

You discuss relapse prevention:

What can you do help keep your depression from coming back?

Including regular sleep and exercise, avoiding drugs and alcohol

What will be the plan if your depression comes back after you have started college? Who will you talk to about it? Where can you get help?

As with completing treatment for anxiety, you discuss how your patient will recognize depression if symptoms return, and what he or she can do to help prevent it. Standard recommendations for relapse prevention for all adolescents should include good sleep hygiene, regular exercise, and the avoidance of alcohol and drugs of abuse. The patient should be able to verbalize specific things that they can do to cope with depression symptoms if they arise. For your patients going off to college, be sure they are aware of on-campus mental health resources, and that they can identify someone they can reach out to for support if needed.

Summary

- Mild or recent-onset depression can be addressed through the cognitive-behavioral model in the context of the individual child and family.
- Moderate, persistent, or severe depression can be treated with therapy or a combination of an SSRI and therapy.
- If response to an initial SSRI is limited, a trial of a second SSRI is appropriate.

Please see the RAMP website for parent and teen resources for depression, and for our chapter on suicide screening and safety assessment. Here is a list of hotline numbers you may want to keep at hand.

National Suicide Prevention: 800 273-8255
National Hopeline: 800 784-2433
Samariteens: 800 252-8336
800 DON'T CUT (366-8288)
Crisis Text Line (Text "START" to 741-741)
The Trevor Project 866 488-7386-LGBTQ youth
CARES line for Medicaid plans 800 345-9049