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Evidence-Based Best Practices for the Management of Major Depressive Disorder in Pediatric Primary Care in South Carolina

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The information contained in this summary is intended to supplement the knowledge of clinicians regarding best practices for the treatment of major depressive disorder in children and adolescents in a primary care setting. This information is advisory only and is not intended to replace sound clinical judgment, nor should it be regarded as a substitute for individualized diagnosis and treatment. Special considerations are needed when treating some populations with certain conditions (e.g., children under 6 years of age, pregnancy/breast-feeding, cardiac disease, liver and renal impairment).

MANAGEMENT OF PEDIATRIC MAJOR DEPRESSIVE DISORDER AT-A-GLANCE

ROUTINE ASSESSMENT INCLUDES:

- **Using a rating tool** for initial and ongoing assessment of depressive symptoms; e.g., Patient Health Questionnaire (PHQ)-2 for initial screening or PHQ-9.[1]
- **Evaluating safety/suicide risk** and establishing a safety plan; securing or removing means of lethal self-harm from home (e.g., guns, medicines, sharp objects).[2]
- **Assessing risk for development of bipolar disorder**; e.g., subtle manic symptoms, medication-induced manic symptoms, family history of bipolar disorder.[2]

PROVIDE PSYCHOEDUCATION AND SUPPORTIVE MANAGEMENT, AND INVOLVE FAMILY AND SCHOOL FOR ALL PATIENTS DURING ALL PHASES OF TREATMENT[2]

- **Family involvement is critical** to the successful treatment of a child or adolescent.

TAILOR THERAPY BASED ON SEVERITY OF MAJOR DEPRESSION

- **Mild or uncomplicated** major depression[2,3]
  - **Provide active support** and monitoring every 1 – 2 weeks.
  - If insufficient after 6 – 8 weeks, **consider psychotherapy** (cognitive behavioral therapy [CBT] or interpersonal therapy [IPT]) and/or antidepressant therapy.
- **Moderate to severe**, or complicated major depression[2,3]
  - **Consider psychotherapy** (CBT or IPT).
  - **Consider antidepressant therapy**, especially if depression is severe or if partially/not improved after 6 – 8 weeks of psychotherapy.

ANTIDEPRESSANT THERAPY[2,3]

- **Adequate trial** of an antidepressant consists of BOTH an adequate dose and duration.[2]
  - Selective serotonin reuptake inhibitors (SSRIs) are considered first line pharmacotherapy.
  - An adequate acute antidepressant trial consists of a minimum period of 8 weeks, including a minimum of 4 weeks at a maximum tolerated dose.
- **Rating scales** such as the PHQ-9 are useful to assess symptom severity before initiating medication and at regular intervals to assess patient response.[1]
  - Remission is achieved with resolution of symptoms (e.g., PHQ-9 score < 5).
- **Treat to remission**, not just response, and inform patients and family that remission is the goal of treatment.[2]
  - Patient education is critical to adherence and treatment success.
- **Treatment should continue** for 6 – 12 months after initial response of a first episode of depression, and potentially indefinitely for severe or recurrent episodes.[2]
  - Patients who received pharmacotherapy during the acute phase treatment (i.e., 6 – 12 weeks) should continue their medication at the same dose that produced therapeutic response for an additional 6 – 12 months after symptom remission.
  - Patients experiencing 2 or more prior major depressive episodes should be maintained in treatment for longer periods of time, up to 2 years or longer, depending on the clinical situation.

WHEN TO REFER

Moderate or severe major depression • Co-morbidities • Psychotic or suicidal patient • 2 failed SSRI trials

MEDICATION MANAGEMENT DECISION POINTS FOR THE TREATMENT OF MAJOR DEPRESSION

Consider active support and monitoring for mild or uncomplicated major depression or psychotherapy for moderate to severe major depression before initiating medications

