MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Juvenile Depression

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Disclosures 2020-2021

My spouse/partner and I have the following relevant financial relationships with commercial interests to disclose:

- *Research support:* Genentech, Headspace Inc., Pfizer Pharmaceuticals, Roche TCRC Inc., Sunovion Pharmaceuticals Inc., Takeda/Shire Pharmaceuticals Inc., and Tris.
- *Consulting fees:* Akili, Avekshan LLC, Jazz Pharma, and Shire/Takeda
- *Honorarium for scientific presentation:* Tris
- *Royalties paid to the Department of Psychiatry at MGH, for a copyrighted ADHD rating scale used for ADHD diagnoses:* Biomarin, Bracket Global, Cogstate, Ingenix, Medavent Prophase, Shire, Sunovion, and Theravance
- Through Partners Healthcare Innovation, I have a partnership with MEMOTEXT to commercialize a digital health intervention to improve adherence in ADHD.

Phenomenology of Major Depression(MDD) in Youth

Pediatric MDD

- Pediatric MDD is prevalent (5%), chronic, and morbid
- Prevalence increases with age
- Male preponderant in prepubertal children
- It is highly comorbid with anxiety disorders, ADHD, other disruptive behavior disorders (ODD and CD) and many other disorders (i.e, Eating disorders, PTSD)

Pediatric MDD

- High risk for suicide and **suicide remains a leading cause of death in the young**
- Although can coexist with adjustment disorders, it needs to be distinguished from it
- Avoid mistaking MDD with “adolescence turmoil”

Pediatric MDD

- MDD emerges insidiously over many years often starting in preschool years
- **Importance of considering subsyndromal manifestations**

DSM 5 Diagnosis

- Criteria for pediatric mood disorders are the same as for adults except dysthymia only requires one year instead of two

Developmental Differences

- Prepubertal MDD is male preponderant
- When irritability is considered, prevalence is similar in adolescents of both sexes

Developmental Differences

- Irritable mood instead of depressed mood is the most common mood disturbance
- Mood tends to be variable and reactive
- Somatic complaints (e.g, stomach aches, headaches)
- “Somatic Disguise” (Leon Eisenberg)”: burden of existing medical illness is highly exaggerated (e.g, mild asthma associated with school refusal)
- anxiety, withdrawal, sad appearance, poor self-esteem
- Behavioral problems, psychomotor agitation

Developmental Differences

- Anhedonia, psychomotor retardation/agitation, hopelessness
- Negativistic, oppositional behaviors, restlessness, aggression, social isolation, school difficulties, substance abuse (in teens)
- Death wishes, suicide attempts and suicide
- Impairment of functioning
- Atypical symptoms are the rule
- Mood reactivity and variability
- Neurovegetative symptoms less common

Etiology

- 50% of the variance in the transmission of mood disorders is genetic
- Having one parent with MDD doubles the risk for child (both parents depressed quadruples the risk)
- Psychosocial factors including family conflict, single parent homes, abuse or neglect, poverty, recent stressor or loss contribute to the risk

Comorbidity

- 40% to 70% have comorbid disorders
- Most common comorbid disorders are:
  - Anxiety Disorders (30% - 80%)
  - ADHD and disruptive behavior Disorders (40% 80%)
  - Substance Abuse (20% - 30%) (in adolescence)
- Psychosis occurs in 25% of youth with MDD When it occurs suspect bipolarity

Sequelae

Increased risks for later adolescence and adulthood:

- **Bipolar disorder**
- **Suicidal behavior**
- **Homicidal behavior**
- **Abuse and Addictions**
- **Impaired interpersonal relationships**
- **Academic deficits**
- **Increased physical problems**
- **Early pregnancy**
- **Impairment in global functioning**

Course

- Recurrence of Major Depression is common:
  - 40% by 2 years, and 70% by 5 years
- Development of Bipolar is also common:
  - 20% to 40% of adolescents with MDD develop Bipolar disorder within 5 years of onset of MDD

