Diagnosis and Treatment of Depression in Children and Adolescents

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Disclosures

• Present (2008-2009 state fiscal year)
  – Research grant to UTHSCSA- Ortho McNeil Janssen Scientific
• Past years
  – Speakers bureau: Shire, McNeil Pediatrics
  – Consultant: Shire, McNeil Pediatrics
  – Research grants: Eli Lilly, Astra-Zeneca, Shire

Objectives

• Discuss the prevalence (current and lifetime) of depression and suicidal ideation in children and adolescents
• Discuss how depression presents in children and adolescents, with particular reference to the differential diagnosis of irritability
• Define the level of severity of depression appropriate to treat in a primary care setting
• Discuss the use of both pharmacological and psychosocial intervention for depression in children and adolescents

Depressive Disorders

• Major depressive disorder- at least 2 weeks of pervasively depressed mood
  – Single Episode
  – Recurrent
• Dysthymia- a year depressed “nearly every day”
• Adjustment disorder with depressed mood
• Point prevalence
  - 1-2% of prepubertal children
  - 3-8% of adolescents

• Lifetime prevalence
  - 20% of adolescents will have met criteria for a depressive episode at least once in their lives by age 18
  - Females more at risk post-puberty


Detecting depression in children and teens

• Sadness vs. Irritability as the core symptom of depression in children and teens

• Irritability is also a major symptom of
  - Oppositional Defiant Disorder (ODD)
  - Mania
  - Mixed States (Bipolar with mood state of mixed depression and euphoria/Irritability)

Types of Irritability

• ODD-type
  - Brief episodes of anger related to frustration, mood returns to normal as soon as frustration passes. Child often denies that he “ever” feels sad or grouchy. Parent reports temper outbursts as being depressed

• Mad-Cranky
  - “Slow burn”- Child has prolonged negativity not related to stresses in life- “in a bad mood”, pessimistic, has blow ups but they are related to “having a bad day” rather than a specific frustration- unipolar in nature

• Super angry/Grouchy
  - Explosive rages, intermixed with silliness, excitement,

Types of Irritability

• Key question- what are the associated affective disorder symptoms associated with the irritability?

• Depressive Disorder (SIGECAPS)
  - Sleep, Interest Loss, Guilt, Energy Loss, Concentration loss, Appetite Loss, Psychomotor retardation, Suicidal ideation

• Mania
  - Less Sleep, Odd Interests, Excessive self confidence, High Energy, Distractibility, Increased sexual interest, Psychomotor agitation, Grandiosity

• Family History – Mania or Depressive Episodes?
**Understanding Comorbidity**

**Children**
- ADHD
- DEP
- ODD/CD

**Adolescents**
- ADHD
- DEP
- ODD/CD

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**Timeline of Comorbidity**

- ADHD almost always presents before depression
- Demoralization vs. True Depression
  - ADHD children become discouraged and dysphoric due to life failures
  - Depression is always related to school/conflict with parents
  - Depression resolves on school breaks, does not meet full MDD threshold
  - Absence of SIGECAPS
  - May well resolve with treatment of ADHD

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**Available treatments**

- Psychosocial
  - Cognitive Behavioral Therapy (CBT)
  - Interpersonal Psychotherapy (IPT)
  - Family/Group Therapy
- Pharmacotherapy
  - Specific Serotonin Reuptake Inhibitors (SSRI)
  - Bupropion
  - Non SSRI’s (venlafaxine, duloxetine)
- Which, if any, should be considered “first line”?

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**Cognitive Behavioral Treatment**

- Psychoeducation and mood monitoring: Providing parents and youths information about the course and characteristics of depression and of the CBT model of treatment, teaching youths to monitor their moods, thoughts, and behaviors to begin to see patterns.
- Pleasant activity scheduling and behavioral activation: Promoting engagement in activities that provide opportunities for mastery or pleasure, both for short-term mood regulation (e.g., pleasant activity scheduling) and to promote a long-term focus on creating a rewarding, non-stressful, and mood-lowering environment (e.g., newer behavioral activation strategies).
- Cognitive restructuring: Helping youths to examine their automatic thoughts and core schemas and assess the accuracy and affective consequences of their views. Teaching youths to engage in rational thinking about themselves, their views. Teaching youths to monitor their moods, thoughts, and information about the course and characteristics of depression and of the CBT model of treatment, teaching youths to monitor their moods, thoughts, and behaviors to begin to see patterns.
- Additional CBT skill-building techniques used in many programs
  - Teaching relaxation techniques to cope with continuing environmental stressors, providing social skills and conflict resolution training to enhance youths’ adaptive behavioral repertoire, and teaching general problem-solving skills.

