Child and Adolescent Depression

Andrés Martin, M.D.
Yale Child Study Center
Carlo G. Carandang, M.D.
Maine Medical Center

Pre-Lecture Exam Question 1

1. **The following statement is true of Major Depressive Disorder (MDD) in youth:**

A. More than 20% of all teens have this diagnosis.

B. It is as common in pre-teens as teens.

C. In pre-teens and in teens, more girls than boys meet criteria for MDD.

D. There is a younger age of onset of MDD in more recent generations.

E. This diagnosis cannot occur in pre-teens because the superego has not yet developed.

Question 2

2. The clinical presentation of MDD differs in pre-teens and teens in one of the following ways:

A. Younger children have less anxiety and less visual hallucinations than do teens.

B. Younger children have less irritability and less temper tantrums and less anxiety than do teens.

C. Younger children have more sleep disturbance and more suicidality than do teens.

D. Younger children have less auditory hallucinations and less anxiety than do teens.

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3. Which statement is true of MDD in youth?

A. A typical episode lasts 3-5 months.

B. The recurrent rate is low: less than 25% by 1-2 years after the onset of MDD.

C. More than 90% have a chronic and protracted course.

D. There is disruption in social, educational, vocations, and interpersonal areas.

E. Risk of suicidal behavior does not persist after the episode remits.

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4. A 16-year-old boy has a history of MDD. He is more of a risk for suicide if which of the following is true:

A. He has had no prior suicide attempts.

B. He has no family history of suicidality.

C. He has a history of substance abuse.

D. He has no history of aggressivity.

E. He has no history of panic attacks.

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5. A 10-year-old boy is being teased at school because he has a learning disorder in reading. After being ridiculed by the class bully, he tells his special education teacher that he feels like he would be "better off somewhere else". After psychiatric evaluation, he is diagnosed with dysthymic disorder. Which of the following statements about his need for medication is true:

A. Because he has mild symptoms, medication is definitely indicated.

B. Because he does not have psychotic symptoms, medication is definitely indicated.

C. Because he does not have "double depression", medication is definitely indicated.

D. Psychotherapy may be tried before a medication trial.

E. He should be given a trial of tricyclic antidepressants.

Question 6

6. **The following statement about SSRI's for the treatment of MDD in youth is true:**

A. There are as many double-blind placebo-controlled (DBPC) studies showing efficacy in youth as there are in adults.

B. There are more than 10 DBPC studies showing efficacy in youth.

C. There are no DBPC studies that show efficacy in youth.

D. There are no DBPC studies that show efficacy in pre-teens.

E. There are fewer than 5 DBPC studies that show efficacy in youth.

Question 7

7. **A 12-year-old boy who has serious MDD and ADHD receives a starting dose of 10 mg of fluoxetine. He becomes edgy and motoric. Which of the following statements is true?**

A. He is very likely to develop manic depressive illness.

B. He is likely to be having “behavioral activation”.

C. His dosage should be increased rapidly to avoid a “switch”.

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A. His sleep is likely to be disturbed.

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9. Wellbutrin SR is being considered to treat MDD in a male teen. Which statement is true?

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B. If he has a history of seizures, bupropion is a good choice since it never is associated with seizure development.

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D. It should not be prescribed in doses greater than 150 mg.

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10. You are preparing a lecture for a lay audience on teen suicide. Which statement is true?

A. Suicide rates have increased more than the rates of MDD in youth.

B. Teen suicide is a leading cause of worldwide mortality in the 15-44 age group.

C. Teens who have access to guns that are kept separate from bullets are at lower risk than those who have access to guns with bullets kept with the weapon.

D. Male teens commit suicide at a higher rate than elderly men.

E. Female teens commit suicide at a higher rate than male teens.

MDD: Prevalence I

- Common Condition
  - Point Prevalence: 2% of children / 4-8% of adolescents
  - Lifetime Prevalence: up to 25% by end of adolescence (Kessler et al. 2001)

MDD: Prevalence II

- Cohort Effect
  - Successive generations after 1940 at greater risk
  - Younger age of onset in more recent generations
  - Increased recognition and diagnostic accuracy
    - Less controversial diagnosis, particularly for children
  - Higher actual rates
    - Biological factors: earlier menarche
    - Putative environmental factors: dietary changes

MDD: Gender and Puberty

- Gender Distribution
  - 1:1 before puberty
  - 2:1 female predominance after, similar to adults
  - Ratio equalizes after menopause

