Depressive Disorders in Children and Adolescents

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Depressive disorders affect

approximately 2 to 3 percent of children

and

up to 8 percent of adolescents

- The higher **(3:1)female-to-male rate** of depression after the onset of puberty may be due to higher rates of anxiety disorder, tendency to rumination, and greater sensitivity to interpersonal stressors in females
- **Early onset of puberty increases the risk of depression in girls**

Childhood depression compared with adolescent-onset depression appears to be ***more heterogenous***

Children's moods are especially vulnerable to the influences of social stressors, such as

- family discord,
- abuse and neglect,
- parental mental illness,
- substance abuse,
- poverty and academic failure.

The effects of these stressors also depends on

- child's cognitive styles
- coping styles with stress,
- IQ,
- genetic factors

- DSM-5 utilizes the same criteria for MDD in youth as in adults, except that for children and adolescents**, irritable mood may replace a depressed mood in the diagnostic criteria.**

Clinical presentation is strongly influenced by the developmental level

Very young children :

- withdrawn and sad appearance,
- listless, apathetic,
- Temper tantrum, irritability
- mood-congruent auditory hallucinations,
- somatic complaints: headaches and stomachaches
- psychomotor agitation

Clinical presentation is strongly influenced by the developmental level

late adolescence :

- pervasive anhedonia,
- hopelessness,
- Melancholic symptoms
- severe psychomotor retardation,
- Delusions
- Suicide attempts

Comorbidity

is the rule rather than the exception

in depressed children and adolescents

Comorbidity

- Anxiety is frequently a precursor
- ADHD and CD , antisocial behavior
- ODD is a strong predictor of eventual depression.
- Alcohol, tobacco, and cannabis use and abuse are more likely to precede and lead to depression
- Inflammatory dysregulation

The risk for bipolar disorder in early-onset depression is estimated to be **10% to 20%,** and is higher in patients who present with

- history of antidepressant induced or spontaneous hypomania,
- psychotic features,
- hypersomnia, and
- family history of bipolar disorder

Treatment

- Psychotherapy should be considered as the *first-line intervention* for the management of depressive disorder in children and adolescents
- Antidepressants are often reserved for more severe illness or when psychotherapy does not work or is not available

Treatment

Well-established evidence-based treatments for adolescent depression :

- antidepressant treatment,
- cognitive behavior therapy (CBT),
- interpersonal therapy (IPT)

For initial treatment of adolescent patients with depressive disorders studies recommends that clinicians offer one of the following:

- Cognitive-behavioral therapy
- Interpersonal psychotherapy adapted for adolescents (IPT-A)

Cognitive Behavior Therapy

- **Cognitive restructuring**—an effort to make the patient aware of negative distortions and to teach the individual how to counteract them
- **Behavioral activation** is encouraging patients to normalize their routine and engage in rewarding activities.
- **Adjunctive skill building elements (e.g., problem solving, relaxation, emotion regulation, assertiveness training)**

INTERPERSONAL THERAPY

- IPT for adolescents (IPT-A) is an adaptation of IPT for adult unipolar depression
- IPT-A is a very developmentally appropriate treatment, since adolescence is a time of role changes, conflicts with parents, and the investment of more emotional capital in peer relationships.

IPT-A is particularly efficacious in youth with

- greater depressive severity,
- comorbid anxiety,
- poorer interpersonal functioning,
- high levels of conflict with parents.

Medications should be

- initiated at low doses,
- lower than adult starting doses
- and increased until therapeutic effect or adverse effects occur.

- **Response:** Greater than a 50% improvement
- **Nonresponse:** less than 25% improvement
- **Partial response:** 25%–49% improvement
- **Remission :** a period of at least 2 weeks and less than 2 months with no or very few symptoms
- **Recovery:** absence of significant symptoms for 2 months
- **Relapse:** a DSM episode during remission
- **Recurrence:** emergence of symptoms during recovery (a new episode)

Treatment

- **Acute** : the goal is to achieve response and full remission (no symptom or significant reduction for at least 2 weeks and less than 2 months)
- **Continuation**: to consolidate response and avoid relapses (an episode during remission)
- **Maintenance**: to avoid recurrence or new episodes (emergence of symptoms during recovery or a new episode)

Acute phase treatment

- Clinical response should be assessed at *4 to 6 week intervals* and if the child tolerated the antidepressant, the dose may be increased if a complete response has not been obtained.
- By about 12 weeks of treatment the goal should be remission of symptoms, and in youth who are not remitted by that time, the alternating treatment options may be warranted.

