“That man is truly good who knows his own dark places.”

Beowulf (8th-11th century)
SSRIs

Learning Objectives

1. Summarize the design and main findings of the following landmark trials of antidepressants in children and adolescents: TADS, ADAPT, TORDIA, TASA, POTS and CAMS
2. Identify adverse effects, risks, and necessary precautions associated with SSRIs in youth
3. Appraise, based on the available evidence, the potential benefits and adverse effects of SSRIs for different pediatric indications (major depression, OCD, and non-OCD anxiety disorders)
4. Explain how to initiate, titrate, and monitor SSRIs in children and adolescents.

Outline

• Indications & clinical use
• Pharmacodynamics & pharmacokinetics
• Efficacy for MDD, OCD, and non-OCD anxiety (including review of the TADS, TORDIA, POTS, and CAMS studies)
• Adverse effects
• SSRI & suicide controversy
• Contraindications & drug interactions
• Monitoring
• Choosing, dosing & discontinuing an SSRI

Selective Serotonin Reuptake Inhibitors (SSRIs)

• Fluoxetine (Prozac)
• Sertraline (Zoloft)
• Paroxetine (Paxil, Paxil CR)
• Fluvoxamine (Luvox)
• Citalopram (Celexa)
• Escitalopram (Cipralex in Canada, Lexapro in the U.S.)

Approved Indications for SSRIs

<table>
<thead>
<tr>
<th></th>
<th>Health Canada</th>
<th>FDA (USA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pediatric</td>
<td>Adult</td>
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<tr>
<td>Fluoxetine</td>
<td>None</td>
<td>MDD, OCD, PD, BN</td>
</tr>
<tr>
<td></td>
<td>MDD (2 yr),</td>
<td>MDD, OCD, PD, BN</td>
</tr>
<tr>
<td></td>
<td>OCD (8 yr)</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>None</td>
<td>MDD, OCD, PD, FTSD, PMDD</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>ODD (≥ 6 yr), OCD, PD</td>
</tr>
<tr>
<td></td>
<td>Illness</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>None</td>
<td>MDD, OCD, PD, SP, GAD, PTSD</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>ODD (≥ 8 yr), OCD, PD</td>
</tr>
<tr>
<td></td>
<td>Illness</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td></td>
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<tr>
<td></td>
<td>Illness</td>
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</tr>
<tr>
<td>Citalopram</td>
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<tr>
<td></td>
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<td></td>
<td>Illness</td>
<td></td>
</tr>
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<td>Escitalopram</td>
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</tr>
<tr>
<td></td>
<td>MDD (≥ 12 yr)</td>
<td>MDD, GAD</td>
</tr>
<tr>
<td></td>
<td>acute and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>maintenance</td>
<td></td>
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<tr>
<td></td>
<td>treatment</td>
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</table>
Clinical Uses of SSRIs in Youth

- MDD and other depressive disorders
- OCD and other anxiety disorders
- Depressive/anxiety symptoms in bipolar and primary psychotic disorders
- Eating disorders
- Repetitive behaviours in pervasive developmental disorders

Pharmacodynamics

- SSRIs interfere with the return of 5-HT into the presynaptic neuron by blocking the 5-HT transporter located on presynaptic nerve terminals
- This results in a rapid increase in extracellular levels of 5-HT; however, clinical effect usually takes at least 3-4 weeks
- The delay in clinical effect suggests that slow neurochemical and/or structural changes take place

Pharmacodynamics (cont.)

- “Neurochemical” Theory:
  - Chronic blockade of the 5-HT transporter leads to a desensitization of the 5-HT autoreceptors, which typically exert an inhibitory influence on 5-HT release
  - With continued blockade of the transporter, the desensitized autoreceptors do not exert their usual inhibitory influence
  - 5-HT release is therefore enhanced, possibly resulting in desensitization of postsynaptic 5-HT2 receptors
  - These processes somehow result in decreased depressive/anxiety symptoms

- “Structural” Theory (Santarelli et al., Science, 2003):
  - Chronic SSRI use causes increased hippocampal neurogenesis
  - Increased hippocampal neurogenesis somehow decreases depressive/anxiety symptoms

Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Tmax in adults (hrs)</th>
<th>T1/2 in adults</th>
<th>% protein-bound</th>
<th>Effect of taking with food</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>6-8</td>
<td>fluoxetine: 4-6 days; norfluoxetine: 4-16 days</td>
<td>94%</td>
<td>negligible</td>
</tr>
<tr>
<td>Sertraline</td>
<td>6-8</td>
<td>24 hrs</td>
<td>18%</td>
<td>increases bioavailability; take with food</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>3-7</td>
<td>24 hrs (wide range: 3-66 hrs)</td>
<td>95%</td>
<td>negligible</td>
</tr>
<tr>
<td>Paxil CR</td>
<td>6-10</td>
<td>15-20 hrs</td>
<td>95%</td>
<td>negligible</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>1.5-6</td>
<td>10-22 hrs</td>
<td>77%</td>
<td>not indicated in CPS</td>
</tr>
<tr>
<td>Citalopram</td>
<td>4</td>
<td>37 hrs</td>
<td>80%</td>
<td>negligible</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>5</td>
<td>27-32 hrs</td>
<td>55%</td>
<td>negligible</td>
</tr>
</tbody>
</table>