Predictors of Manic Switches

- Predictors of manic switching:
  - family history
  - psychomotor retardation
  - psychosis
  - rapid onset of depression
  - earlier onset of depression
  - Severity of depression
  - atypicality
  - affective storms- tantrum quality
  - Activation by antidepressants and stimulants
  - No antidepressant uniquely “safe”

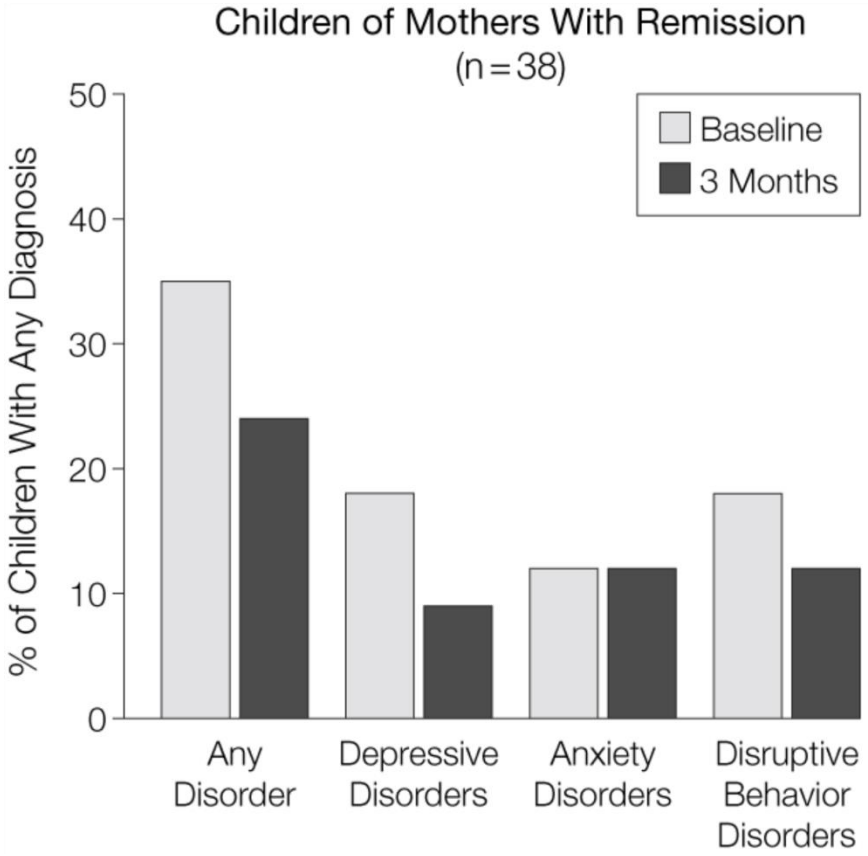
The Conundrum of Disruptive Mood Dysregulation Disorder (DMDD)

