Treating Complex Depression in Children & Adolescents

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TORDIA
Tolerability - Efficacy
Exposure
Sequencing
LCn-3
Vortioxetine
Vilazodone
Desvenlafaxine
At risk
Bipolar depression

"At risk"
Bipolar depression
Vortioxetine
Vilazodone
Desvenlafaxine
LCn-3
Sequencing
TORDIA

SSRI Non-responders (>2 mos of tx)

SSRI
Citalopram
Paroxetine
Fluoxetine

SSRI + CBT
Citalopram + CBT
Paroxetine + CBT
Fluoxetine + CBT

Population:
N=334
Age: 12-18 years
Dx: MDD + no response to 2-month initial SSRI

Primary Outcome:
CGI-I <2 + >50% decrease in CDRS-R and dCDRS-R

Pharmacotherapy: TORDIA

- **Primary Outcome:** CGI-I ≤2 (much or very much improved) and a ↓ of ≥50% in the CDRS-R and δCDRS-R.
- **Findings:**
  - CBT plus a switch to either medication regimen → better response (54.8%) than a medication switch alone (40.5%, p=0.009)
  - No difference in response rate between venlafaxine and a second SSRI (48.2% vs 47.0% p=0.83).

Adolescent MDD: Impact of Insomnia

- 2 double-blind, placebo-controlled studies of fluoxetine (Emslie et al., 1997, 2002)

<table>
<thead>
<tr>
<th></th>
<th>Insomnia N=172</th>
<th>No Insomnia N=157</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescents (≥12 yrs)</td>
<td>59.3% (102)</td>
<td>53.3% (73)</td>
<td>0.29</td>
</tr>
<tr>
<td>Female</td>
<td>50.0% (86)</td>
<td>44.5% (61)</td>
<td>0.34</td>
</tr>
<tr>
<td>Caucasian</td>
<td>79.1% (136)</td>
<td>83.2% (114)</td>
<td>0.33</td>
</tr>
<tr>
<td>First Episode</td>
<td>65.7% (113)</td>
<td>73.0% (100)</td>
<td>0.14</td>
</tr>
<tr>
<td>Episode Duration (wks)</td>
<td>40.2 ±8.5</td>
<td>55.4 ±8.2</td>
<td>0.07</td>
</tr>
<tr>
<td>Baseline CGI Severity</td>
<td>4.8 ±0.70</td>
<td>4.3 ±0.59</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Baseline CDRS-R</td>
<td>60.3 ±10.3</td>
<td>52.3 ±9.6</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

TORDIA: Insomnia

**Importance of Early Response: Remitters vs. Non-Remitters**

![Graph showing CDRS-R scores for Remitters vs. Non-Remitters over 24 weeks.](Emslie et al., 2010)

**TORDIA: Ten Years in 1 Slide**

- 50% of patients will respond to a change in medication (Brent et al. 2008).
- Response rates for switching to another SSRI (47%) or venlafaxine (48%) are similar (Brent et al. 2008); however, venlafaxine is associated with more side effects and increased suicidality (Brent et al. 2008).
- Medication change + CBT → higher response rate (55%) than a medication change alone (41%) (Brent et al. 2008).
- > 9 CBT sessions is associated with 2.5 times the likelihood of an adequate response (Kennard et al. 2009).
- Who responds best to combination treatment versus medication mono-treatment?
  - Patients with > comorbid conditions
  - lack of any history of abuse
  - < hopelessness (Asarnow et al. 2009).
- 1/3 of patients remit by 24 weeks of treatment
  - higher likelihood of remission if clinical response was achieved by 12 weeks (Emslie et al. 2010).


**TORDIA: Effect of Treatment on Hazard of a Suicidal Event**

![Graph showing cumulative hazard ratio for different treatments.](Brent, et al. Am J Psychiatry 2009; 166:418–426)
CITALOPRAM = FLUOXETINE > PAROXETINE

% Responders

SSRI

Paroxetine
Citalopram
Fluoxetine

TORDIA SSRI Switching Efficacy

- Mean difference for citalopram compared to fluoxetine = 0.067 (p=0.247)
- Mean difference between fluoxetine and paroxetine = 0.104 (p=0.11).
- Citalopram trended towards being superior to paroxetine, mean difference (0.171, p=0.055)
  - A patient would be 17 times more likely to respond to citalopram than to paroxetine.