Limitations of CBT

- Very cognitively demanding on patient
- Teens may find it boring or banal
- Therapists not commonly trained it, though manuals and web sites are available
- Early studies showed superior effect over supportive therapy (~65% vs 40%) but CBT was not superior to placebo in NIH Treatment of Adolescent Depression Study (TADS), recent metaanalysis show smaller effect that previously thought (Weersing & Brent, Child Adolesc Psychiatric Clin N Am 15:939, 2006)
- Should not be considered the gold standard

History of antidepressant use in children and teens

- In 1980’s case reports of positive responses of tricyclic antidepressants (TCA) in children and teens with depression.
- Widespread use of this agents ensued, then multiple double blind placebo controlled trials showed TCA’s to be ineffective in children and adolescents
- In 1987 first positive trial of fluoxetine was published, all serotonin reuptake inhibitors (SSRI’s) gained widespread use
- In 2000’s multiple negative trials of other SSRI’s came to light
- In 2003, FDA issued warning on the use of Paxil in children due to increased suicidal ideation
- In 2004, FDA required boxed warning of risk of increased SI with all antidepressants in children and teens

Children and Adolescents With MDD: Score on the CDRS-R

<table>
<thead>
<tr>
<th>Visit Week</th>
<th>Placebo</th>
<th>FLX alone</th>
<th>CBT alone</th>
<th>FLX + CBT</th>
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<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>70</td>
<td>60</td>
<td>75</td>
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<td>2</td>
<td>70</td>
<td>60</td>
<td>50</td>
<td>70</td>
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<td>3</td>
<td>60</td>
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<td>40</td>
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<td>50</td>
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<td>30</td>
<td>50</td>
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<td>5</td>
<td>40</td>
<td>30</td>
<td>20</td>
<td>40</td>
</tr>
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<td>6</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>30</td>
</tr>
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<td>7</td>
<td>20</td>
<td>10</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
</tbody>
</table>

CDRS-R = Children’s Depression Rating Scale-Revised, Wagner KD et al. (2003), JAMA 290(8):1033-1041

Treatment of Adolescent Depression Study (TADS)

- FLX + CBT: 71% response
- FLX alone: 61%
- CBT alone: 43%
- Placebo: 35%
- SI present in 29% at baseline, all groups improved significantly

TADS—Suicidal Ideation

Intent to Treat Cases

Suicidal Ideation Questionnaire: Jour High School Edition

Harm and Suicide Related Events
Escitalopram in Children vs. Adolescents

- Post hoc analysis, view with caution
- Children—Clinical Global Imp (CGI) Score at week 8
  - Placebo: 2.0
  - Escitalopram: 2.0
- Adolescents—CGI at week 8
  - Placebo: 2.7
  - Escitalopram: 2.2, p=0.038
- Note: adolescents less likely to respond to placebo


Venlafaxine in children and adolescents


Venlafaxine vs. Placebo: children—no sign effect


Venlafaxine vs. Placebo: adolescents—post hoc effect


FDA Meta-Analysis

- Pooled all studies, published and unpublished
- Blinded reviewers at Columbia assessed each adverse event as to its self harm potential
- N ~4,000
- No suicides
- 4% SI on drug, 2% on placebo, statistically significant
- Results led to Boxed Warning

Hammad TA et al. (2006), Arch Gen Psychiatry 63(3):332-338

Recent Meta Analysis

- Reviewed 27 studies of MDD, OCD and anxiety disorders in children and adolescents
  - 15 MDD studies
  - 6 OCD studies
  - 6 anxiety studies
- Included studies not in FDA review
- Number of participants
  - MDD: 3,430
  - OCD: 718
  - Anxiety: 1,162