Continuation

- After acute response every child and adolescent should continue treatment for at least 6-12 months
- Once a youth has been asymptomatic for approximately 6-12 months, the clinician must decide whether maintenance therapy is indicated .

Maintenance (1 year or longer)

- More than 2 episodes of depression
- Severe or chronic depression
- Double depression
- Psychosis
- Suicidality
- Ongoing stressors
- Lack of support

- Selective serotonin reuptake inhibitors are the first-line antidepressant agents for children and adolescents diagnosed with depression.
- Fluoxetine is approved by the Food and Drug Administration (FDA) for children 8 years of age and older.
- Escitalopram is approved for ages 12 years and older.

- Studies showed **no difference between TCAs and placebo.**
- **SSRIs are superior to placebo**
- **Fluoxetine is the best-studied antidepressant with the strongest efficacy data, for the treatment of depression in both children and adolescents**

Treatment of Adolescent Depression Study (TADS)

Fluoxetine, **CBT**, **Fluoxetine + CBT** , **placebo**

Response :

61% , **43%** , **71%** , **35%**

- “Fluoxetine (alone or in combination with CBT) seems to be the best choice for the acute treatment of moderate-to-severe depressive disorder in children and adolescents.”

Zhou X, Teng T, Zhang Y, et al. Comparative efficacy and acceptability of antidepressants, psychotherapies, and their combination for acute treatment of children and adolescents with depressive disorder: a systematic review and network meta-analysis. Lancet Psychiatry 2020; 7: 581–601.

- sertraline is effective for adolescent depression, but sertraline combined with CBT is more effective.

Liu W, Li G, Wang C, Wang X, Yang L. Efficacy of Sertraline Combined with Cognitive Behavioral Therapy for Adolescent Depression: A Systematic Review and Meta-Analysis. Comput Math Methods Med. 2021 Dec 28;2021

Adverse effects

- Meta-analyses have also found that **antidepressant-treated youth** have about **twice the incidence of hostility and aggression and a much higher incidence of mania** compared to those treated with placebo with **the risk greatest of mania in those under the age of 14**
- **SSRI have an increased risk of behavioral disinhibition or activation when prescribed for children, especially preschoolers**

Adverse effects

- Increased incidence of sleep disruption, vivid dreams,
- nausea and gastrointestinal distress,
- agitation, akathisia, anxiety, headache,
- serotonin syndrome
- bruising (due to a prolongation of clotting time)

- Nearly 40% of adolescents remain depressed after initial treatment, *and over half* of that population remain depressed despite switching medications or adding psychotherapy.

Treatment-resistant depression

Clinically impairing depression symptoms despite

an adequate trial of an evidence-based psychotherapy

and

an antidepressant with Grade A evidence for treating depression in pediatric population (fluoxetine, escitalopram, or sertraline)

Strategies for treatment-resistant depression

- A thorough evaluation to reassess alternative explanations for the depressive symptoms (trauma, untreated anxiety, bullying,…)
- evaluating adherence

Dwyer JB, Stringaris A, Brent DA, Bloch MH. Annual Research Review: Defining and treating pediatric treatment-resistant depression. J Child Psychol Psychiatry. 2020 Mar;61(3):312-332.

