Primary Care Treatment Strategies for Depression: Childhood Through Young Adulthood

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Objectives

- Describe the latest guidelines for treating major depressive disorder (MDD) in children, adolescents and young adults;
- Identify barriers to appropriate treatment of those with MDD; and,
- Discuss how HCPs can implement best practices for treating MDD in the clinical setting.

What does depression look like?

- **Clinical diagnosis with depressed mood and/or boredom/anhedonia**– most days for ≥2 weeks + 4 more symptoms:
  - Worthlessness
  - Impaired concentration
  - Suicidal ideation/behavior
  - Guilt
  - Impaired sleep
  - Impaired appetite
  - Functional impairment

Why is it important to screen?

- Very common– about 20% have at least one episode during adolescence
- Less than 50% of depressed youth are getting diagnostic-specific treatment
- The longer the depression, the harder it is to treat

Sequelae of untreated depression

- Associated with long term relational, educational, and occupational attainment
- Bi-directional relationship with alcohol and substance abuse
- Associated with other risk behaviors
- Dramatically increases the risk of suicide attempts and suicide
- Health care costs of untreated depression are $2726 higher than in non-depressed youth

Differential Diagnosis

- **Bipolar spectrum**– presence of hypomania, mania, suspect with family history, psychotic depression
- **Seasonal affective disorder**—most commonly fall/winter, hypersomnia, low energy, carbohydrate craving, respond to light treatment
- **Psychotic depression**—associated with depression temporally, often, but not always in content

Differential Diagnosis

Disorder	Differential
ADHD	Demoralization due to peer, school, family problems, improves with treatment
Asperger's	Demoralization due to peer rejection
Anxiety Disorder	Dysphoria only in anxiogenic situations
OCD	Upset by obsessive thoughts, impairment due to rituals, OR inability to complete them
Eating Disorder	Secondary to nutritional issues, reverses with weight restoration; may also be sad because being forced to gain weight

Differential Diagnosis

Disorder	Differential
Conduct Disorder	Precipitated by legal/disciplinary difficulties, but also peer and family conflict, erosion in developmental competencies
Substance use	Can mimic affective symptoms, temporal order, change with abstinence
Pre-psychosis	Abnormal development prior to onset, family history, course
Medical illness	Fatigue, concentration, anhedonia secondary to illness or treatment

Medical conditions that can mimic or contribute to depression

- Anemia
- Thyroid disease
- Occult inflammatory disorders
- Mononucleosis
- Lyme disease
- Sleep apnea
- Low folate
- Low Vitamin D
- Diseases of inflammation
  - IBD
  - Asthma
  - Eczema
- CNS diseases
  - Epilepsy
  - Migraine
  - MS
  - Concussion

Get lab tests on everyone?

- Very low yield, so not on everyone
- Very prominent fatigue in the absence of prominent sleep disorder
- Depression unresponsive to first treatment (some would wait longer)

Detecting and Assessing Depression

- Well-child care PHQ-9
- On the basis of other risk factors
  - Parental depression
  - History of maltreatment
  - Bereavement
  - Concussion
  - Peer victimization
  - ADHD, Anxiety, ODD
- On the basis of other behaviors
  - Change in level of function and motivation
  - Withdrawal from friends
  - Risk-taking behavior
  - Frequent service use
  - Somatic complaints
  - Self-harm
  - Sleep or appetite changes.

Patient Health Questionnaire (PHQ)*

Version	Sensitivity	Specificity
PHQ-2≥3	74%	75%
PHQ-9≥11	89.5%	77.5%

Prediction of persistent depression at 6 months, 16% increased likelihood for each point increase in PHQ-9 above 11

*Richardson et al., 2010a,b

Patient Health Questionnaire (PHQ-2)

Over the past 2 weeks, how often have you been bothered by any of the following problems	Not at All	Several Days	More Than Half the Days	Nearly Every Day
1. Little interest or pleasure in doing thing	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3

3. Trouble falling asleep, staying asleep, or sleeping to much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you're a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating of things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or, the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

Now that you've screened, then what?