MDD: Age-related changes

- Biological
  - Sexual maturation and hormonal changes
  - Differential ontogeny of neural pathways:
    - Serotonergic pathways mature earlier on
    - Noradrenergic pathways continue development into young adulthood
- Environmental
  - Social and academic expectations
  - Increased exposure to adverse life events, stressors and losses
  - Increased autonomy and abstract thinking

MDD: Clinical Presentation I

- SIGECAPS for 2+ weeks
- Dysthymia: 1 vs 2 year criterion)

– **S**leep Disturbance
– ***I****rritability* (core symptom in youth)
– **G**uilt
– **E**nergy
– **C**oncentration
– **A**ppetite
– **P**sychomotor Agitation or Retardation
– **S**uicidality

MDD: Clinical Presentation II

- Children are not little adults
  - Younger children: more anxiety (especially separation), somatic sxs, auditory hallucinations, temper tantrums and behavioral problems
  - Middle / late childhood: dysphoria, low self-esteem, guilt, hopelessness, “burden on family”
  - Adolescents: sleep and appetite changes, suicidality, neurovegetative sxs, irritability, explosive and conduct sxs and “acting out”, substance abuse

MDD: Clinical Presentation III

- Depression in Preschoolers
  - "Masked" symptoms (somatic sxs, regression, separation anxiety, etc.) appeared as less sensitive and specific manifestations of depression (Luby et al 2003)
  - Depressed preschool children displayed "typical" symptoms of depression more frequently than "masked" symptoms and DSM-IV criteria can be applied to preschool children when modified for age-appropriate symptom manifestations(Luby et al 2003)
  - Significantly less imaginative play (Mol Lous et al 2002)

MDD: Comorbidity I

- Dysthymia ("double depression")
  - Dysthymia as "gateway" disorder
- Anxiety disorders (often precedes depression in youth)
- Disruptive disorders (attention deficit, oppositional defiant, conduct)
- Substance abuse
- Somatoform disorders
- Personality disorders or traits (teenagers)

MDD: Comorbidity II

- Manic Depressive Illness (MDI)
  - MDD may be the first presentation of underlying MDI
  - Mixed states are common in youngsters
  - “Switch” rates are reported to range between 25- 40%
  - Legitimate “switches” may be hard to interpret in the face of treatment or concurrent substance use

MDD: Clinical Course I

- Typical episode duration: 7-9 months
  - Relapse (during remission; 2wks to 2 months) is common (~50%)
  - Recurrence rates (during recovery; after 2 months) are high: 50% by 1 to 2 years / 70% by 5 years
  - Childhood onset MDD has a 60-70% risk of recurrence in adulthood; 20-40% develop bipolar disorder within 5 years (Weller and Weller 2000)

MDD: Clinical Course II

- Protracted, chronic course in ~10% of cases.
  - Earlier onset, number and severity of prior episodes, poor compliance, psychosocial adversity, psychiatric illness in parents, adverse life events

MDD: Clinical Course III

- Disruption in several developmental areas:
  - Social, educational, vocational, cognitive, interpersonal
  - Attachment and relationships with parents and siblings
- Risks often persisting after episode remission:
  - Suicidal behavior
  - Substance abuse
  - Teenage pregnancy
  - Physical illness

MDD and Suicide I

- Suicide risk has increased parallel to rates of MDD
  - 4x increase since the 1950s
    - (2.5 to 11.2 per 100,000)
- {Latest mean worldwide annual rates of suicide per 100 000 were 0.5 for females and 0.9 for males among 5-14-year-olds, and 12.0 for females and 14.2 for males among 15-24-year-olds, respectively} (Pelkonen & Marttunen 2003)
  - 2d (F) and 4th (M) leading cause of worldwide mortality, ages 15-44
    - Only tuberculosis and accidents have higher rates

MDD and Suicide II

- Predisposing factors
  - Previous suicide attempts
  - MDD, MDI, panic attacks, substance abuse
  - Family history
  - Impulsivity / aggressivity
  - Male gender (as opposed to suicide attempts)
- Means: always inquire about firearm availability
  - Keeping guns separate from bullets: false reassurance

MDD: Assessment I

- Clinical history
  - Child, family, school and other sources
- Lifetime mood chart, mood diary
- Standardized clinical instruments (e.g. K-SADS)
- Diagnosis based on all available sources
  - Best-estimate
  - PLASTIC
    - Prospective, Longitudinal, All source, Impairment, Clinical Presentation