Pediatric PK Considerations

- At least for FLX, SER, and PAR, child and adult PK are similar after adjusting for weight
- FLV has lower oral clearance in children 6-11 years, and a gender effect has also been found such that girls 8-11 years may benefit from lower doses (Rodriguez et al., 2008)
- For SER, PAR, FLV, CIT, and ECIT:
  - Because of children’s increased rate of drug metabolism, some recommend BID dosing at lower dosages to minimize the risk of daily withdrawal symptoms
### CYP450 Properties

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Inhibitor</th>
<th>Inducer</th>
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<tbody>
<tr>
<td>Fluoxetine 2D6</td>
<td>2D6 +++ 2C ++ 3A4 ++</td>
<td>None</td>
</tr>
<tr>
<td>Sertraline 3A4</td>
<td>2C ++ 2D6 +/- 3A4 ++</td>
<td>None</td>
</tr>
<tr>
<td>Paroxetine 2D6</td>
<td>2D6 +++</td>
<td>None</td>
</tr>
<tr>
<td>Fluvoxamine 1A2 2D6</td>
<td>1A2 +++ 2C ++ 3A4 +/− 2D6 +/-</td>
<td>None</td>
</tr>
<tr>
<td>Citalopram 2C 3A4 2D6 +/-</td>
<td>2D6 +/- 2C +/-</td>
<td>None</td>
</tr>
<tr>
<td>Escitalopram 2C 3A4 2D6 +/-</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

### Efficacy: Pediatric MDD

#### Efficacy of SSRIs for Pediatric MDD

- Efficacy of SSRIs for MDD in children and adolescents remains controversial
- Sources of bias, confusion, and controversy:
  - Unpublished negative trials
  - Criteria for determining efficacy (clinical vs. statistical significance)
  - Most trials are supported by drug companies

#### DBPC Trials of SSRI for Pediatric MDD (Published)

- **Fluoxetine:**
  - Emslie et al., 1997
  - Emslie et al., 2002
  - TADS, 2004
  - Emslie et al., 2004 (prevention of relapse)
  - Emslie et al., 2008 (prevention of relapse)
- **Paroxetine:**
  - Keller et al., 2001
  - Berard et al., 2006
  - Emslie et al., 2006
- **Citalopram:**
  - Wagner et al., 2004
  - von Knorring et al., 2006
- **Escitalopram:**
  - Wagner et al., 2006
  - Emslie et al., 2009

Number needed to treat (NNT)=5-10

### Interpretation of Efficacy Data

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>MHRA</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine (March '04)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fluoxetine (Emslie '97)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fluoxetine (Emslie '92)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Paroxetine (Keller '01)*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Paroxetine (Berard '06)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Paroxetine (Emslie '06)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sertraline (Wagner '03)**</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Negative in primary outcome but positive in many secondary outcomes
**Two studies: pooled were positive; separate, 1 trended to positive, 1 negative

### Interpretation of Efficacy Data

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>MHRA</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram (Wagner '04)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Citalopram (von Knorring '06)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Escitalopram (Wagner '06)</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Escitalopram (Emslie '09) (for adolescents)</td>
<td>?</td>
<td>*</td>
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</table>

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Efficacy Data (CGI)

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>Drug-Placebo Difference</th>
<th>P</th>
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<tbody>
<tr>
<td>Fluoxetine (March ’04)</td>
<td>26%</td>
<td>0.001</td>
</tr>
<tr>
<td>Fluoxetine (Emslie ’97)</td>
<td>23%</td>
<td>0.02</td>
</tr>
<tr>
<td>Fluoxetine (Emslie ’02)</td>
<td>16%</td>
<td>0.03</td>
</tr>
<tr>
<td>Paroxetine (Keller ’01)</td>
<td>22%</td>
<td>0.02</td>
</tr>
<tr>
<td>Paroxetine (Berard ’06)</td>
<td>12%</td>
<td>NS</td>
</tr>
<tr>
<td>Paroxetine (Emslie ’06)</td>
<td>3%</td>
<td>NS</td>
</tr>
<tr>
<td>Citalopram (Wagner ’04)</td>
<td>2%</td>
<td>NS</td>
</tr>
<tr>
<td>Citalopram (von Knorring ’06)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Sertraline (Wagner ’03)</td>
<td>10%</td>
<td>0.05</td>
</tr>
<tr>
<td>Escitalopram (Wagner ’06)</td>
<td>11%</td>
<td>NS</td>
</tr>
<tr>
<td>Escitalopram (Emslie ’09)</td>
<td>11%</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Meta-analysis of Published & Unpublished Studies

- Tsapakis et al., 2008:
  - Meta-analysis of 30 published and unpublished antidepressant-PBO contrasts in RCTs involving 3069 youth with depression
  - The pooled antidepressant/PBO response rate ratio was modest, with little separation between antidepressant types: RR=1.22 (1.15-1.31)
  - 22/30 yielded an RR ≥1.0, but only 6/30 met the criterion that the lower limit of the C.I. should be >1.0
  - By the same criterion, only 5/12 trials involving an SSRI were positive (3 FLX, 1 SER, 1 PAR)

Tsapakis et al., 2008 (cont.)

