Pediatric Depression and Its Treatment

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Question 1

- 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

- 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

- 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

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

- Which of the following statements best characterizes dysthymic disorder in youth?
- A-Not ssociated 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:

- 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

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

Epidemiology

- 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

- 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

- 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

- 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 neurovegative symptoms

Dysthymia Diagnostic Criteria: DSM-IV

- 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

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

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

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

Clinical Variants of MDD: Psychotic Depression

- 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

- 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

- 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

- 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

- 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

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

Comorbidity

- 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

- 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

- 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

- 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

- 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

- 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

- 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

- 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

- 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

- 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

- <u>Recurrence predictors:</u>
- 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

- 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

- 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

- 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

- 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

- 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.

- 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.

- 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

- 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

- 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

- 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

- 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)

- 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

- 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%

Combination Treatment of MDD

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

Treatment Resistant Study

- 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

- 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

- 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

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Answers

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