

# An Overview of Pediatric Depression

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Cynthia R. Pfeffer, M.D.

# Teaching points

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- Prevalence of Major Depressive Disorder (MDD) is around 2% in children and 4%-8% in adolescents
- Clinicians should recognize developmental variations in MDD with presentations including anxiety, irritability and behavioral problems in children and adolescents
- Initial acute treatment depends on: severity of MDD symptoms, number of prior episodes, chronicity, age, contextual issues in family, school, social issues, negative life events, compliance, prior treatment response and motivation for treatment

# Question 1

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- A prepubertal child with a diagnosis of MDD is likely to have which of the following symptoms
- A-auditory hallucinations
- B-paranoid delusions
- C-drug abuse
- D-rosy glow
- E-all of the above

# Question 2

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- A teenager with MDD is NOT likely to have which of the following symptoms
- A-Hypersomnia
- B-Overeating
- C-Delusions
- D-Separation Anxiety Disorder
- E-Suicidal ideation

# Question 3

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- Which of the following is a predictor of recurrence of MDD in youth
  - A-Later age at onset
  - B-Decreased number of prior episodes
  - C-Psychosis
  - D-Intelligence
  - E- All of the above

# Question 4

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Which of the following is a predictor of the likelihood of the development of bipolar disorder in youth with MDD?

- A-Co-morbid ADHD
- B- Psychomotor agitation
- C-Co-morbid anxiety disorder
- D-Family history of non-psychotic depression
- E-Heavy familial loading for mood disorders

# Question 5

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- Which of the following statements best characterizes dysthymic disorder in youth?
- A-Not associated with increased risk of MDD
- B-10% of youth with Dysthymia have MDD
- C-Dysthymia has mean episode of 3-4 years for clinical & community samples
- D-First MDD episode usually occurs 10 years after onset of Dysthymia,
- E-None of the above

# *Need for Treatment and Prevention of MDD and Dysthymic Disorder Because:*

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- These disorders are prevalent & recurrent
- Have high rates of comorbidity
- Accompanied by poor psychosocial outcomes
- Associated with high risk for suicide
- Associated with high risk for substance abuse



# *Problems in Reducing MDD in Children and Adolescents*

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- Problems of diagnosis
- Developmental variations
- Complexity of factors associated with clinical course
- Need specificity of treatments

# Epidemiology

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- MDD prevalence: 2% children, 4%-8% adolesc.
- Male:female ratio: childhood 1:1, adolesc 1:2
- Cumulative incidence by age 18 years: 20%
- Since 1940, each successive generation at higher risk for MDD
- Dysthymia prevalence: 0.6%-1.7% children, 1.6%-8% adolesc.
- Often under-recognized

# *Complexities in Diagnosing MDD in Children and Adolescents*

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- Overlap of mood disorder symptoms
- Symptoms overlap with comorbid disorders
- Developmental variations in symptom manifestations
- Etiological variations of mood disorders involving gene-environment interactions
- Are disorders spectrum or categorical disorders
- Effects of medical conditions

# MDD Diagnostic Criteria: DSM-IV

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- At least 2 weeks of pervasive change in mood manifest by either depressed or irritable mood and/or loss of interest and pleasure.
- Other symptoms: changes in appetite, weight, sleep, activity, concentration or indecisiveness, energy, self-esteem (worthless, excessive guilt), motivation, recurrent suicidal ideation or acts.
- Symptoms represent change from prior functioning and produce impairment
- Symptoms attributable to substance abuse, medications, other psychiatric illness, bereavement, medical illness

# *Need to Recognize Developmental Variations of MDD*

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## ■ CHILDREN:

- More symptoms of anxiety (i.e. phobias, separation anxiety), somatic complaints, auditory hallucinations
- Express irritability with temper tantrums & behavior problems, have fewer delusions and serious suicide attempts

## ■ ADOLESCENTS:

- More sleep and appetite disturbances, delusions, suicidal ideation & acts, impairment of functioning
- Compared to adults, more behavioral problems, fewer neurovegetative symptoms