MDD: Assessment II

- Rating scales
  - Self
    - Childhood Depression Inventory (CDI, ages 7-18)
    - Beck (BDI, 13-18)
    - Clinical cutoff value for BDI/CDI: 10
  - Clinician
    - Childhood Depression Rating Scale (CDRS-R)
    - Baseline value 17 / Clinical cutoff: 35

MDD: Overall Treatment

- Least-restrictive setting in continuum of care
- Outpatient, home-based, partial hospital, inpatient
  - Suicidal risk
  - Medical, substance abuse and psychiatric comorbidity
  - Family involvement, protective services involvement

MDD: Psychotherapy I

- Psychoeducation
  - "Is it adolescence or is it depression?"
- Cognitive-Behavioral Treatment (CBT, Brent)
  - Cognitive distortions, generalization, overattribution
- Interpersonal Psychotherapy (IPT, Mufson)
  - Areas of loss and grief, interpersonal roles and disputes, role transitions

MDD: Psychotherapy II

- Dialectic Behavioral Therapy (DBT, Linehan)
  - Strategies helpful in treatment of parasuicidal behaviors, comorbid personality dzs (teens)
- Psychodynamic Psychotherapy (Fonagy)

MDD: Psychotherapy III

- CBT most frequently investigated treatment for depression in youth
  - Depressed children and CBT: 4 of 5 child CBT studies demonstrate short-term efficacy; 1 study demonstrated efficacy maintained 9 months later
  - Depressed adolescents and CBT: 7 of 9 adolescent CBT studies demonstrate short-term efficacy

  (Curry 2001)

MDD: Psychotherapy IV

- IPT: 2 controlled studies show efficacy short-term
- Studies needed comparing CBT, medication, and combination treatment in youth with depression

  (Curry 2001)

MDD: Pharmacotherapy I

- Medication may not always be first-line, except:
  - Severe symptoms or suicidal risk
  - Psychotic and certain (non-rapid cycling) bipolar depressions
  - Symptoms prevent participation in psychotherapy
  - Adequate psychotherapy trial ineffective
  - Chronic or recurrent depression

How are SSRIs alike

- More selective than TCAs in blocking reuptake of serotonin
- No fast Na channel acitivity->no QTc changes, low side effects of seizures, relatively safe in overdose

MDD: Pharmacotherapy I

- TCAs generally not effective
- Tremendous increase in SSRI usage from 1984->1996 in different sites, between 3.6-to-10.4 fold (Zito 2000)
- FDA approval for fluoxetine in treatment of depression, but new wording for product information.
- Recent DPPC trial for sertraline
- Paroxetine FDA “talk paper” warning and British “FDA” warnings
- Venlafaxine “Dear health professional letter” and British “FDA” warnings

Fluoxetine

- Fluoxetine: FDA approved for treatment of depression in Youth
- 3 published randomized, placebo-controlled studies
  - Simeon et al.1990: NEGATIVE study N=40, age 13-18, dosing 60mg qd, 8 weeks
  - Emslie et al. 1997: superior to placebo N=96, age 7-17, dosing 20mg qd, 8 weeks
  - Emslie et al. 2002: superior to placebo
    N=219, age 8-17, dosing 20mg qd, 8 weeks Effects modest and not all outcome measures positive--- Remission 41% v 20 % placebo
    - Available: Prozac 10 (scored) tab, 10/20/40 caps; 20/5ml oral soln. Dose range 2.5-20 QAM (40-60 OCD)
    - Prozac Weekly 90mg caps= 20 mg/day. No safety data in youth.

FDA Changes for Fluoxetine

- Effectiveness established in patients 7-17 years of age for OCD
- Effectiveness established in patients 8-17 years of age for MDD
- Decreased weight gain has been observed in association with the use of fluoxetine, as with other SSRIs. In one 19-week clinical trial pediatric subjects treated with fluoxetine gained an average of 1.1cm less in height (p=0.004) and 1.1 kg less in weight (p=0.008) than those treated with placebo. Therefore, height and weight should be monitored periodically in pediatric patients treated with fluoxetine.
- Mania/hypomania led to discontinuation of 1.8% of fluoxetine treated patients vs. 0% of placebo controlled patients in the three placebo-controlled trials combined. Regular monitoring for the occurrence of mania/hypomania is recommended
- Higher average steady state fluoxetine and norfluoxetine concentrations were observed in children than in adolescents. These differences were almost entirely explained by differences in weight.
- Separate dosing recommendations in lower weight children

SSRIs II

- Paroxetine
- Single dose half life 11.1 hrs v 21 hrs adults (Findling 1999)
- FDA “talk paper” against the use of paroxetine for youth with depression under the age of 18 years after UK -based on 1134 OCD patients in which no efficacy and emotional lability (crying, mood fluctuations, suicide thoughts) 3.2% v 1.5% placebo
- In Keller 2001, only 1 of 2 outcome measures positive, 11 dropouts for emotional lability, suicidality or hostility v 5 for IMI and 2 for placebo.