Strategies for treatment-resistant depression

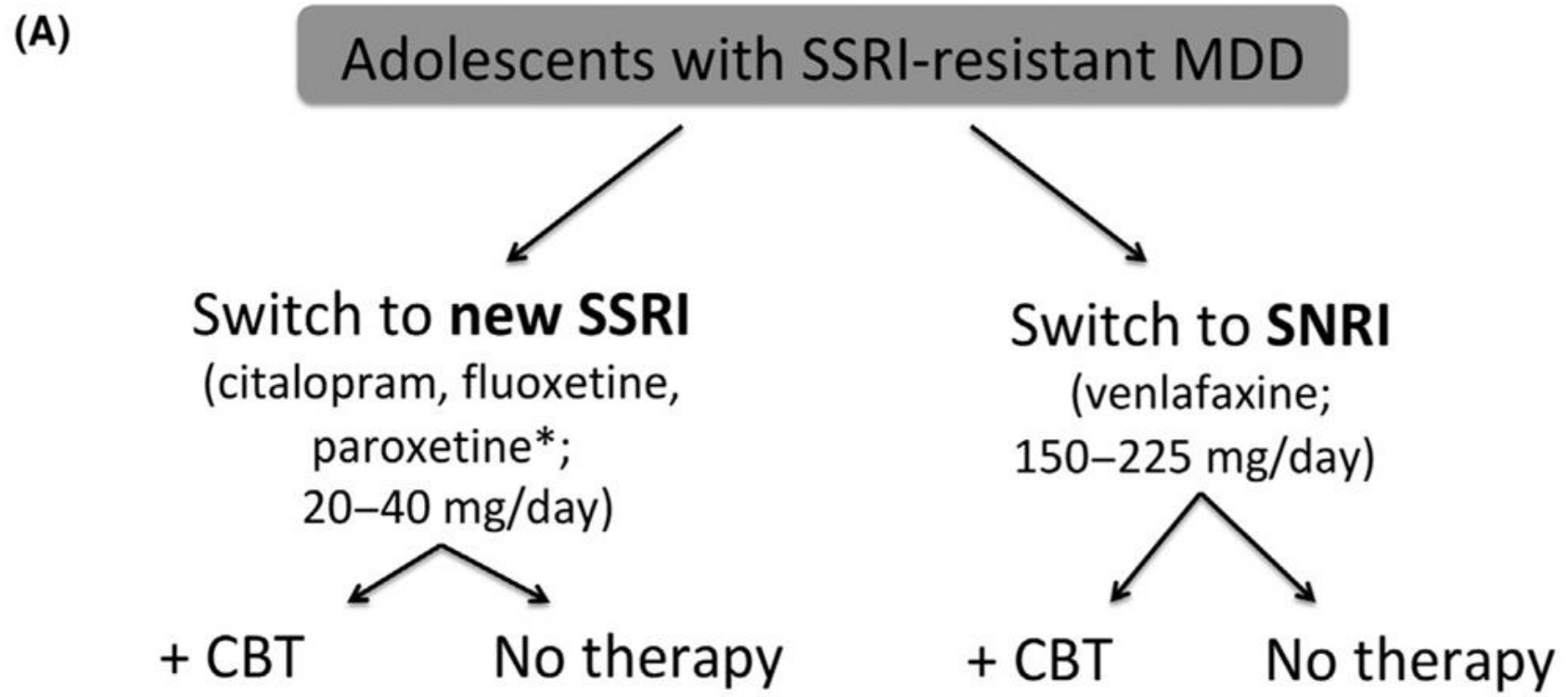
(a) medication switch;

(b) pharmacologic augmentation strategies,

(c) psychotherapy augmentation strategies, and
(d) interventional depression treatments

Treatment of Resistant Depression in Adolescents (TORDIA)

- *The study examined the use of a second SSRI or venlafaxine with or without CBT in adolescents who failed to respond to an initial SSRI trial*
- *Combination treatment was superior to medication monotherapy*
- *No difference in response rates was observed between a second SSRI versus venlafaxine*



(B) TORDIA Take-home points:

(1) Higher response rates with CBT with either medication class switch
(2) Similar response rates with a switch to a different SSRI vs. switching to venlafaxine
(3) However, venlafaxine has a significantly greater side effect burden than SSRIs

Treatment-refractory depression

Clinically impairing depression symptoms despite

an adequate trial of an evidence-based psychotherapy

and

at least 2 antidepressants with Grade A evidence for treating depression including at least 1 with Grade A evidence in pediatric populations (fluoxetine, escitalopram, or sertraline)

- Many medications with evidence of efficacy in adult depression have failed to demonstrate significant benefits in pediatric populations.
- Non-SSRI antidepressants that have failed to show significant differences from placebo in clinical trials include venlafaxine, mirtazapine, duloxetine , tricyclic antidepressants, and selegiline.

- Paroxetine is not superior to placebo for adolescent depression and carries the risk of increased suicidality compared with other SSRIs and increased sedation in the pediatric and young adult population.