# Dysthymia Diagnostic Criteria: DSM-IV

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- Persistent, long-term change in mood, less intense but more chronic than MDD
- Extensive psychosocial impairment
- Depressed mood or irritability on most days for most of the day for at least 1 year
- At least 2 other symptoms: appetite, sleep, self-esteem, concentration, decision-making, energy, hope
- Person is not without symptoms for more than 2 months at a time and has not had MDD for the first year of disturbance; never had manic or hypomanic episode

# *Dysthymia: Other symptoms not included in DSM-IV Criteria- May affect recognition*

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- Feelings of being unloved
- Anger
- Self-deprecation
- Somatic complaints
- Anxiety
- Disobedience

# Clinical Variants of MDD: *Need for Different Intervention Strategies*

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- Psychotic Depression
- Bipolar Depression
- Atypical Depression
- Seasonal Affective Disorder
- Subclinical or Subsyndromal Depression
- Treatment-Resistant Depression



# Clinical Variants of MDD: Psychotic Depression

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- MDD associated with mood congruent or incongruent hallucinations and/or delusions (unlike adolescents, children manifest mostly hallucinations)
- Occurs in up to 30% of those with MDD
- Associated with more severe depression, greater long-term morbidity, resistance to antidepressant monotherapy, low placebo response, increased risk of bipolar disorder, family history of bipolar and psychotic depression

# Clinical Variants of MDD: Bipolar Depression

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- Presents similarly to unipolar depression
- Risk for bipolar disorder indicated by: psychosis, psychomotor retardation, psychopharmacologically induced hypomania, family history of bipolar disorder
- Adolescents likely to have rapid cycling or mixed episodes & increased suicide risk & difficulty in treatment
- Need to rule out bipolar II disorder: more prevalent in adolescents, often overlooked or misdiagnosed

# Clinical Variants of MDD: Atypical Depression

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- Not yet studied in children or adolescents
- Usual onset in adolescence
- Manifest by increased lethargy, appetite & weight, & reactivity to rejection, hypersomnia, carbohydrate craving
- In adults, it is genetically distinct from MDD

# Clinical Variants of MDD: Seasonal Affective Disorder

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- Usual onset in adolescence in those living in regions with distinct seasons
- Symptoms similar to those of atypical depression but are episodic
- Does not include increased reactivity to rejection
- Should be differentiated from depression precipitated by school stress since it usually overlaps with school calendar

# Clinical Variants of MDD: Treatment-Resistant Depression

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- No clear definition of treatment-resistant depression in children & adolescents
- Approximately 6%-10% of depressed youth suffer chronic depression
- In adults, treatment resistance is defined as patients who had at least two trials with two different classes of antidepressants administered at similar doses for at least 6 weeks each

# *Complexities of Comorbidity: May Affect*

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- Recognition & diagnosis of MDD
- Types and efficacy of treatment
- Psychosocial outcomes

# Comorbidity

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- Present in 40%-90% of youth with MDD; two or more comorbid disorders present in 20%-50% youth with MDD
- Comorbidity in youth with MDD: Dysthymia or anxiety disorders (30%-80%), disruptive disorders (10-80%), substance abuse disorders (20%-30%)
- MDD onset after comorbid disorders, except for substance abuse
- Conduct problems: May be a complication of MDD & persist after MDD episode resolves
- Children manifest separation anxiety; adolescents manifest social phobia, GAD, conduct disorder, substance abuse

# *Differential Diagnosis: Complexities of Diagnosing MDD*

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- Overlap of symptoms with nonaffective disorders (i.e., anxiety, learning, disruptive, personality, eating disorders):
- Overlapping symptoms include: poor self-esteem, demoralization, poor concentration, irritability, dysphoria, poor sleep, appetite problems, suicidal thoughts, being overwhelmed