TORDIA SSRI Switching Efficacy-Tolerability

- For efficacy-tolerability models, citalopram was superior to paroxetine (p=0.047).
- Fluoxetine was superior to paroxetine (p=0.035).
- There were no statistically significant differences between fluoxetine and citalopram (p=0.204)

TORDIA: Increased Risk for Self-Harm in High Ideators Treated with Venlafaxine

- Low ideators
- High ideators

**Citalopram & Escitalopram**  
*Metabolism and Outcome Relevance*

- **R-Citalopram**
  - 2C19 3A4 2D6
  - 2D6: Citalopram N-oxide

- **S-Citalopram**
  - 2C19 3A4 2D6
  - 2D6: Citalopram N-oxide

**Effect of 2C19 Polymorphism on Escitalopram Concentrations**


**TORDIA: Drug Plasma Concentration and Response**

Effect of 2C19 Polymorphisms on Therapeutic Failure in Adults


Effect of 2C19 Polymorphisms on Therapeutic Failure in Youth


Escitalopram Concentrations and CYP2C19 in Adolescents


### Pediatric Sertraline Concentrations and CYP2C19 in Adolescents

<table>
<thead>
<tr>
<th>CYP2C19 phenotype</th>
<th>Exposure ratio</th>
<th>Calculated dose equivalent (mg/day)</th>
<th>Formulated (available) dose equivalent (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor metabolizer</td>
<td>2.89</td>
<td>51.94</td>
<td>50</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>1.38</td>
<td>122.62</td>
<td>125</td>
</tr>
<tr>
<td>Normal metabolizer</td>
<td>1</td>
<td>155</td>
<td>150</td>
</tr>
<tr>
<td>Rapid metabolizer</td>
<td>0.79</td>
<td>189.00</td>
<td>175</td>
</tr>
<tr>
<td>Ultrarapid metabolizer</td>
<td>0.63</td>
<td>238.02</td>
<td>225</td>
</tr>
</tbody>
</table>

*Adapted from Chang et al. 2014. *Adapted from Wang et al. 2001.

### Sertraline Concentrations and CYP2C19 in Adolescents

**Non-Remitters** vs. **Remitters**

<table>
<thead>
<tr>
<th>Week</th>
<th>CDRS-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
</tr>
<tr>
<td>12</td>
<td>55</td>
</tr>
<tr>
<td>24</td>
<td>50</td>
</tr>
</tbody>
</table>

Emslie et al., 2010

- Bipolar depression
- "At risk"
- Tolerability-Efficacy
- Exposure
- TORDIA
- Sequencing
- Desvenlafaxine
- Vilazodone
- Vortioxetine
- LCn-3

Importance of Early Response: Remitters vs. Non-Remitters
When to Adjust Treatment in Adolescent MDD

IPT-A Early decision

- >20% reduction: Continue IPT-A
- <20% reduction: Partial response

IPT-A Late decision

- >40% reduction: Continue IPT-A
- <40% reduction: Partial response

Pediatric SSRI-Resistant MDD

Open Label LCn-3 Supplementation

- LOW-DOSE (n=7)
- HIGH-DOSE (n=7)

Vortioxetine: Mechanism of Action

- **5-HT**
- **5-HT2A,2B,2C**
- **5-HT3**
- **5-HT7**
- **5-HT1A**
- **5-HT1B**
- **5-HIAA**
- **MAO**
- **5-HT transporter**
- **5-HT reuptake inhibitor**
- **Na+ Ca+2 Cation flux**

Vortioxetine Pediatric PK Summary

- Exposure of vortioxetine increased with increasing dose in an approximately dose-proportional manner in both adolescents and children.
- Exposure (e.g., Cmax and AUC) lower in adolescents than in children.
- Clearance (CL/F) > in adolescents (59 L/h) than in children (38 L/h) or adults (33 L/h).
  - Per the study authors: “It could be hypothesized that non-adherence to treatment in the present study may have led to over-estimations of CL/F (and V/F) and could be the reason for higher oral clearance in the adolescents.”
- Weight a VD (VSS/F).
- Gender, height, ADHD and concomitant stimulant treatment did not affect PK variables.

Vortioxetine in Anxious and Depressed Youth

- Outpatients ages 7–17 years.
- DSM-IV-TR diagnosis of depressive or anxiety disorder
- Included co-occurring ADHD with “concomitant stable treatment with a stimulant (>4-week stable tx)"

Vortioxetine: Pediatric Tolerability

- Children (n=24)
- Adolescents (n=24)


Durgam et al. A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study of Vilazodone in Adolescents with Major Depressive Disorder. Pediatric Drugs. 2018;20:353-363
Desvenlafaxine in Adolescent MDD


**IMPACT of Age on SSRI/SNRI Adverse Effects in Youth at Risk for Bipolar Disorder**

- 57% of at-risk youth had an adverse event (AE)
- Higher risk in younger patients (P<0.02)
- No baseline clinical differences
- The solid line represents the predicted probability of an AE leading to discontinuation

Antidepressants for Depression in Adolescents with Bipolar Disorder

- Retrospective small study (n=59)
- SSRIs were most effective treatment for acute bipolar depression
  - Relative risk, 6.7 (95% CI, 1.9-23.6); \( P = 0.003 \)
  - Greater effectiveness than mood stabilizers
- Greater probability of relapse of manic symptomatology
  - Relative risk, 3.0 (95% CI, 1.2-7.8); \( P = 0.02 \)