Available: Paxil 10 (scored), 20 (scored), 30, 40 tab; 10/5ml oral susp. Dose range: 10-30 QHS

Paxil CR 12.5, 25, 37.5 tab. No safety data in youth. Paxil CR has reduced absorption rate compared with Paxil IR. May improve tolerability.

PAROXETINE STUDIES

- N=275, 8 wks, 3 Arms with supportive psychotherapy, 20-40 mg: 66% improved v 52% IMI and 48% Placebo (Wagner 1998)
- Negative study-Milin 1999
- 3 Arms, 20-40 mg, 63% improved v 50% IMI v 46% Placebo <HAM-D< or+ 8, CGI 1 or 2 not HAM-D total or mean CGI (Keller 2001)

SSRIs III

- Citalopram: 1 unpublished randomized, placebo-controlled study
  - Paul Tiseo PhD, 2001 (cited in Findling et al. 2002)
  - Superior to placebo
  - N=178, age 7-17, dosing 20-40mg qd, 8 weeks
    - Available: Celexa 10, 20 (scored), 40 (scored) tabs; 2mg/ml oral soln. Suggested dose range 10-30 qd.
    - Lexapro 10 (scored), 20 (scored) tab. No safety data in youth. Pure S-enantiomer (single isomer) of the racemic bicyclic phthalane derivative citalopram. Lexapro's advantages over Celexa unclear .

SSRIs -SERTRALINE

- new DBPC study n=367, flexible dose of 50-200 mg, 69% v 59% placebo improved 40%CDRS;treatment effect size modest, with children showing a borderline statistical difference
- 24% n=46 discontinued the study
- 17 AEs of whom 13 were children
- 2 suicide attempts, 3 suicide ideation 1 aggression 6/185 (3.2%) v 2 suicide attempts in placebo 2/179 (1.1%)
- Mean dose of 131mg (Wagner 2003)
  - Pharmacokinetic study in teens- mean half life at 50 mg was 15.3 hrs, 100-150mg =20.4 hrs (Axelson 2002)
  - FDA Indication for juvenile OCD (ages 6-17)
    - Available: Zoloft 25 (scored), 50 (scored), 100 (scored) tabs; 20mg/ml oral conc. Dose range 25-200 qd.

SSRIs V

- Fluvoxamine: no randomized placebo-controlled study
  - 2 open-label prospective studies: all show improvement
  - Indication for juvenile OCD (ages 8-17)
    - Available: Luvox 25, 50 (scored), 100 (scored) tabs. BID dosing. Dose range: Age 8-11: 50-200 daily; age 12-17:100-300 daily.

SSRIs: Side Effects

- ABCs of SSRIs
  - **A**ctivation / **A**kathisia
  - **B**ipolar switching
  - **C**ytochrome P450-based interactions. Common:
    - FLUOX / PAR: CYP 2D6 (⇑TCAs)
    - FLUV: CYP 2C9 (⇑Phenytoin)
    - FLUV: CYP 1A1/2 (⇑Theophylin)
  - **D**iscontinuation syndrome
  - **E**volving Psychopathology

Nefazodone

- Hepatic failure rate in patients treated with nefazodone is 3-4 times estimated background rate of liver failure. True risk may be considerably higher secondary to under-reporting. (PDR 2003)
- Removed from some European countries

Venlafaxine

- Letter 8/2003 No efficacy in children for MDE or anxiety. Increased S/Es of hostility, suicidality 2% v 0-1% placebo
- Only published study n=40, low dosing, Negative (Mandoki 1997).
- Dual mechanism of action / dose-dependent
  - Low dose (<150mg): SSRI
  - High dose (>200): SSRI + SNRI
- May be useful in ADHD
- Systemic hypertension dose-related
    - Available: Effexor 25, 37.5, 50, 75 & 100 tabs (all scored); TID dosing. Effexor XR 37.5, 75, 150 caps; QAM dosing. Limited safety data in youth.