# Differential Diagnosis: Nonaffective Psychiatric Disorders

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- Anxiety disorders: separation anxiety, GAD, etc
- Disruptive and ADHD Disorders
- Learning Disorders
- Substance abuse
- Eating Disorders: Anorexia Nervosa
- Personality Disorders
- Premenstrual Dysphoric Disorder

# Differential Diagnosis: Adjustment Disorder with Depressed Mood

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- Mood change & impairment of functioning within 3 months of stressor; do not meet criteria of MDD
- Self-limited disorder, less mood disturbance, fewer symptoms, no relapse
- Consider other disorders if symptoms last more than 6 months or have criteria for other disorders, i.e., Dysthymia

# *Differential Diagnosis: Complexities of General Medical Conditions*

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- May be accompanied by symptoms of depression
- Impact course of depressive disorder
- MDD can be diagnosed if depressive symptoms preceded or not solely due to medical illness or medications to treat medical illness
- Incidence of MDD higher in certain medical illnesses
- Chronic illness may affect sleep, appetite, energy
- Guilt, worthlessness, hopelessness, suicidal ideation usually not attributed to medical illness but suggest MDD

# Differential Diagnosis: Medical Conditions Often with Depressive Symptoms

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- Cancer, hypothyroidism, lupus erythematosus, acquired immunodeficiency syndrome, anemia, diabetes, epilepsy
- Chronic Fatigue Syndrome: symptoms similar to MDD but with more somatic symptoms, less mood, cognitive, social symptoms
- Medication induced symptoms: stimulants, neuroleptics, corticosteroids, contraceptives

# Differential Diagnosis: Bereavement

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- Similarity of symptoms
- Diagnosis of MDD made if bereaved child/adolescent has moderate or severe functional impairment, psychosis, suicidal ideation or acts, prolonged course
- Following bereavement, predisposition to MDD may be related to prior MDD or family history of MDD (uncomplicated bereavement often remits in 6-12 months after death)

# Clinical Course: MDD Episode

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- Median Duration:  
Clinically referred youth: 7-9 months  
Community youth: 1-2 months
- Predictors of longer duration: depression severity, comorbidity, negative life events, parental psychiatric disorders, poor psychosocial functioning
- Remission is defined as a period of 2 weeks to 2 months with 1 clinically significant symptom
- 90% MDD episodes remit 1-2 years after onset
- 6%-10% MDD are protracted

# Clinical Course: Relapse

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- Relapse is an episode of MDD during period of remission
- Predictors of relapse:
  - Natural course of MDD
  - Lack of compliance
  - Negative life events
  - Rapid decrease or discontinuation of therapy
- 40%-60% youth with MDD have relapse after successful acute therapy
- *Indicates need for continuous treatment*

# Clinical Course: Recurrence

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- Recurrence is emergence of MDD symptoms during period of recovery (asymptomatic period of more than 2 months)
- Clinical & nonclinical samples probability of recurrence 20%-60% in 1-2 years after remission, 70% after 5 years
- Recurrence predictors:
  - Earlier age at onset
  - Increased number of prior episodes
  - Severity of initial episode
  - Psychosis
  - Psychosocial stressors
  - Dysthymia & other comorbidity
  - Lack of compliance with therapy



# Clinical Course: Risk of Bipolar Disorder

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- 20%-40% MDD youth develop bipolar disorder in 5 years of onset of MDD
- Predictors of Bipolar I Disorder Onset:
- Early onset MDD
- Psychomotor retardation
- Psychosis
- Family history of psychotic depression
- Heavy familial loading for mood disorders
- Pharmacologically induced hypomania

# Clinical Course: Other Factors

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- Risk for depression increases 2-4 times after puberty, especially in girls
- Genetic & environmental factors influence pathogenesis of MDD: nonshared intrafamilial & extrafamilial environmental experiences (how individual parents treat each child), those at high genetic risk more sensitive to adverse environmental effects

# Clinical Course: Genetic Factors

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- Children with depressed parent 3x likely to have lifetime episode of MDD (lifetime risk 15%-60%)
- Prevalence of MDD in first-degree relative of children with MDD is 30%-50% (parents of MDD children also have anxiety, substance abuse, personality disorders)