Negative Antidepressant Reactions in Youth with Bipolar Disorder


Lamotrigine in Pediatric Bipolar Spectrum Disorders: Open-Label Study

- Outpatients with bipolar I or II disorder (N=193)
- LS mean changes in CDRS-R total score decreased with quetiapine XR (-29.6) and placebo (-27.3)
  - Between-treatment group difference of -2.29 was not statistically significant (\( P = 0.25 \))
  - Rates of response and remission did not differ significantly between treatment groups
    - NNT (response) = 13; NNT (remission) = 9; number needed to harm (NNH) (≥7% weight gain) = 16.


Quetiapine XR in Youth With Acute Bipolar Depression

- LS mean changes in CDRS-R total score decreased with quetiapine XR (-29.6) and placebo (-27.3)
  - Between-treatment group difference of -2.29 was not statistically significant (\( P = 0.25 \))
  - Rates of response and remission did not differ significantly between treatment groups

Quetiapine XR for Bipolar Depression: Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Quetiapine XR, n (%)</th>
<th>Placebo, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>20 (21.7)</td>
<td>12 (12.0)</td>
</tr>
<tr>
<td>Sedation</td>
<td>7 (7.6)</td>
<td>6 (6.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (6.5)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>6 (6.5)</td>
<td>4 (4.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (5.4)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (5.4)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (5.4)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Irritability</td>
<td>2 (2.2)</td>
<td>5 (5.0)</td>
</tr>
</tbody>
</table>

Mean (SD) weight gain: quetiapine XR group, 1.3 (2.14) kg; placebo group, 0.6 (2.39) kg.

Eleven (12.5%) of the quetiapine XR group and 6 (6.0%) of the placebo group experienced weight gain >7%.


Olanzapine/Fluoxetine Combination for Youth with Bipolar Depression

- Children and adolescents with bipolar I disorder (N=255) randomized to double-blind OFC or placebo.
- Mean decrease in CDRS-R for OFC: -28.4 and for placebo: -23.4.
- Between-treatment group difference of -5.0 was statistically significant.
- Response rate and time to remission were significantly better in OFC group.

MRRM = mixed-model repeated measures; NNT (response) = 6; NNT (remission) = 7; NNH (≥7% weight gain) = 3.


A Double-Blind, Placebo-Controlled Trial of Lurasidone for Youth With Bipolar Depression

- Primary Endpoint: Change from baseline to week 6 in the Children’s Depression Rating Scale-Revised (CDRS-R) total score compared with placebo.
- Key Secondary Endpoint: Change from baseline to week 6 in the Clinical Global Impression-Bipolar Version-Severity of Illness (CGI-BP-S) score (depression) compared with placebo.

Change From Double-Blind Baseline in CDRS-R Total Score

Mean dose lurasidone: 32.8 mg/day
Median dose lurasidone: 30.0 mg/day

Adverse Event Rates During Open-Label Treatment

<table>
<thead>
<tr>
<th>Event, %</th>
<th>Lurasidone (N=305)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>22.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>11.1</td>
</tr>
<tr>
<td>Somnolence</td>
<td>9.5</td>
</tr>
<tr>
<td>Weight increased</td>
<td>8.9</td>
</tr>
<tr>
<td>Anxiety</td>
<td>8.5</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>8.2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7.9</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6.9</td>
</tr>
<tr>
<td>Extrapyramidal symptoms (non-akathisia)</td>
<td>6.6</td>
</tr>
<tr>
<td>Akathisia</td>
<td>4.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.6</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>79.7</td>
</tr>
</tbody>
</table>

Lurasidone Two-Year Open-Label Study: Weight and BMI

BMI-change: ACTUAL +0.20 +0.65 +0.87 +0.93 +1.13
BMI-change: EXPECTED +0.08 +0.41 +0.68 +0.91 +1.22

Summary

- SSRI-resistant MDD is common and residual symptoms are common, even in “responders”
- Lack of symptoms ≠ well.
- Response in first 6 weeks critical period.
- Goal of treatment is REMISSION.
- Need to do better with treatments we have.
  - Dose is maximization
  - Visits more frequent when initiating or changing medication or dose.
  - Treatment decisions are based on response.
    - Monitor for improvement utilizing rating scales (Trivedi et al., 2007).
    - Monitor for other behavioral AEs: anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania.
- For youth with a family history of bipolar disorder experiencing MDD, antidepressants may be poorly tolerated.
- For Bipolar I Disorder, current episode depressed:
  - Antidepressants may be associated with treatment-emergent manic symptoms.
  - Lurasidone, OFC supported by positive RCTs; however, tolerability varies considerably between these treatments.