- PHQ-2 or 2 or greater– do rest of PHQ-9
- PHQ-9 of 10 or greater
- Slightly lower scores– ask how they are doing, watch them and re-screen in 1 month.
- Sleep item correlates highly with Insomnia Severity index
- Suicide item predicts future attempts and suicides (Simon et al., 2013)

Talking points

- According to your screen, it is likely that you are depressed. I cannot promise complete confidentiality– things that could have a severe effect your health I need to disclose, but I will not tell your parents anything without discussing it with you first.
- I would like to follow-up with a few questions:
  - Are you having difficulty with school, friends, parents?
  - Assess suicidal thoughts and plans (more about that later)
  - A more thorough assessment would be a good idea
  - After that, we can come up with some ideas for treatment? Does that sound okay?
  - Need to also get parents on board

If a patient discloses that he/she is suicidal

- To what extent to you intend to carry this out?
- Do you have a plan?
- Do you have a location picked out?
- What is keeping you from acting on your suicidal thoughts
- What would drive you to act on your thoughts in the future?
- Don’t promise absolute confidentiality.

Developing a safety plan in a hurry

- What are triggers for your suicidal thoughts (or what makes them worse)?
- What are your reasons for staying alive?
- What can you do to avoid these triggers?
- How can we cope with these triggers?
  - Distraction
  - Review of Reasons for Living
  - Relaxation/Deep breathing/Mindfulness
  - Reaching out to other people
  - Reaching out to professionals
  - Emergency help

Launching the Safety Plan

- Ask patient to explain plan to parents
- Get parental feedback
- Ask both parents and patient what might get in the way of implementing the plan
- Consider either ways to overcome those barriers, or revision in the plan
- Removal/securing lethal agents

When to Refer for Emergency Evaluation

- Clear expression of suicidal intent and unwilling to commit to safety plan.
- Clinical conditions that would impede ability to adhere to a safety plan:
  - Psychosis
  - Bipolar disorder– rapid cycling or mixed state
  - Alcohol and drug abuse
  - Traumatic brain injury
- The lower parental support and monitoring, the lower your threshold for emergency referral should be.

Addressing common barriers to treatment

Barrier	Possible response
Hopeless and low motivation	These are symptoms of depression. What might motivate you to give it a try for a few sessions to see if it could make some difference?
Alternative explanation ("just wants attention", "just normal adolescence")	Depression is "no one's fault." It is disease like diabetes, with biological changes in the brain that affect mood and motivation.
Mental health treatments are ineffective or take forever to work	There are several good alternative treatments that are effective in a matter of 2-3 months

Barriers	Possible Response
Afraid of institutionalization, medication, ECT, etc.	• You and your parents get to choose what kind of treatment you want. • No one will force you to take medication and there are good alternatives. • At present, your depression does not require hospitalization, which we would only do if we were concerned about your safety.
Cost, time from work, travel, school	• We can try to identify a sliding fee or a lower cost provider. • The treating clinician can conference you on the phone to update you for at least some meetings. • We can try to find someone closer to your home. • We can help get school accommodations, and find times after school.

Getting the patient and parent to pursue treatment

- Education about depression– it is a brain disease that often runs in families and is no one's fault.
- It is highly treatable. 80% of people recovery fully with proper treatment within one year.
- Treatment and recovery takes time and time investment.
- It is often recurrent so we will need to make a life plan for prevention.