# Clinical Course: Other Factors Associated with MDD

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- Poor school success, low parental satisfaction with child, learning problems, other psychiatric disorders that interfere with child's learning
- Personality traits: judgmental, anger, low self-esteem, dependency
- Cognitive style & temperament: negative attributional styles
- Early adverse experiences: parental separation or death
- Recent adverse events
- Conflictual family relations & neglect, abuse
- Biological factors: inability to regulate emotions or distress

# Clinical Course: Relation of Dysthymia & MDD

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- Associated with increased risk of MDD
- 70% of youth with Dysthymia have MDD
- Dysthymia has mean episode of 3-4 years for clinical & community samples
- First MDD episode usually occurs 2-3 years after onset of Dysthymia, a gateway to developing recurrent MDD
- Risk for Dysthymia: chaotic families, high family loading for mood disorders, particularly Dysthymia

# Prospective Studies: MDD Risk Factor for Suicidal Tendencies in Children/Adolesc.

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- Kovacs et al. (1993): 9 year FU of prepubertal children: FU of initial 58 MDD 74% SI, 28% SA, 23 dysthymia 78% SI, 17% SA, 18 adjust disorder with depressed mood 50% SI, 6% SA, 48 without mood disorder 48% SI, 8%SA
- Pfeffer et al. (1993): 6-8 year FU prepubertal inpatients: 5 times risk for SA in adolesc. with prepubertal mood disorder

# Prospective Studies: MDD Risk Factor for Suicidal Tendencies in Children/Adolesc.

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- Andrews & Lewinsohn (1992): One-year incidence of SA in epidemiologic adolescent sample was associated with 12 & 15 times greater risk imparted by MDD in males & females, respectively.

# *Concerns about Treatment of MDD*

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- Treatment research is relatively sparse for MDD in children and adolescents
- Varied opinions about whether psychotherapy or pharmacotherapy, or a combination should be the first-line treatment
- Initial acute treatment depends on: severity of MDD symptoms, number of prior episodes, chronicity, age, contextual issues in family, school, social, negative life events, compliance, prior treatment response, motivation for treatment



# Treatment of MDD in Children & Adolescents

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- Psychotherapy for mild to moderate MDD
- Empirical effective psychotherapies: CBT, ITP
- Antidepressants can be used for: non-rapid cycling bipolar disorder, psychotic depression, depression with severe symptoms that prevents effective psychotherapy or that fails to respond to adequate psychotherapy
- Due to psychosocial context, pharmacotherapy alone may not be effective

# Treatment of MDD in Children & Adolescents

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- Few studies of acute treatment with medication for MDD
- Few pharmacokinetic & dose-range studies
- SSRI's may induce mania, hypomania, behavioral activation (impulsive, silly, agitated, daring)
- No long-term studies of treatment of MDD; long-term effects of SSRI's not known

# Treatment of MDD in Children and Adolescents

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- Small number of case reports (King et al, 1991; Teicher et al., 1990) described association between SSRI's treatment and increased suicidal tendencies, possibly linked to behavioral activation or akathisia
- Abrupt discontinuation with SSRI's with shorter half-lives may induce withdrawal symptoms that mimic MDD
- SSRI's inhibit metabolism of some medications metabolized by hepatic enzymes (P450 isoenzymes)
- SSRI's interact with other serotonergic medications (MAOI's) to induce serotonergic syndrome (agitation, confusion, hyperthermia)

# Treatment of MDD: Tricyclic Antidepressants (TCA's)

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- TCA's: imipramine, desipramine, amitriptyline, nortriptyline, doxepin
- Tricyclic antidepressants (TCA's) have 50%-60% response rate for MDD; but studies limited by sample size, duration of treatment, dose of TCA's, inclusion of patients with mild MDD
- Findings suggest that TCA's have little benefit in children & adolescents

