# On the Frontlines: Pediatric Major Depressive Disorder

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# Disclosure

In the past 12 months, I have had no relevant financial relationships with the manufacturers of any commercial product or providers of commercial services discussed in this CME activity. I do not intend to discuss an unapproved or investigative use of a commercial product or device in my presentation.

# Learning Objectives

At the conclusion of this session, participants will be able to:

- Understand the diagnosis of Major Depressive Disorder and other depressive illnesses in the pediatric population.
- Understand developmental differences in depression between children, adolescents and adults.
- Understand the types of treatment for pediatric depression.
- Understand current literature on depression treatment in the pediatric population.

# “Types” of Depression

- Major Depressive Disorder
- Dysthymic Disorder
- Depressive Disorder NOS
- Bipolar I Disorder
- Bipolar II Disorder
- Bipolar Disorder NOS
- Adjustment Disorder with Depressed Mood

# Epidemiology

- MDD prevalence- 2% children, 4%-8% adolescent
- 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% adolescent.
- Often under-recognized.

# 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.

# 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.

# Depressive Disorder NOS

- "Everything Else"
- Still significantly effects Function.
- More common to Diagnose in Children.

# Dysthymic Disorder

- Chronic low levels of depression.
- Can be combined with Major Depressive Episodes – “Double Depression”.
- Temperament versus Biology – Is there a choice to Pessimism?

# Bipolar Disorder

- Concept of Bipolar vs. Unipolar Depression.
- Bipolar I requires Mania.
- Bipolar II requires Hypomania and Major Depressive Episode.
- Most difficult morbidity with Depressive symptoms.

# 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.

# Differences in Adolescent Depression

# Differences in Adolescent Depression.

- More irritability.
- Developmental factors of being a teenager – anhedonia is a key.
- Think depression with physical ailments and/or sleep disturbance.
- Think depression with sudden school, extracurricular or social changes.
- Social/interpersonal difficulties leading to self-esteem issues and isolation.

# *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

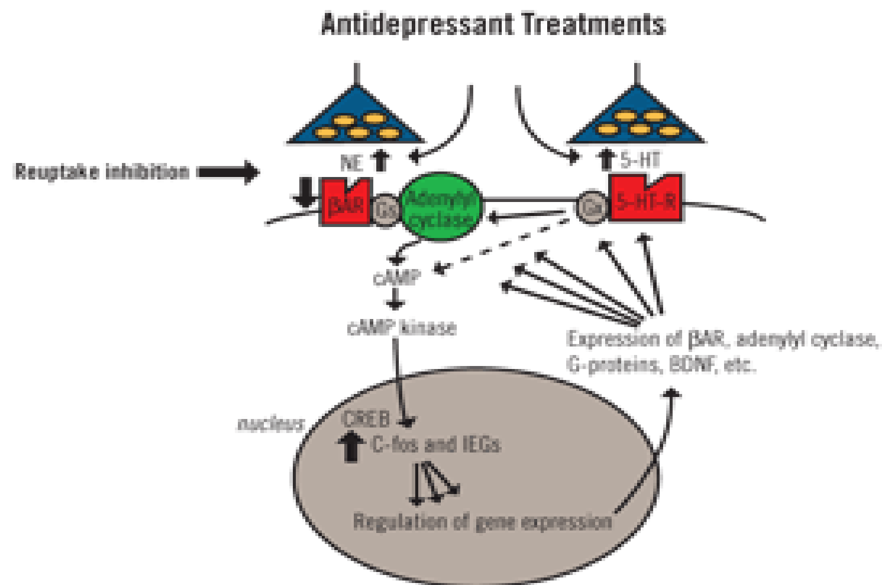
# Treatments for Depression

- Psychotherapy or “Talk Therapy” – Data for CBT and IPT.
- Medications
  - SSRI (Prozac, Paxil, Zoloft, Luvox, Celexa/Lexapro)
  - SNRI (Cymbalta, Effexor/Pristiq)
  - Other (Wellbutrin, Remeron)
  - Tricyclic (Nortriptyline, Amitriptyline)
  - MAOI (Nardil, Parnate)
- Combination better than either one alone.