At week 0 **Initiate an SSRI**	**First line: Fluoxetine[4]** **Second line: citalopram, escitalopram, or sertraline[4]** **Effective antidepressant doses in adolescents are similar to those used in adults except for lower initial doses to optimize tolerability; lower starting doses and maximum doses are generally recommended in children[2]** **Monitor symptoms and tolerability by phone or in person every 1 – 2 weeks[2,4]** **Consider discontinuing or reducing dose if agitation, anxiety, new onset or worsening of suicidal thoughts AFTER INITIATING TREATMENT OR AFTER INCREASING DOSE AT SUBSEQUENT DECISION POINTS[4]**
At 4 weeks	**Continue current regimen if full resolution of symptoms (e.g., PHQ-9 < 5)[2,3]** **If no improvement or partially improved, consider increasing the dose (as tolerated) and/or adding psychotherapy[2]**
At 8 weeks	**Continue current regimen if full resolution of symptoms (e.g., PHQ-9 < 5)[2,3]** **If no improvement or minimal improvement, consider maximizing dose, augmentation or switching antidepressant, and/or addition of psychotherapy[2,3]** **Augmentation is usually for partial response; switching is recommended if lack of response or if side effects are intolerable[2]** **Adding CBT to an alternate antidepressant (either a different SSRI or different class) was shown to be more effective than only switching antidepressants in adolescents with non-response[2]**
At 12 weeks	**Continue current regimen if full resolution of symptoms (e.g., PHQ-9 < 5) [2,3]** **Consider alternative treatment if not at remission[2]** **If partial response, consider augmentation and/or addition of psychotherapy** **If poor response or minimal improvement despite adequate medication trial, assess medication adherence, comorbid substance abuse including alcohol, or undiagnosed bipolar disorder[2]**
At remission	**Continue regimen for additional 6 – 12 months[2,3]** **Monitor at least monthly[2,3]**

PSYCHOSOCIAL THERAPIES[3]

- **Psychoeducation** consists of education on causes, symptoms, course, and different treatments of depression and the risks associated with these treatments as well as no treatment at all.
- **Supportive management** may include active listening and reflection, restoration of hope, problem solving, coping skills, and strategies for maintaining participation in treatment.
- **Active support and monitoring** includes: scheduling frequent visits; promoting good sleep, healthy eating, exercise, and increased social support and peer interactions; reviewing self-management goals.
- **Psychotherapy**
  - **Interpersonal Therapy (IPT)** is based on the principle that depression affects relationships and that relationships affect mood. The goal is to address interpersonal problems that may be contributing to or resulting from depression.
  - **Cognitive Behavioral Therapy (CBT)** is based on the principle that thoughts, feelings and behaviors affect one another. The goal is to modify negative thoughts and behaviors to improve mood.

ANTIDEPRESSANT DOSING GUIDELINES[4,5]

Medication (i) (Brand)	Initial Daily Dose (mg) (ii)	Literature Based Maximum Daily Dose (mg) (iii)	FDA Maximum Daily Dose (mg)	Recommended Administration	Comments
SSRIs (iv)					
Citalopram (v) (Celexa®)	Children: 10 Adolescents: 10-20	40	Not approved for pediatrics	AM	
Escitalopram (Lexapro®)	Adolescents: 5-10	30	MDD (12 – 17 yo): 20	AM	
Fluoxetine (Prozac®)	Children: 5-10 Adolescents: 10	60	MDD (8 – 18 yo): 20 OCD (7 – 17 yo): 60	AM	
Paroxetine (Paxil®)	Adolescents: IR 10; CR 25	Adolescents: IR 40; CR 50	Not approved for pediatrics	AM or HS	Not recommended in children
Sertraline (Zoloft®)	Children: 12.5-25 Adolescents: 25-50	200	OCD (6 – 17 yo): 200	AM	
SNRIs					
Duloxetine (Cymbalta®)	Adolescents: 40	Adolescents: 60	Not approved for pediatrics	Once daily or BID	
Desvenlafaxine (Pristiq®)	Adolescents: 50	Adolescents: 100	Not approved for pediatrics	Once daily	
Venlafaxine (vi) (Effexor®)	Adolescents: 37.5	Adolescents: 375	Not approved for pediatrics	IR : BID – TID XR : Once daily	
Others (vii, viii)					
Bupropion (ix) (Wellbutrin®)	Adolescents: 75	Adolescents: 400	Not approved for pediatrics	IR : BID – TID SR : BID XL : Once daily	Avoid if eating disorder
Mirtazapine (Remeron®)	Adolescents: 15	Adolescents: 45	Not approved for pediatrics	HS	

