Juvenile Depression

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Lifetime Prevalence of Adolescent Depression

- National Comorbidity Survey–Adolescent Supplement
- Face-to-face study of 10,123 US adolescents, ages 13 to 18 years
- Modified version of World Health Organization Composite International Diagnostic Interview

<table>
<thead>
<tr>
<th></th>
<th>Sex</th>
<th>Age</th>
<th>Total</th>
<th>Severe Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female %</td>
<td>Male %</td>
<td>13-14</td>
<td>15-16</td>
</tr>
<tr>
<td>MDD or Dysthymia</td>
<td>15.9</td>
<td>7.7</td>
<td>8.4</td>
<td>12.6</td>
</tr>
</tbody>
</table>

Top Ten Causes of Death Among Adolescents

- Road Injury
- HIV/AIDS
- Self-Harm
- Lower respiratory Infections
- Interpersonal Violence
- Diarrhoeal Diseases
- Drowning
- Meningitis
- Epilepsy
- Endocrine, Blood, Immune Disorders

Long-Term Outcome of Adolescent Depression

- 140 adolescents with depressive disorders
- Psychosocial and/or antidepressant treatment
- Outcome 3-9 years (mean 6yrs)
  - 93% full remission from index episode
  - 53% recurrence of depressive disorder
  - 79% developed non-mood disorder (anxiety, substance use, eating disorders)
  - Only 15% had no subsequent depressive episode or other non-mood disorder

Melvin GA et al. *J Affective Disorders*. 2013; 151:298-305
FDA Approval for Acute Treatment of Major Depressive Disorder

<table>
<thead>
<tr>
<th>Medication</th>
<th>Ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine (3 studies)</td>
<td>8-17</td>
</tr>
<tr>
<td>Escitalopram (1 study)</td>
<td>12-17</td>
</tr>
</tbody>
</table>
Other Controlled Pediatric Depression Trials

<table>
<thead>
<tr>
<th>Medication</th>
<th>Ages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive studies</strong></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>7-17</td>
</tr>
<tr>
<td>Sertraline (a priori pooled analysis)</td>
<td>6-17</td>
</tr>
<tr>
<td><strong>Negative studies</strong></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>13-18</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>6-17</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td></td>
</tr>
<tr>
<td>Nefazadone</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td></td>
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</tbody>
</table>

# Meta-analysis of Antidepressant Trials

## Depression in Youth

<table>
<thead>
<tr>
<th></th>
<th>Response Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td>61%</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>50%</td>
</tr>
</tbody>
</table>

Antidepressant Treatment Duration in Children and Adolescents

- Review of electronic prescription records of 8,837 children and adolescents with major depression prescribed antidepressants
- Rate of 6-month antidepressant use
  - 46%
- Reasons for discontinuation
  - More days without medication between first prescription and refill

Treatment of Adolescent Depression Study (TADS)

- 439 adolescent outpatients with major depression
- Randomized to 12 weeks
  - Fluoxetine (10 mg/day to 40 mg/day)
  - CBT with fluoxetine (10 mg/day to 40 mg/day)
  - CBT alone
  - Placebo

CBT, cognitive behavioral therapy

Treatment for Adolescents with Depression Study (TADS) Study Team. JAMA. 2004;292:807-820.
## Response Rates in Treatment for Adolescents with Depression Study (CGI ≤2)

<table>
<thead>
<tr>
<th>Week</th>
<th>FLX + CBT</th>
<th>FLX</th>
<th>CBT</th>
<th>PLB</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>73%</td>
<td>62%</td>
<td>48%</td>
<td>35%</td>
</tr>
<tr>
<td>18</td>
<td>85%</td>
<td>69%</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>86%</td>
<td>81%</td>
<td>81%</td>
<td></td>
</tr>
</tbody>
</table>

FLX, fluoxetine; PLB, placebo

Treatment of SSRI-Resistant Depression in Adolescents Trial

- 334 adolescents with major depression who failed to respond to 8 weeks of SSRI
- Randomized to 12 weeks of:
  - Different SSRI
  - Different SSRI + CBT
  - Switch to venlafaxine
  - Switch to venlafaxine plus CBT

SSRI, selective serotonin reuptake inhibitor

Clinical Response by Treatment Group (CGI ≤2 and decrease CDRS-R ≥50%)

*P=0.02

MED, medical intervention
Bupropion

- No controlled trials for pediatric depression
- Open trial of bupropion SR for 11 depressed adolescents: Response Rate (CGI-I ≤2) 73%
- Open trial of bupropion SR augmentation of SSRIs for 23 depressed adolescents: 65% of patients improved