Bridge JA et al. (2007), JAMA 297(15):1683-1696
Recent Meta Analysis (Cont.)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Treatment Response (%)</th>
<th>Placebo Response (%)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD</td>
<td>61</td>
<td>50</td>
<td>0.001</td>
</tr>
<tr>
<td>OCD</td>
<td>52</td>
<td>32</td>
<td>0.001</td>
</tr>
<tr>
<td>Anxiety</td>
<td>69</td>
<td>39</td>
<td>0.001</td>
</tr>
<tr>
<td>Treatment SI (%)</td>
<td>Placebo SI (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDD</td>
<td>3</td>
<td>2</td>
<td>0.08</td>
</tr>
<tr>
<td>OCD</td>
<td>1</td>
<td>0</td>
<td>0.57</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1</td>
<td>0</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Observed and Estimated Change in HDRS Scores Following Treatment With ADM and Placebo

Bridge JA et al. (2007), JAMA 297(15):1683-1696

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Relationship of Suicide and SSRI Prescription Rate

Number of Suicides per 100,000

Higher SSRI Prescription Rate


Medication - PCP or Psychiatry?

- Primary Care
- Age 9-17 years
- MDD/Dysthymia only
- ADHD only comorbidity
- No substance abuse
- No psychosis
- Only passive suicidal ideation
- Refer to Psychiatry
- < 9 years of age
- Atypical depression
- Aggression, severe ODD or substance abuse present
- Persecutory delusions or hallucinations present
- Suicidal intent, clear plan

Office Management of Depression

- High placebo response rate in controlled trials of antidepressants suggest effectiveness of supportive aspects of research study environment
- Psychotherapy is an acceptable first line treatment, especially for mild to moderate depression, or where there is clearly a psychosocial issue which can be a focus of therapy
- Pharmacotherapy not indicated for minor depression or adjustment disorders

Office Management

<table>
<thead>
<tr>
<th>Medication Immediately</th>
<th>Psychosocial First</th>
<th>Combination Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has already had &gt; 4 sessions of therapy without improvement</td>
<td>Therapy has not been tried</td>
<td>Therapy has not been tried</td>
</tr>
<tr>
<td>Prominent neurovegetative signs</td>
<td>Minimal neurovegetative signs, no SI</td>
<td>Prominent neurovegetative signs, strong negative thinking</td>
</tr>
<tr>
<td>Family hx of response to antidepressant</td>
<td>Oppositional Defiant symptoms (Family IX)</td>
<td>Comorbid ADHD, ODD,</td>
</tr>
<tr>
<td>No clear stressor precipitating depression</td>
<td>Stressor contributing to Depression</td>
<td>Stressor; family dysfunction, contributing to Depression</td>
</tr>
</tbody>
</table>
Office Management

- Based on FDA meta-analysis, we tell families there is a 2-4% of SI vs. 1-2% on placebo; TADS study shows 60-70% chance of improvement of MDD
- Fluoxetine generally the first line
- Other SSRI acceptable\(^1\)
- Non SSRI (Venlafaxine, bupropion, duloxetine) not a first line, no advantage to using these
- Tell parents and child to watch for and report all feelings of self harm or increase in agitation

Antidepressant dosing

<table>
<thead>
<tr>
<th></th>
<th>Child dose (mg/day) Start</th>
<th></th>
<th>Adolescent dose (mg/day) Start</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Max</td>
<td></td>
<td>Max</td>
</tr>
<tr>
<td>Citalopram</td>
<td>10</td>
<td>20</td>
<td>10-20</td>
<td>40</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>5</td>
<td>20</td>
<td>5-10</td>
<td>20</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>5-10</td>
<td>20</td>
<td>10-20</td>
<td>60</td>
</tr>
<tr>
<td>Sertraline</td>
<td>25-50</td>
<td>100</td>
<td>50</td>
<td>200</td>
</tr>
</tbody>
</table>

Titrate to max dose over 3 weeks, allow 4 weeks at max dose to observe full effect

Office Management

- Schedule follow up at a minimum in one month
- Schedule in 1-2 weeks in more severe MDD or if not in therapy
- Have parent call nursing/office staff after one week to report progress/SUPPORT therapist can see weekly
- Discontinue SSRI if agitation, SI increase, refer to psychiatry or refer for psychiatric hospitalization
- If good acute response, see monthly for two months, if depression resolves quarterly follow up for medication management acceptable

Long term treatment

- Responders should be maintained on antidepressant until depression free for 1 year
- In reality, many patients will take themselves off antidepressant earlier than that
- Fluoxetine will self taper if discontinued due to long half life, although it common to taper if patient on > 40 mg
- Citalopram and Sertraline should be reduced by ½ dose every five days, then discontinue