Bupropion

- No data in youths with MDD; Mechanism: NDRI?
- In minors, best studied as ADHD non-stimulant alternative
- Lower switch rate reported in adults; tic exacerbations
- Contraindications: untreated seizures and bulimia nervosa Seizure risk 0.1% to 0.4%; likely dose-dependent effect:
  - IR: Maximum daily dose 250-300/d in minors; never prescribe >150/dose or <6hrs between doses
  - SR: Maximum daily dose 300/d in minors; never prescribe >200/dose or <8hrs between doses
    - Available: Wellbutrin 75 & 100 tabs; TID dosing. Wellbutrin SR 100, 150, 200 tabs; BID dosing.

Mirtazapine

- No empirical data in youth.
- Unique mechanism: alpha-2 presynaptic + 5HT2A/3 postsynaptic antagonism
  - Net effect: ⇑ NOR ⇑ 5HT1A
- Marked somnolence and appetite/ weight increases (“sleepy whale”)
- Somnolence: peaks at *lower* doses ***(7.5mg sleeper)***
  - Available: Remeron 15 (scored), 30 (scored), 45 tabs. Remeron SolTab 15, 30, 45 tabs (not easily cut…disintegrates). No published safety data in youth.

MonoAmine Oxidase Inhibitors (MAOIs)

- Traditional agents: irreversible and non-specific
  - Phenelzine* (Nardil), Isocarbozacide (Marplan) & Tranylcipromine (Parnate)
  - Tyramine reaction + dietary restrictions
  - Serotonin syndrome: long “moratorium” before introducing 5HT-enhancing agents
- Renewed interest in reversible / selective agents
  - RIMAs (moclobemide, brofaromine): MDD, GAD
  - RIM-B (selegiline*)

Electroconvulsive Treatment (ECT)

- Last resort treatment
- Perhaps under-utilized, especially in psychotic or seriously suicidal cases. Geographic variation:
  - Not permitted in certain states (e.g. Texas)
  - Parental consent, patient assent and 3 expert opinions needed (e.g. CT)

ECT II

- Safety and acceptance of treatment well established
  - Meta analysis of close to 400 cases (Walter & Rey 1997)
- No clear consensus for minors:
  - Unilateral (⇓ memory loss) *vs*
  - Bilateral (⇓ total treatments)
- No controlled studies

Novel Antidepressants and Future Directions I

- Substance P receptor antagonists
  - Serendipitously discovered
    - MK-869 studied as a (failed) central analgesic
    - Antidepressant comparable to paroxetine (n=68 adults)
  - Solubility and bioavailability still problematic

Novel Antidepressants and Future Directions II

- Corticotropin-Releasing Hormone Antagonists
  - CRH: Central mediation of hypercortisolemia, dexamethasone non-supression
  - Direct neuroregulatory effects at limbic level
  - Early traumatic events (e.g maternal separation) can have long-lasting effects on CRH regulation
    - Potential for biological interventions early in life
    - Novel mechanism of action / pathogenesis
- rTMS and CVNS: No data or FDA approval

MDD Algorithm I

- Texas Children's Medication Algorithm Project
- http://www.mhmr.state.tx.us/centraloffice/medicaldirector/mddalgo.pdf
  - Largely based on expert consensus rather than empirical support (JAACAP 11/99)
  - 1 & 2: SSRI 1 & 2
  - 3: Alternative class monotherapy
    - (VLF, NEF, BUP, TCA, MIR)
  - 4 & 5: Combinations
    - (e.g. "Wellzac") or Li+monotherapy
  - 6: MAOI
  - 7: ECT

MDD Algorithm II

- Augmentation, combination
  - Limited empirical data
  - Lithium augmentation: 1 open-label prospective
    Strober et al. 1992: Imipramine + Li helpful
    N=24, mean age 15.4, dosing variable, 3 weeks
  - Lamotrigine augmentation: retrospective study
    Carandang et al., in press, 2003
    LTG augmentation helpful for refractory depression
    N=9, ages 14-18, dosing 25-200mg daily 1 patient developed benign rash

MDD Algorithm III

- Maintenance
  - Single episode: 6 - 12 months?
  - Multiple or severe episodes: 1 - 5+ years?
  - Similar agents and dose, as tolerated
- Weigh exposure risks to those of untreated illness
- Alliance with youth and family

Post Lecture Exam
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D. Male teens commit suicide at a higher rate than elderly men.

E. Female teens commit suicide at a higher rate than male teens.

Answers to Pre & Post Competency Exams

1. D
2. E
3. D
4. C
5. D
6. E
7. B
8. D
9. D
10. C