Depression is a disease

- Runs in families, about 50% effects are genetic
- Has alterations in neurotransmitters in the brain
- Altered connectivity and processing of emotional material
  - High reactivity and bias toward negative emotional cues
  - Low pre-frontal modulation of emotional responses
  - Low reward response
  - High amount of self-reference (associated with rumination)

Natural History of Depressive Disorders

- **Persistent depressive disorder**– high risk of MDD, bipolar disorder, average duration > 5 years
- **MDD**– average episode length 4-8 months
- **Recurrence**– 40% in 5 years, nearly 100% by adulthood, especially in adolescent-onset
- Risk of **bipolar disorder** around 10-20%
  - psychotic depression
  - family history of bipolar disorder
  - previous hypomania, even during treatment

Most people can be helped

- Psychotherapy
  - Cognitive behavior therapy
  - Interpersonal therapy
  - Attachment-based family therapy
- Medication– one best studied and most effective is fluoxetine
- Response rates for both around 60% by 12 weeks, 80% by 24 weeks
- If don't respond to the first medication, 50% response to second intervention

When can the patient be treated as an outpatient?

- Adequate level of function– self-care, school attendance
- No imminent harm to self or others
- Diagnostic impression is clear
- Patient and family likely to be adherent
- Other levels of care besides hospital
  - Partial hospital
  - Intensive outpatient programs
  - Home-based family-centered care
  - Case management

Deciding which patients to manage

- Patient can be treated on an outpatient basis
- Is not at imminent risk for suicide
- Does not have a co-morbid condition that would interfere with the treatment of depression
  - Alcohol and substance abuse
  - Eating disorder
  - Comorbid medical illness that is interacting with depression (e.g., diabetes, asthma)
  - Severe sleep problems
- Bipolar, psychotic
- Contextual factors that require psychotherapy
  - Family discord or maltreatment
  - Peer victimization
  - Issues of sexual orientation or gender identity

Guidelines for treatment of adolescent depression

- Mild depression: watchful waiting and support
- Moderate depression: either medication or psychotherapy (CBT, IPT, ABFT)
- Severe and/or treatment resistant depression (combination treatment)
- Duration of initial treatment 8-12 weeks
- Then need continuation treatment for at least 6 months after symptom response

Making a treatment plan

- Treatment preferences and availability
- Level of impairment
- Comorbidity
- Contextual factors

Important contributors that factor into treatment plan

- Parental depression
- Parent-child discord
- Maltreatment– especially if ongoing or threatened
- Assault
- Peer victimization
- Academic difficulties
- Bereavement

Indicated psychotherapies for adolescent depression

- **Cognitive Behavior Therapy (CBT)**
  - Cognitive restructuring
  - Social skills and problem solving
  - Behavior activation
- **Interpersonal Therapy (IPT)**
  - Alter interpersonal relationships to make them more rewarding, less discordant
- **Family-based Attachment Therapy**
  - Improves connection between parent and child

Antidepressants in MDD

- **Fluoxetine (FLX)** (NNT=5), **Escitalopram** FDA-approved.
- **Citalopram=FLX<Paroxetine** in TORDIA
- **Paroxetine**– overall not shown effective
- **Sertraline** (NNT=10)
- **Venlafaxine**—post-hoc show efficacy in adolescents, not kids (low doses used). In TORDIA, VLX=SSRI.
- **Nefazodone**– One positive trial, rarely used due to hepatotoxicity (1/1,000,000 doses)

Antidepressants in MDD (Cont.)

- **Bupropion**– Open trials positive, never been studied with RCT and probably never will be
- **Atomoxepine**– Not effective
- **Mirtazapine**, one trial, negative
- **Tricyclic antidepressants**– Not effective, don't use! May be helpful as augmenting agent, in management of migraine

Effects of Antidepressant by Age (Risk Difference) (Bridge et al., 2007)

Indication	Children	Adolescents
MDD	7%	13%
MDD-FL	20.5%	20.0%
OCD	24%	18%
ANX	29%	46%

SSRIs and suicidal events

- **Increased risk of suicidal events** (new or increased ideation or attempt) in drug vs. placebo in RCTs– risk difference: 0.9%
- **Response rate 10% risk difference**: so 11 times more patients will respond than will have a suicidal event.
- **Pharmacoepidemiological studies** show that **increased** prescription of SSRIs associated with a **decrease** in suicide rate and vice versa
- **Due to Black Box Warning**, decline in SSRIs, diagnosis of depression, units of treatment in adolescents