CR = controlled release **IR** = immediate release **MDD** = major depressive disorder **OCD** = obsessive compulsive disorder
SNRIs = serotonin-norepinephrine reuptake inhibitors **SSRIs** = selective serotonin reuptake inhibitors **yo** = years old

(i) The following antidepressants can inhibit certain CYP metabolizing enzymes and increase the plasma levels of other medications: bupropion, duloxetine, fluoxetine, fluvoxamine, and paroxetine.
(ii) Doses can be increased after 4 weeks if tolerated and clinically indicated.[2,4]
(iii) Consider decreasing maximum dose by one-third for children.[4]
(iv) Fluvoxamine was not included in the table based on a lack of controlled data in pediatric depression.
(v) Citalopram maximum daily dose of 20 mg is recommended in poor metabolizers of cytochrome P450 2C19 (CYP2C19) or with concomitant use of strong CYP2C19 inhibitors (e.g., omeprazole) in adults per FDA package labeling.
(vi) Evidence does not support efficacy of venlafaxine in the management of MDD in children; venlafaxine, the only SNRI included in the FDA suicidality meta-analysis, had the highest risk ratio for suicidality.[6]
(vii) Tricyclic antidepressants (TCAs) were not included due to a lack of evidence of efficacy in pediatric MDD and safety concerns, particularly with high risk of death by overdose.
(viii) Bupropion and mirtazapine starting doses and maximum daily doses may need to be reduced by one-third in pre-pubertal children.[4]
(ix) Some clinicians use bupropion off-label to manage ADHD.

ANTIDEPRESSANT SWITCHING AND DISCONTINUATION

Antidepressant Switching Strategies [8,16,17]

- In general, if the first antidepressant is being discontinued due to intolerance following a ***brief exposure*** (< 7 days), it can be stopped and the second medication started (a **direct switch**).
- If the first drug is being discontinued due to symptomatic breakthrough or inadequate response after a ***longer exposure*** (more than 7 days), the approach selected should be based on the risk of discontinuation symptoms, side effects, and drug interactions. Switching may be accomplished by **direct switching** or **cross tapering**.
- **Tapering** is advised with some medications. For example, abrupt discontinuation of some antidepressants can cause discontinuation syndrome. Discontinuation syndrome is more likely with: more than 5 weeks of therapy; higher doses; and use of medications with short half-lives (e.g., paroxetine, venlafaxine).
- In **cross tapering**, the first medication dose is generally decreased over 3 – 7 days while initiating the new antidepressant.

First Antidepressant Discontinued	Switching To Antidepressant	Recommendation
Selective Serotonin Reuptake Inhibitor (SSRI) *except Fluoxetine*	SSRI, Mirtazapine	Switch directly or cross taper
	SNRI	Switch directly
	Bupropion	Cross taper
Fluoxetine (long half-life)	SSRI, Mirtazapine	Switch directly or cross taper; start with a low antidepressant dose, consider allowing a 4-7 day medication free period prior to starting new antidepressant
	SNRI	Switch directly
	Bupropion	Cross taper
Serotonin-Norepinephrine Reuptake Inhibitor (SNRI)	SSRI or SNRI	Switch directly or cross taper
	Bupropion, Mirtazapine	Cross taper
Bupropion	SSRI, SNRI, Mirtazapine	Switch directly
Mirtazapine	SSRI	Switch directly or cross taper
	SNRI, Bupropion	Cross taper

Antidepressant Treatment Discontinuation

Discontinue gradually at the end of continuation or maintenance phases to prevent the occurrence of discontinuation syndrome, and to monitor for any re-emerging depressive symptoms.[1,2]

- A slow taper over 2 – 3 months may be appropriate for most patients.
- A slower taper over 4 – 6 months may benefit patients with recurrent depression, a history of hospitalizations or suicide attempts.[1]
- Monitor closely during taper and for 2 – 3 months after discontinuation.
- Consider discontinuation during times of reduced stress or during summer.[2]

Discontinuation Syndrome

A discontinuation syndrome can occur following abrupt cessation of antidepressant therapy, particularly for those antidepressants with short half-lives (e.g., paroxetine, venlafaxine). The syndrome is characterized by disequilibrium, electric shock sensations, general somatic complaints, gastrointestinal symptoms, sleep disturbance, and anxiety/irritability. This syndrome is more likely with length of therapy greater than 5 weeks or high doses of medications. Onset is usually from 1 day to 1 week after cessation and can last up to 3 weeks. Initiating a medication taper does not always prevent its occurrence but may minimize severity.[7]