# Published double-blind, placebo-controlled studies: SSRI efficacy for MDD

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- Studies of children & adolescents:
- Emslie et al (1997): modest fluoxetine efficacy: fluoxetine 58%, placebo 32%
- Keller et al (2001): paroxetine efficacy: paroxetine 63%, imipramine 50%, placebo 46%, 1 of 2 primary outcome measures was significant; 2 other studies were negative
- Emslie et al (2002): fluoxetine efficacy: effects modest (fluoxetine 41%, placebo 20%) & not all outcome measures were significantly different than placebo
- Wagner et al (2003): sertraline efficacy: sertraline 69%, placebo 59%
- TADS Team (2004): CBT + fluoxetine 71%, fluoxetine 61%, CBT 43%, placebo 35%
- Wagner et al (2004): citalopram 36% and 24% placebo
- Wagner et al (2006): no significant differences between escitalopram and placebo

# Combination Treatment of MDD

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- NIMH sponsored “The Treatment of Adolescents with Depression Study” (TADS):
- Multicenter controlled clinical trial
- 439 12-17 year olds with MDD
- Compared efficacy of fluoxetine, CBT, combination, & placebo in 36 weeks with 1 year follow-up.

# Treatment Resistant Study

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- NIMH funded multicenter study “Treatment of Resistant Depression in Adolescents (TORDIA)
- Aims to benefit treatment resistant adolescents, age 12-18 years old
- Compare fluoxetine, paroxetine, or venlafaxine, either alone or in combination with CBT for 24 weeks with 1 year follow-up

# FDA Review of Studies for Antidepressant Drugs

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- 20 placebo-controlled studies of 4100 pediatric patients for 8 antidepressant drugs (citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine)
- Excess of suicidal ideation & suicide attempts when receiving certain antidepressant drugs; no suicides
- FDA could not rule out an increased risk of suicidality for any of these medications
- Data was adequate to establish effectiveness in MDD only for fluoxetine based on 2 studies (by Emslie et al)



# Summary: MDD in Children & Adolescents

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- MDD: complex & heterogeneous regarding: clinical course, comorbidities, predictors of course, need for specificity of treatment, developmental variations of symptoms
- MDD: chronic, recurrent, with serious morbidity including suicidal tendencies
- Few treatment studies limit knowledge of methods to reduce symptoms & morbidities associated with psychosis, atypical MDD, bipolar & seasonal affective disorders, medical illness, comorbid psychiatric disorders & treatment resistant MDD
- Need clarity for indications for pharmacotherapy & psychotherapy, alone or in combination, & maintenance Rx

# Question 1

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- A prepubertal child with a diagnosis of MDD is likely to have which of the following symptoms
- A-auditory hallucinations
- B-paranoid delusions
- C-drug abuse
- D-rosy glow
- E-all of the above

# Question 2

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- A teenager with MDD is NOT likely to have which of the following symptoms
- A-Hypersomnia
- B-Overeating
- C-Delusions
- D-Separation Anxiety Disorder
- E-Suicidal ideation

# Question 3

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- Which of the following is a predictor of recurrence of MDD in youth
  - A-Later age at onset
  - B-Decreased number of prior episodes
  - C-Psychosis
  - D-Intelligence
  - E- All of the above

# Question 4

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Which of the following is a predictor of the likelihood of the development of bipolar disorder in youth with MDD?

- A-Co-morbid ADHD
- B- Psychomotor agitation
- C-Co-morbid anxiety disorder
- D-Family history of non-psychotic depression
- E-Heavy familial loading for mood disorders

# Question 5

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- Which of the following statements best characterizes dysthymic disorder in youth?
- A-Not associated with increased risk of MDD
- B-10% of youth with Dysthymia have MDD
- C-Dysthymia has mean episode of 3-4 years for clinical & community samples
- D-First MDD episode usually occurs 10 years after onset of Dysthymia,
- E-None of the above

# Answers

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- 1-A
- 2-D
- 3-C
- 4-E
- 5-C