SR, sustained release
Selegiline Treatment for Adolescent Depression

- 308 adolescents with major depression
- Randomized to selegiline transdermal system flexible dosing (6 mg/24h, 9 mg/24h, or 12 mg/24h) or placebo

<table>
<thead>
<tr>
<th>CDRS-R</th>
<th>EMSAM®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>56.7</td>
<td>57.9</td>
</tr>
<tr>
<td>Endpoint</td>
<td>35.4</td>
<td>36.4</td>
</tr>
</tbody>
</table>

Controlled Trials of Duloxetine for Pediatric (7-17 years) Major Depression

Desvenlafaxine Treatment for Pediatric (7-17 years) Major Depression

Fluoxetine 20mg
Desvenlafaxine 25, 35 or 50mg

Vortioxetine: Pharmacokinetics and Safety

- 48 youth, ages 7-17 years with depression and anxiety disorders
- Open-label study of vortioxetine 5mg, 10mg, 15mg or 20mg for 14-20 days
- Higher doses titrated over 2-6 days
- Findings
  - PK of vortioxetine concentration proportional to dose

<table>
<thead>
<tr>
<th>Medication</th>
<th>Status</th>
</tr>
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<tbody>
<tr>
<td>Vilazodone</td>
<td>Pediatric MDD study completed</td>
</tr>
<tr>
<td>Levomilnacipran</td>
<td>Adolescent MDD study in progress</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Adolescents with treatment refractory MDD study in progress</td>
</tr>
</tbody>
</table>
Treatment Resistant Depression Algorithm

SSRI* fluoxetine/escitalopram
If no response maximum dose, minimum 8 wks

Alternate SSRI* fluoxetine/escitalopram/citalopram/sertraline
If no response maximum dose, minimum 8 wks

Augment aripiprazole, lithium or bupropion
Partial response

Different class of antidepressant bupropion/venlafaxine/duloxetine/desvenlafaxine
If no response maximum dose, minimum 8 wks

Augment aripiprazole or lithium
Partial response

Newer Antidepressants vortioxetine, vilazodone, levomilnacipran
If no response maximum dose, minimum 8 wks

* Add CBT
28 children (ages 6 to 12 years) with first episode major depression randomized to Omega-3 (1000 mg/day; contained 400 mg EPA and 200 mg DHA) or placebo for 16 weeks

<table>
<thead>
<tr>
<th>Groups</th>
<th>Response Rate, % (&gt;50% Reduction in CDRS)</th>
<th>Remission, % (CDRS &lt;29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omega-3</td>
<td>70</td>
<td>40</td>
</tr>
<tr>
<td>Placebo</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

DHA, docosahexaenoic acid
Repetitive Transcranial Magnetic Stimulation (rTMS) for Treatment Resistant Depression

- 9 adolescents open-label rTMS for 20 treatments
  - Response rate 33% (≥ 30% reduction; CDRS-R)
- 8 adolescents adjunctive rTMS (added to SSRI) for 30 treatments
  - Significant reduction in baseline CDRS-R
- Three year follow-up of 9 adolescents treated with rTMS
  - Maintained clinical improvement

Increase awareness of and screening for depression in children and adolescents
Screening for Depression in Children and Adolescents

- Recommendation from US Preventative Task Force
  - Screening for major depressive disorder in adolescents ages 12 to 18 years
    (PHQ-A highest positive predictive value)
  - Adequate systems to ensure accurate diagnosis, effective treatment, and appropriate follow-up
  - Current evidence insufficient to assess balance of benefits and harms of screening for major depressive disorder in children ≤ 11 years

Components of AACAP Presidential Initiative

- Education of parents and youth about depression
  - Symptoms, course, treatment

- AACAP online Depression Resource Center
  - Up-to-date, evidence-based information

- Collaboration with national organizations dealing with children’s mental health
AACAP Presidential Initiative Projects

▪ Clinical Practice Guideline on Assessment and Treatment of Depression in Children and Adolescents

▪ Update Parent Medication Guide on Depression

▪ Online Depression Resource Center
  ▪ Update existing materials
  ▪ Create a section for teenagers

(Continued)
AACAP Presidential Initiative Projects

- JAACAP Connect Call for Papers
  - Programs with depression screening and referral system

- Child and Adolescent Psychiatric Clinics
  - Special populations

(Continued)
AACAP Presidential Initiative Projects

- JAACAP submissions on depression
  - Master clinician reviews
  - Clinical perspectives
  - Case conferences

- AACAP Annual meeting
  - Request for submissions on depression