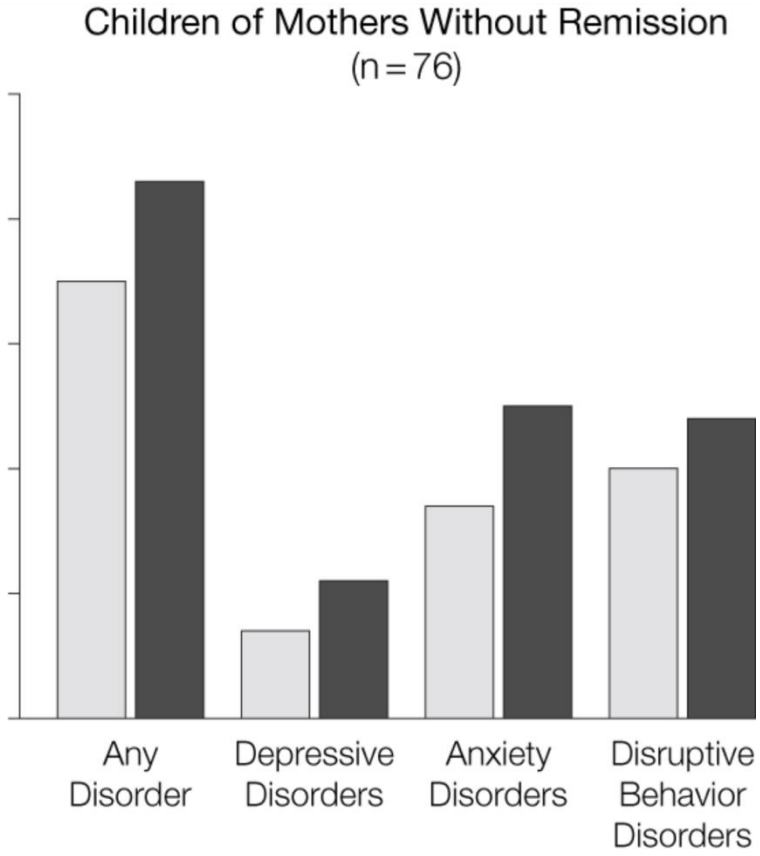
- DMDD was added to DSM-5 by committee concerned with the increase in diagnosis of pediatric bipolar disorder
- This is a political decision and not a clinical one
- Was designed to capture children with chronic, non-episodic irritability and temper tantrums but without mania
- DMDD has no evidence of validity and it is impossible to distinguish it for atypical forms of pediatric BP disorder

Treatment Considerations

- Treat early and aggressively
- Treat co-morbidity
- Psychopharmacology: Antidepressants
- CBT: 5 positive and 1 negative trial to date in children and 6 positive and 1 negative in adolescents
- Consider hospitalization if suicidal or dangerous

Treating Mothers?





Caveat

- **Do not blame the mother for the child's depression**
- Mothers do not cause depression in their children
- Pediatric depression is neurobiological disorder of genetic etiology

Psychopharmacology

- ***SSRIs, SNRIs, Atypical Antidepressants*** favored in practice due to relative safety in overdose and lower side effect burden
- ***TCAs*** generally avoided due to potential lethality and side effect burden
- ***MAOIs* to be avoided;** 80% of adolescents do not comply with dietary restrictions
- **Combined pharmacotherapy common**
- **Augmentation strategies**

Evidence: Antidepressants

- **Fluoxetine and Escitalopram** are the only FDA approved agents

Treatment of Adolescent Depression Study (TADS)