Dose, Concentration, and Response

- Non-responders more likely to respond to an increased dose of fluoxetine vs. continuing at the same dose (Heiligstein, 2007)
- Dose and plasma concentration are both related to serotonin transporter binding in vitro
- Around 80% binding is associated with response
- Response associated with higher levels and greater adherence (Sakolsky, 2011; Woldu, 2011)

SSRIs: Half-Lives

Drug	Half-life	Developmental Effect
Fluoxetine	4-6 days	Higher levels in children than adults
Paroxetine	11 hours	Higher levels in children than adults
Sertraline	15.3-20.4 hrs.	Non-linear, lower than in adults
Citalopram	16.4-19.2 hrs.	Lower than in adults
Venlafaxine	9-13 hrs.	Lower than in adults
Nefazadone	3.9 vs. 7 hrs.	Lower than in adults

Implications of Pharmacokinetics of Antidepressants

- Need adequate exposure to affect serotonergic reuptake inhibition; 5 times the half-life to achieve steady state
- For many drugs, half-life is shorter than in adults
- Therefore, may need higher doses/BID doses in order to achieve response and avoid withdrawal effects.
- Sertraline has non-linear kinetics; this is most relevant at lower doses.

Some general guidelines for antidepressant use with adolescents

- Both parent and adolescent must be on board and understand risks and benefits
- Start low, go slow
- Need to see weekly for first 4 wks, then every other week until week 12
- Don't change dosage more frequently than every 3-4 weeks
- Monitor for symptom change, suicidal ideation/behavior, and side effects
- Ultimate goal is remission

Topics to cover in session

- Overall function
- Mood (1-10, can fill out PHQ-9)
- Suicidal thoughts (how often, intensity, can resist?, plan, what will push in either direction?)
- Sleep
- Other side effects
- Adherence
- Safety plan

Recommended visit schedule

- Weekly for first 4 weeks
- Every other week until week 12
- Monthly for next 6 months.
- Can do some of this over the phone

Dosing Parameters

Drug	Dose (Week)								Range
	1	2	3	4	5	6	7	8	Range
Fluoxetine	10	20	20	20	40	→			20-80 mg
Citalopram	10	20	20	20	40	→			10-40 mg
Escitalopram	5	10	10	10	20	→			10-40
Sertraline	25-50	50-100	→		100-150	→			50-200
Venlafaxine XR	37.5	75	→	150	→				150-375
Bupropion XL	100-150	→		300	→				150-450

FDA warning about citalopram

- Citalopram may cause QTc prolongation
- Therefore, do not go above 40 mg
- Get baseline ECG, prior to, and after each dose increase
- Related to metabolite didemethylcitalopram (DDCT) (in beagles!)

Contraindications to antidepressants

- Mild to moderate depression– just as likely to respond to psychotherapy
- Psychosis– needs an antipsychotic in addition
- Mania or family history (then use very carefully)
- Allergy

Side Effects of SSRIs

- Nausea, weight loss, weight gain
- Sleep difficulties, vivid dreams (monitor and manage)
- Mania
- Lower clotting time/easier bruising
- Nervousness, restlessness (fluoxetine)
- Disinhibition, memory problems, irritability
- Sweating
- Fatigue (sertraline, fluvoxamine, paroxetine)
- Sexual side effects

Management of side effects

- Akathisia, irritability, increased depression, mania, significant cognitive changes– need to stop drug.
- Risk of mania about 10% vs. .45% drug vs. placebo
- If have responded but still irritable, will add DBT or CBT, lithium, antipsychotic, or lamotrigine
- Weight loss, usually transient, can add mirtazapine
- Weight gain, can switch to another SSRI

Sleep Difficulties / Fatigue

- R/O medical causes, sleep apnea, restless legs syndrome
- Shift or divide dose
- Sleep hygiene
- CBT for insomnia
- Diphenhydramine, melatonin, mirtazapine
- For fatigue and residual symptoms, augmentation with bupropion