# Why do Antidepressants take so Long?

FIGURE 1

**ANTIDEPRESSANTS PROMOTE SYNTHESIS OF NEUROTROPHIC FACTORS VIA SECOND MESSENGER-MEDIATED ALTERATIONS IN GENE TRANSCRIPTION[56]**




NE=norepinephrine; 5-HT=serotonin; Gs=glutamine synthetase; Gx=glycine xylidine; cAMP=cyclic adenosine monophosphate; βAR=β-adrenergic receptor; BDNF=brain-derived neurotrophic factor; CREB=cAMP response element-binding; C-fos=transcription factor; IEG=immediate early gene.

Lydiard BR. *Primary Psychiatry*. Vol 14, No 4. 2007.

# Questions to ask in reading Depression treatment clinical studies.

- Who sponsored the Study?
- What is the study designed to answer? Is the study double-blinded and placebo-controlled?
- What is the length of the study, and was the medication adequately dosed?
- What is the type and number of participants?
- What measures did they use to indicate response? (what about remission?)
- What is application to everyday clinical practice?

# Treatment of Adolescent Depression Study (TADS)

- Examine 3 Treatment modalities for Adolescent Major Depressive Disorder.
  - Combined (CBT and Fluoxetine)
  - Medication only (Fluoxetine)
  - CBT only (Cognitive Behavioral Therapy)
  - Placebo only (Sugar Pill)

# A Closer Look at TADS

- Done by NIMH = Less Bias.
- Double blind to medicines with Raters Blinded.
- Designed to evaluate short term (12 weeks) and  Longer-term (36 weeks) effectiveness of treatments.
- Dosing 10-40mg of Fluoxetine.
  - Mean dosing 28.4mg in COMB, 33.3 in FLX

# Type and Number of Participants in TADS

- N = 439 (12-17y/o with Dx. of MDD)
- Average age was 14.6 years
- 45.6% Male, 73.8% White, 12.5 AA, 8.9% Hispanic.
- 96% fell into moderate to severe range of MDD.
- 86% single episode – Avg. duration 71.6 weeks.
- 51.9% with Comorbid Psychiatric Disorder.
- Modal Family income 50-74k
- Overall Good representative Sample

# Take home message of Results

**COMB>FLX>CBT≥Placebo**

# Remission in TADS?

- Remission is CDRS-R of ≤28
- By week 12 – 23% of all participants in remission.
- COMB (37%), FLX (23%), CBT (16%), PBO (17%)
- Residual Symptoms = Mood, Fatigue, Concentration and Sleep.
- Length of TX and Polymorphic nature of Depression.

# Question of Drug Safety

- Fluoxetine is safe and effective in treatment of Adolescent MDD.
  - **NNT = COMB (3), FLX (4), CBT (12) Pooled FLX (3.7)**
  - **NNH (Suicidal event) = COMB(50) FLX (43)**
  - **NNH (Completed Suicide) = FLX 20,000 for boys and 180,000 for girls**
    - No completed suicides in FDA or TADS
    - In 2004 – year of Black Box warning = increased Teenage Suicide Rate of 18.2% with previous steady decline.

# Application to Clinical Practice

- Fluoxetine with CBT is better!
  - Higher response and remission rates.
  - 1.5X greater response rate than meds alone.
  - CBT is protective.
    - Suicide event rates = FLX (9.2%), COMB (4.7%), CBT (4.5%)

# Treatment Resistant Study

- NIMH funded multicenter study “Treatment of Resistant Depression in Adolescents” (TORDIA).
- 334 Adolescents 12-18 with non-response to 2 month course of SSRI randomly assigned to one of 4 interventions.
  - Switch to another SSRI—paroxetine (Paxil), citalopram (Celexa) or fluoxetine (Prozac).
  - Switch to a different SSRI plus cognitive behavioral therapy (CBT).
  - Switch to venlafaxine (Effexor)—another type of antidepressant called a serotonin and norepinephrine reuptake inhibitor (SNRI)
  - Switch to venlafaxine plus CBT

# TORDIA

- 54.8% who switched to either type of medication with addition of CBT responded.
- 40.5% of those who switched to another medication alone responded.
- No differences between different SSRI medications, or between SSRI and SNRI.
- Generally first choice is SSRI because it is better tolerated.

# 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%

# Thank You.

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"I have a family history of mental illness. My sister had a case of Beatlemania and my brother was cuckoo for Cocoa Puffs."