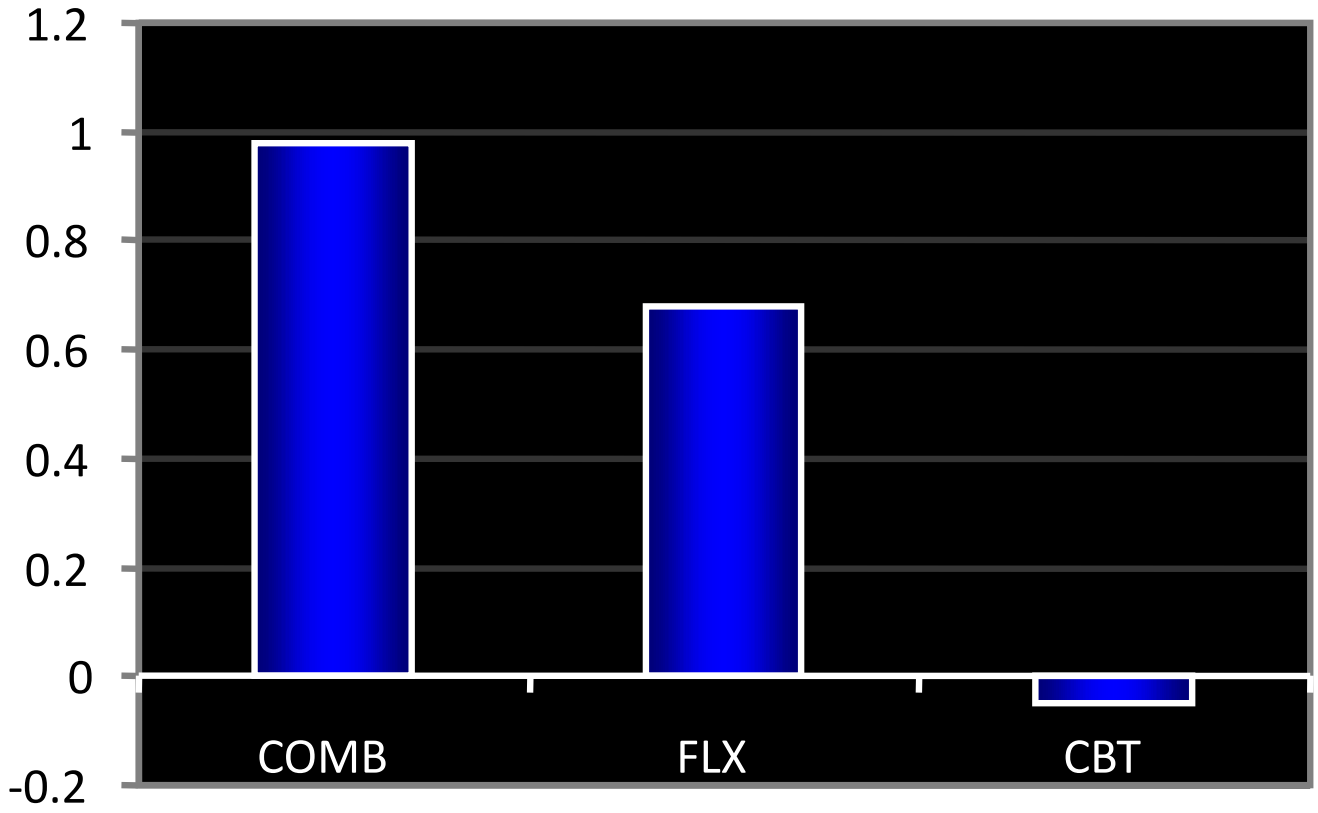
- NIMH sponsored multi-center controlled clinical trial
  - 13 sites
- 12-17 year olds with MDD
  - N=439
- Aim to compare efficacy of fluoxetine, CBT, combination, & placebo over 36 weeks with 1 year follow-up.
  - Fluoxetine 10-40 mg/day

March et al., JAMA, (2004) 292 (7):807-820

TADS

- TADS study assessed fluoxetine alone, fluoxetine + CBT, and CBT alone
- Rates of improvement:
  - 71% for combo
  - 61% for fluoxetine alone
  - 43% for CBT alone
  - 35% for placebo

Treatment of Adolescent Depression Effect Size for CDRS (ITT)



March et al. *JAMA*. (2004) 292 (7):807-820.

Treatment of SSRI-Resistant Depression in Adolescents (TORDIA)

- Adolescents (12-18) who failed 8 weeks of SSRI
  - N=334 patients; 6 centers
- Randomized to 12 weeks of switch to
  - Another SSRI
    - Paroxetine, citalopram or fluoxetine (20-40 mg)
  - Another SSRI + CBT
  - Venlafaxine (150- 225 mg)
  - Venlafaxine + CBT
- CBT 9 times in 12 weeks

Brent et al. JAMA 2008

TORDIA

- Higher response rate to switch to
  - New Medication + CBT (54.8%) vs.
  - New Medication alone (40.5%)
- No difference in response rate to switch to
  - Venlafaxine (48.2%) vs.
  - Second SSRI (47%)
    - No difference between the SSRIs
- No difference between treatments in
  - Adverse events
  - Self harm or suicidal adverse events
  - 17 subjects attempted suicide; no completers