Withdrawal Syndrome

- Result of abruptly stopping SSRI or SNRI
- Flu-like symptoms– Malaise, GI distress, dizziness, anxiety, dysphoria
- Taper gradually, warn patient about possibility

Drug Interactions & SSRIs

- NSAID and GI bleeding
- Tryptans, Linezolid– serotonin syndrome
- 2D6 (FLX)– increase levels of haloperidol, risperidone, opiates, TCAs
- 3A4 (NFL)– sertraline, TCAs, benzodiazepines, carbamazepine
- **Bottom line: No one can remember all of these drug interactions; check with the hospital pharmacy!**

How to recognize Serotonin Syndrome

- Most common in those with polypharmacy
- Spontaneous clonus
- Inducible clonus or ocular clonus + agitation or diaphoresis
- Tremor + hyper-reflexia
- Hypertonia + >38 C temp + ocular clonus or spontaneous clonus

Treatment of Serotonin Syndrome

- D/c Serotonergic agents
- Benzodiazepines for agitation
- Supportive treatment
- Cyproheptadine– serotonergic antagonist

Approach to Patients with Suboptional Response

- Document improvement and lack thereof
- Establish adherence and adequacy of treatment, evaluate exposure
- Psychosocial stressors
- Comorbid illness, sleep
- Medication side effects
- Convey hope

Residual Symptoms: Management

- **Augment vs. switch**– if had response, but still significant residua and no side effects
- **Anhedonia**: activity scheduling, bupropion
- **Sleep difficulties**: sleep hygiene, melatonin, mirtazapine, sleep studies
- **Irritability**: psychotherapy, lithium, antipsychotic (for the latter two, must be severe)
- **Fatigue:** sleep hygiene, switch time of dosage, add buproprion (and rule out other medical causes). Behavior activation

Treatment Resistant Depression

- Switch to second SSRI (as good as switching to venlafaxine and fewer side effects)
- Consider bupropion if prominent fatigue, ADHD, does not have prominent anxiety
- Consider SNRI if has prominent pain syndrome like migraine, fibromyalgia, also good for comorbid anxiety
- After that: nefazodone (comorbid anxiety), lamotrigine, MAOI, augmentation with lithium, T3, or antipsychotic augmentation

Continuation treatment

- High risk of relapse unless continue treatment for 6-12 months after complete symptom relief– timing also based on practical considerations.
- For people with recurrent or chronic depression, may want them to continue in treatment longer
- Same dose of medication as got them well
- Addition of CBT helpful

Special issues with patients going to college

- Depression is a life-long issue
- Choose a school with reasonable supports, accomodations, and resources for MH treatment
- Make sure have an appointment set up
- Prepare for transition
  - Have fill own prescriptions and make own appts.
  - Anticipate challenges
    - Sleep
    - Roommates
    - Alcohol/Drugs
    - Academic challenges

Implementation in your practice

- Have a response plan for positive screens, including suicidal ideation
- Decide what level of complexity and severity you are comfortable treating
- Have trusted referral sources handy
- Provide education and motivation, taking into account patient and parent treatment preferences
- If manage antidepressants in your practice, follow frequently and assess suicidality, side effects, and response, prepared to switch if non-response

Collaborative care

- Co-located– makes referral and collaboration much easier
- Nurse clinicians- can do medication and psychotherapy
- Psychotherapists
- Communication with PCP so that can handle any office or after hours calls
- Telepsychiatry– for areas where on-site available of mental health specialists is limited

Summary points

- Adolescent depression is a life-long, often recurrent illness that requires long-term management
- Screening with the PHQ-9 is an quick and effective way to detect most depressions
- Bipolar disorder is the most important differential
- Psychoeducation about depression, conveyance of hope, hearing treatment preferences and barriers to treatment are a key part of making an effective referral
- Evidence-based psychotherapies and medications are effective in helping the majority of depressed youth to recover
- Continuation treatment to prevent relapses
- Transition plan when patient leaves home to take more responsibility for own care.

Thank you for your attention!