- *No difference between vortioxetine and placebo.*
- *The overall favorable safety profile of vortioxetine in an adolescent patient population was consistent with that seen in adults.*

Vortioxetine for Major Depressive Disorder in Adolescents: 12-Week Randomized, Placebo-Controlled, Fluoxetine-Referenced, Fixed-Dose Study. Journal of the American Academy of Child & Adolescent Psychiatry. Volume 61, Issue 9, September 2022, Pages 1106-1118.e2

Pharmacologic augmentation strategies

Despite the limited evidence, augmenting agents for pediatric patients often include

- atypical antipsychotics(aripiprazole, quetiapine)
- lithium;
- omega-3 fatty acids, folate
- bupropion; and
- mirtazapine

- **Bupropion** may be beneficial for patients with comorbid ADHD or a tobacco use disorder.
- **Mirtazapine** is beneficial for patients with sleep disturbances but may also cause weight gain.

- Adjunctive Citalopram might be efficacious in the treatment of chronic severe irritability in youth resistant to stimulant treatment alone.

Towbin K, et al. A Double-Blind Randomized Placebo-Controlled Trial of Citalopram Adjunctive to Stimulant Medication in Youth With Chronic Severe Irritability. J Am Acad Child Adolesc Psychiatry. 2020 Mar;59(3):350-361.

- To date, two randomized controlled trials on TMS in adolescent depression have been published, and the only large-scale randomized trial suggests TMS is not more effective than sham stimulation.

Transcranial magnetic stimulation in the treatment of adolescent depression: a systematic review and meta-analysis of aggregated and individual-patient data from uncontrolled studies. Eur Child Adolesc Psychiatry (2022).

- Children and adolescents with MDD appear to be *more responsive to placebo than adults* in randomized placebo-controlled trials (RCTs) of second and newer generation antidepressants

Meister R etal. Placebo response rates and potential modifiers in double-blind randomized controlled trials of second and newer generation antidepressants for major depressive disorder in children and adolescents: a systematic review and meta-regression analysis. Eur Child Adolesc Psychiatry. 2020 Mar;29(3):253-273.

- The placebo effect is too high, masking the actual effect of the drugs;
- The studies misdiagnosed kids as having depression when their symptoms were actually due to something else;

- *The drugs simply do not work for children and adolescents*. Their reasoning for this is that the drugs were “developed for adults”.
- The studies aren’t sensitive enough to detect the actual effect of the drugs;

Feeney A, et al . Antidepressants in children and adolescents with major depressive disorder and the influence of placebo response: A meta-analysis. J Affect Disord. 2022 May 15;305:55-64.

- In general, the standardized drug-placebo difference is ***small*** and varies significantly by disorder, with effect sizes ranging from
- 0.20 for Depressive Dis., to
- 0.39 for OCD, and
- 0.56 for Anxiety Dis.

Meta-Analysis: Pediatric Placebo Response in Depression Trials Does Not Replicate in Anxiety and Obsessive-Compulsive Disorder Trials.

Journal of Child and Adolescent PsychopharmacologyVol. 16 Dec 2021

Treatment of Bipolar Depression

- Olanzapine/fluoxetine combined has been approved for youths aged 10–17 years.

Olanzapine/Fluoxetine Combination in Children and Adolescents With Bipolar I Depression: A Randomized, Double-Blind, Placebo-Controlled Trial. VOLUME 54, ISSUE 3, P217-224, MARCH 01, 2015

Walker DJ, DelBello MP, Landry J, D'Souza DN, Detke HC. Quality of life in children and adolescents with bipolar I depression treated with olanzapine/fluoxetine combination. Child Adolesc Psychiatry Ment Health. 2017 Jul 12;11:34.

- A high placebo response rate proved that quetiapine was not better than the placebo in treating pediatric bipolar depression.
- Side effects: headache, somnolence, gastric upset, and weight gain, increase in triglyceride levels.

Srinivas S, Parvataneni T, Makani R, Patel RS. Efficacy and Safety of Quetiapine for Pediatric Bipolar Depression: A Systematic Review of Randomized Clinical Trials. Cureus. 2020 Jun 2;12(6):e8407.

- Evidence indicated that *lurasidone and olanzapine/fluoxetine combined , but not quetiapine, were efficacious for the treatment of bipolar depression in youths.*
- Lurasidone was associated with less weight gain and smaller impacts on cholesterol and triglycerides compared with quetiapine and OFC.

DelBello MP, Kadakia A, Heller V, Singh R, Hagi K, Nosaka T, Loebel A. Systematic Review and Network Meta-analysis: Efficacy and Safety of Second-Generation Antipsychotics in Youths With Bipolar Depression. J Am Acad Child Adolesc Psychiatry. 2022 Feb;61(2):243-254.

Thanks for your attention