Brent et al. JAMA 2008

Black Box Warning

Black Box Warning

"Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Drug Name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Drug Name] is not approved for use in pediatric patients…"

Black Box Analyses

- Examined Suicidality in 4,582 cases in 24 controlled clinical trials on all antidepressants in pediatric patients.
  - Text search with blind recoding
  - Risk ratio for depression trials 1.66
  - Risk difference 0.02 (excess of 1-3 patients/100)

Hammad et al. AGP, 2006
Simon et al., Am J Psychiatry 163:41-47, January 2006
Bridge, J. A. et al. JAMA 2007;297:1683-1696

FDA issues Black Box Warning: Suicide Risk with Antidepressant

- 78 out of 4,400 cases in controlled clinical trials on all antidepressants in pediatric patients suffered increases in suicidal ideation and/or self-harm
  - 52 patients (3.8%) randomized to medications
  - 26 patients (2.1%) randomized to placebo
- No patients committed suicide or seriously harmed self

AACAP Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Advisory Committee September 28, 2004

FDA

- September 2004,FDA reported increase in suicidality
  - Defined as
    - new onset SI
    - worsening of SI
    - new or increased suicidal behaviors
  - 3.8% on SSRIs v 2.1% on placebo

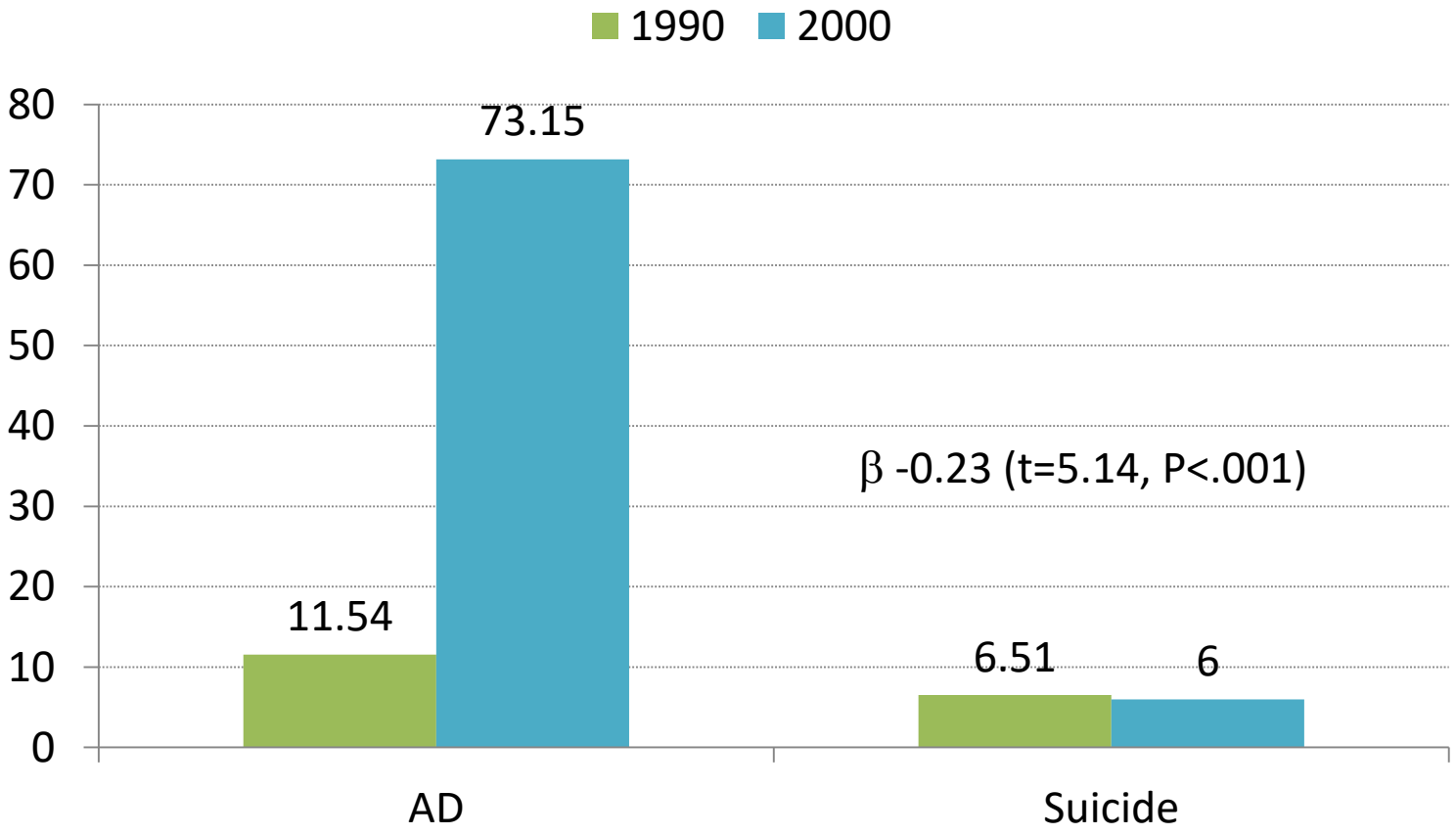
FDA

- Limitations
  - Post-hoc analyses, multiple sub-analyses
    - none of original 24 studies were designed to evaluate this
  - Few events of “suicidality” (78/4400) despite threshold
  - Substantial differences between studies in classification
  - Nonadherence not considered
  - Patients with severe pathology excluded
  - Increasing number of sites rapidly to accelerate trial
  - Aggressive advertising to recruit patients
  - Age of participants
  - No increase in suicidality on clinician rating scales
  - No patients committed suicide or seriously harmed self

Black Box Revision

- February 2005
  - FDA altered warning
    - No “causal” relationship had been detected
    - Conclusion based on short-term studies
    - No suicides occurred in any of studies

Antidepressant Medication and Suicide in Adolescents



AD= Antidepressant rate per 1000 Medication Users

Olfson et al., (2003) AGP 60 (10): 978-982

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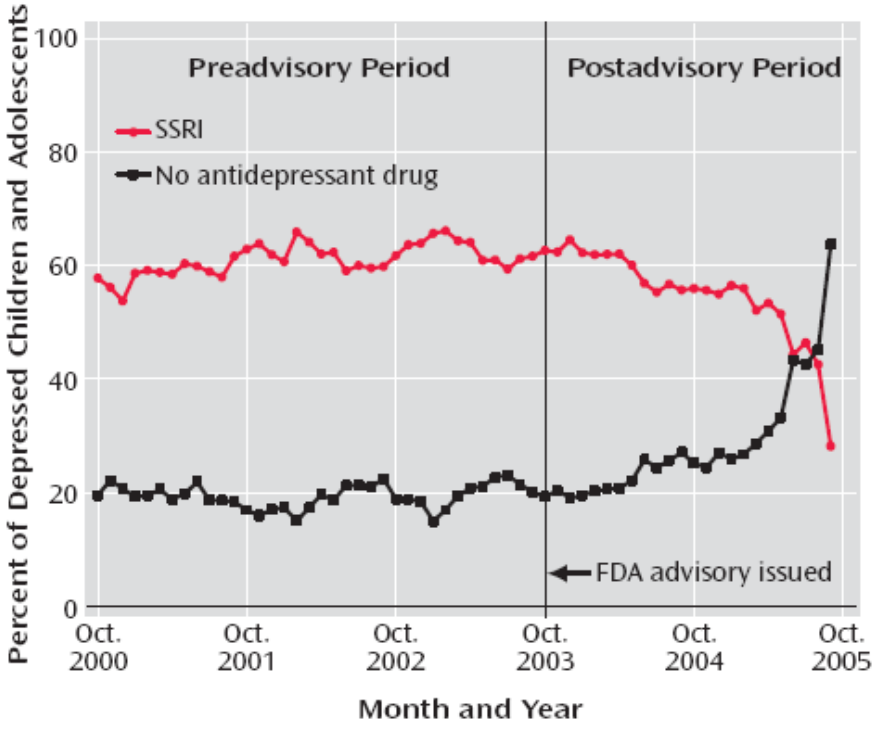