SELECT SIDE EFFECTS OF ANTIDEPRESSANTS[2,8]

Medication Class	Side Effects (i)	Comments
SSRIs	Most common (> 10-30%): GI (e.g., abdominal pain, appetite changes, diarrhea, nausea), headaches, restlessness, sexual dysfunction, sleep changes (e.g., insomnia or somnolence, vivid dreams, nightmares), sweating Less common (> 2%): agitation, anxiety, hostility, impulsivity, irritability Rare: increased bleeding (e.g., bleeding gums, nose bleed), QTc prolongation (citalopram) (ii), serotonin syndrome, and suicidality (Black Box warning)	Most side effects are dose-related and appear to subside over time. If necessary, side effects can be managed with dose reduction or medication change.
SNRIs (iii)	Same as above; rare elevation in blood pressure and pulse	
Bupropion	Most common (> 10%): agitation, insomnia, sweating Rare: seizures (dose-related, especially > 450 mg/day) (iv)	
Mirtazapine	Most common (> 30%): dry mouth, sedation, increased appetite, weight gain	

(i) Side effect profile may influence medication selection e.g., mirtazapine may be therapeutic when insomnia and poor appetite are a problem; **(ii)** Citalopram use is generally not recommended in patients with congenital long QT syndrome, bradycardia, hypokalemia, hypomagnesemia, or in patients taking other medications that can prolong the QTc interval; **(iii)** Venlafaxine, the only SNRI included in the FDA suicidality meta-analysis, had the highest risk ratio for suicidality;[6] **(iv)** Bupropion use is contraindicated in patients with seizure disorders, eating disorders, during withdrawal from alcohol or benzodiazepine use; patient factors such as traumatic brain injury or concomitant use of other medications that lower the seizure threshold can also increase the risk of seizures.

Suicidality Black Box Warning

The 2004 FDA Black Box warning announced the increased risk of suicidality in children treated with antidepressants after a meta-analysis of randomized controlled trials showed a small increase (4% vs 2%) in suicidal thoughts and behaviors (but no completed suicides) versus placebo. In 2007, the FDA qualified its warning stating "depression and certain other serious psychiatric disorders are themselves the most important causes of suicide". Overall, certain SSRIs have demonstrated improved depression and reduced suicidality; but some studies indicate a few patients may experience worsening or new-onset suicidality.[9]

Although research has not yet linked the following symptoms to suicidal thoughts, urges, or behaviors in patients beginning antidepressant therapy, providers should:

- Monitor closely for suicidality and appearance or worsening of behavior such as anxiety, agitation, insomnia, irritability, hostility, impulsivity, restlessness, and mania.[2]
- Consider changing or discontinuing the antidepressant medication should appearance or worsening of this behavior occur.[4]
- Schedule frequent follow-ups; the FDA recommends weekly follow-ups for the first 4 weeks, and biweekly thereafter.[2]
- Consider closer follow-up if increased risk of suicide (e.g., those with higher levels of suicidality at baseline, prior suicide attempts, family conflict, drug or alcohol use, peer conflict, family history of suicide, exposure to the suicidal behavior of others, easy access to lethal methods, and stressful life event or loss).[2,10,11]
- Educate parents and children about:
  - suicide risk in youth with psychiatric disorders;[2]
  - the risks and benefits of medication treatments;[2] and
  - resources available, including detailed contact information for the suicide hotline or mental health crisis response team.[12]
- Inform parents/caregivers, away from the child, about risk reduction by limiting access to lethal means.[13]
- Recognize that communication between the parent, child, and prescriber is critical.
- Provide families with contact information for the suicide hotline or mental health crisis response team.[12]

For additional information, see SCORxE Winter 2014-2105 FAQ at:
https://www.sccp.sc.edu/sites/default/files/FAQ-Suicide_Risk_w_ADs_in_Ped_2014-15_winter10-29-14.pdf

Serotonin Syndrome

Serotonin syndrome (characterized by delirium, agitation, diaphoresis, tachycardia, hypertension, tremor, myoclonus, hyperreflexia, clonus, hyperthermia) can develop when SSRIs or SNRIs are used concomitantly with other serotonergic agents; e.g., tramadol, linezolid, MDMA (Ecstasy), synthetic cathinones ("bath salts"), St John's Wort. The syndrome can range from mild to life-threatening. It typically develops within a week of increased serotonergic exposure and resolves within a week of reduced serotonergic exposure.[14,15]

HIGHLIGHTS OF SELECT RESOURCES

Resource	Web Link/Key Contact Information
Ask Suicide Screening Questions (ASQ) (National Institute of Health)	http://www.nimh.nih.gov/news/science-news/ask-suicide-screening-questions-asq.shtml
Four-item screening tool for pediatric patients presenting to the emergency department.	
Bright Futures* (Georgetown University)	www.brightfutures.org/mentalhealth/pdf/tools.html
Provider assessment & evaluation tools (e.g., pediatric symptom checklists for mood disorders and substance abuse issues). Multiple patient education resources and handouts on behavioral and developmental issues that providers can offer (e.g., Symptoms of Depression in Adolescents, Tips for Parenting the Anxious Child).	
GLAD – PC Toolkit (The Reach Institute)	http://www.thereachinstitute.org/guidelines-for-adolescent-depression-primary-care
Comprehensive free toolkit for management of adolescent depression includes: evidence-based treatment recommendations, rating scales, non-pharmacological interventions including active monitoring examples, medication information handouts and educational handouts that providers can offer adolescents and parents.	
National Alliance on Mental Illness South Carolina Chapter of NAMI SC*	http://www.namisc.org
Connects individuals living with mental illness as well as their families with local affiliates, available services and resources using education, support and advocacy (e.g., Parents and Teachers as Allies - a two hour in-service mental health education program for school professionals; NAMI Basics - a free course taught by trained parents/caregivers of a child/youth who developed symptoms of mental illness before age 13 to parents/caregivers of children/adolescents experiencing symptoms of mental illness).	
National Suicide Prevention Lifeline*	www.suicidepreventionlifeline.org Tel. 24-hour Hotline 1-800-273-TALK
24 hour hotline and online chat, other resources.	
Partnership Access Line (PAL)* (Washington state)	http://www.palforkids.org/resources.html
Provider assessment & evaluation tools (e.g., PHQ-9, SCARED rating scale for parent and child), treatment algorithm and medication information. Crisis Prevention Tools and Handouts (Crisis Prevention Plan Aid for Parents, General Home Safety Recommendations After a Child Crisis Event, Crisis Prevention Plan form to aid and determine action plan with child and family). Patient/family education resources on depression that providers can offer.	
Teen Link (Washington state)	http://866teenlink.org Tel. 24-hour Toll Free Hotline 1-866-TEENLINK (1-866-833-6546)
Hotline & on-line chat support for ages 13-20 using trained teen volunteers every evening between 6pm - 10pm Pacific Standard Time (PST).	
Federation of Families of South Carolina*	www.fedfamsc.org Tel. 1-800-779-0402
A statewide network to provide information, training and support for SC families of children identified at risk or with an emotional or behavioral disorder. Some limited teacher resources as well.	
Trident United Way 2-1-1 Hotline* (South Carolina)	http://www.tuw.org/2-1-1-hotline Tel. 24-hour Hotline - Dial 2-1-1 or (843) 744-HELP or 1-800-922-2283 Business Phone: 843-747-3007
Statewide 24-hour hotline and online chat (Tele-interpreters available for multiple languages), also directs callers to resources.	
SCORxE* (SouthCarolina)	http://www.sccp.sc.edu/scorxe
Patient education aides such as: Healthy Sleep Habits (English) https://www.sccp.sc.edu/sites/default/files/27842-SCORXE_HSH_PADS.pdf Healthy Sleep Habits (Spanish) https://www.sccp.sc.edu/sites/default/files/Habitos_saludables.pdf Depression Symptoms Response to Treatment (English) https://www.sccp.sc.edu/sites/default/files/00875-DEPRESS_MED_SHEET.pdf Depression Symptoms Response to Treatment (Spanish) https://www.sccp.sc.edu/sites/default/files/0447_Phar_SCORE_SpanDepres.pdf	

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Acknowledgements (and Disclosures for Pharmaceutical Industry Relationships): Christopher Wisniewski, Pharm.D. (None).

December 2014