SSRI prescriptions for pediatric patients fell after the first FDA advisory on suicidality risk **(Libby et al., p. 884)**

Pediatric Depression Treatment Declines After FDA Advisory on Antidepressants

Diagnoses of new cases of major depression in children and adolescents, and their antidepressant treatment, declined sharply over the 2 years following the first Food and Drug Administration (FDA) advisory about suicidality risk for pediatric patients taking selective serotonin reuptake inhibitors (SSRIs). Decreases in SSRIs and non-SSRI antidepressants for depressed patients ages 5–18 are shown by claims in a national database of managed health care plans analyzed by Libby et al. (p. 884). Psychotherapy did not increase after the advisory. This comparison of the 5 years before the FDA advisory in October 2003 with the 2 years afterward encompassed more than 65,000 children and adolescents with a new diagnosis of major depressive disorder. In addition, population-level depression rates fell in 2005 after steadily increasing. Dr. Cynthia Pfeffer comments on these trends in an editorial on p. 843.

Am J Psychiatry 164:38A, June 2007

Autopsy Studies of Suicide Victims

- 151 youth suicides studied in Utah
  - Of 137 with toxicology, only 4 with detectable levels of AD, AP, or MS
- 41 youth suicides studied in NYC, 1999-2002
  - Of 36 with toxicology, only 1 AD detected
- 1419 adult suicides studied in NYC, 2002-2004
  - 13.9% of young adults (18-24 years) had AD present on toxicology

Gray DB, et al. *J Am Acad Child Adolesc Psychiatry*. 2002;41:427-34;
Leon AC, et al. *J Am Acad Child Adolesc Psychiatry*. 2006;45:1054-8;

Leon AC, et al. *J Clin Psych*. 2007;9:1399-403.

Treatment Considerations

- Frequency of visits
- SSRIs remain first line
- Start low and increase slowly
- Diligent attention to deteriorations in mood/ manic switching
- Treat comorbidity

Combined Pharmacotherapy

- Simple cases: monotherapy could be sufficient and should be preferred
- Complex cases: monotherapy may be insufficient and combined pharmacotherapy needs to be considered

Indications for Combined Pharmacotherapy

- Comorbidity
- Treatment resistant cases: Augmentation
- Treatment emergent adverse effects
- Poor tolerability with therapeutic doses of individual medicines

Wilens et al. JAACAP. 1995 Jan;34(1):110-2

Treatment Approaches Summary

- Mild forms of MDD – therapy/CBT
- Moderate to severe MDD– antidepressants alone or combined with therapy/CBT
- Pharmacological options: Monotherapy if possible, combined pharmacotherapy, augmentation strategies
- Address Comorbidities
- Risk for manic switches
- ECT and Ketamine for TRD
- Continue antidepressants for I calendar year after remission
- Slow taper when discontinuation is considered

Conclusions

- Depression in children & adolescents is common, morbid, and chronic but also identifiable and treatable
- Psychotherapy acceptable in mild cases
- Based on FDA meta-analysis, share with families
  - there is a 2-4% of SI vs. 1-2% on placebo.
  - TADS study shows 60-70% chance of improvement of MDD with medication treatment alone
  - increase in agitation or uncharacteristic behavior change or Suicidal/Self-Injurious Thoughts/Behaviors **suggest manic activation**

Conclusions

- Fluoxetine and Escitalopram are the only FDA approved to treat MDD in Children and Adolescents (although may have good reason to use others)
- Educate families to watch for and report
  - increase in agitation or uncharacteristic behavior change or Suicidal/Self-Injurious Thoughts/Behaviors and how to get help if concerned

Thank you!