- NNT:
  - Overall=9
  - By drug class:
    - TCAs=14
    - SSRI=9 (FLX=6; SER+PAR+CIT+VEN=12)
    - Other AD (meclobemide, mirtazapine & nefazodone)=8
  - By age: children=21, mixed ages=10, teens=8
- Conclusion: "Antidepressants of all types showed limited efficacy in juvenile depression, but fluoxetine might be more effective, especially in adolescents."

Something Special About Fluoxetine for Younger Children?

- Mayes et al., 2007:
  - Pooled analysis of 2 DBPC trials of FLX for pediatric MDD (Emslie et al., 1997 & 2002), comparing efficacy outcomes for children (<12 yrs) & adolescents (≥12 yrs)
  - Response rates with FLX vs. PBO:
    - Children: 57% vs. 33% (p=0.009)
    - Adolescents: 51% vs. 39% (p=0.1)
- Conclusions:
  - "Fluoxetine is the only antidepressant to demonstrate better efficacy than placebo in children <12 years of age."
  - "It is premature to say that antidepressants are not very effective in children"

TADS

- Treatment of Adolescents with Depression Study (TADS Team, JAMA, 2004)
- Federally funded, multisite RCT conducted in the U.S.
- Subjects were 439 adolescents (12-17 years) with moderate to severe MDD

TADS: Randomization

- 4 treatment groups (12 weeks):
  1. Fluoxetine 10-40 mg/day (FLX)*
  2. CBT (CBT)**
  3. Fluoxetine 10-40 mg/day + CBT (COMB)**
  4. Placebo (PBO)*
- *Blinded  **Unblinded

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TADS: Main Outcome Measures

• Change in the Children’s Depression Rating Scale-Revised

• Response rate using the Clinical Global Impression (CGI) scale:
  – Positive response defined as “much” or “very much” improved

TADS: Interventions

• CBT:
  – 15 sessions (50-60 min), including 2 parent-only sessions and 1-3 conjoint parent and adolescent sessions

• Fluoxetine:
  – Started at 10 mg/d; ↑ to 20 mg/d at week 1; if necessary, ↑ to max of 40 mg/d by week 8
  – Mean highest dose of FLX/PBO:
    • FLX: 33.3 mg/d
    • COMB: 28.4 mg/d
    • PBO: 34.1 mg/d

TADS: Efficacy Results

• CDRS-R:
  – Analysis 1 (planned):
    • COMB > PBO, COMB > FLX, COMB > CBT
    • FLX > CBT
    • FLX = PBO, CBT = PBO
  – Analysis 2 (supportive):
    • COMB = FLX > CBT = PBO

TADS: Efficacy Results (cont.)

• CGI response rate:
  COMB (71%) = FLX (61%) >
  CBT (43%) = PBO (35%)

TADS: More Efficacy Results at 12 Weeks
(March et al., 2006; Curry et al., 2006)

• Effect sizes compared with PBO:
  – COMB (0.98) > FLX (0.68) > CBT (-0.03)

• Specific measures:
  – COMB > PBO on 15/16 measures
  – COMB > CBT on 14/16 measures
  – COMB > FLX on 8/16 measures
  – FLX > CBT on 8/16 measures
  – FLX > PBO on 7/16 measures
  – CBT = PBO on 14/14 measures

• CDRS-R results in the severely depressed subgroup: COMB = FLX > CBT = PBO

TADS: Adverse Event Results

• Emslie et al., 2006:
  – Nonpsychiatric medication-related AEs (≥2% of patients on FLX and ≥2x the rate seen in patients on PBO): sedation, insomnia, vomiting, upper abdominal pain
  – Psychiatric AEs besides suicide-related events:

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Spontaneously Reported Psychiatric Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom</td>
<td>COMB</td>
</tr>
<tr>
<td>Mania</td>
<td>1.0%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0.0%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.0%</td>
</tr>
<tr>
<td>Other</td>
<td>0.0%</td>
</tr>
<tr>
<td>No. of patients</td>
<td>6/39</td>
</tr>
<tr>
<td>Event rate</td>
<td>5.6%</td>
</tr>
</tbody>
</table>
TADS: Suicide-Related Events

- Emslie et al., 2006:
  - SI was present in 29% of the sample at baseline
  - SI improved significantly in all 4 groups, but COMB showed the greatest improvement (see next slide)
  - 24 suicide-related events occurred during the study: COMB=6, FLX=10, CBT=5, PBO=3
  - Statistically, only FLX had more suicide-related events than PBO (p=0.04, OR=3.7 [1.0-13.7])
  - 5 suicide attempts occurred: COMB=2, FLX=2, CBT=1, PBO=0
  - No completed suicides

TADS at 12 Weeks: Conclusions

- March et al., 2006:
  - "COMB appears to accelerate recovery relative to CBT and, for some outcomes, FLX alone, while minimizing the risk of suicidality relative to FLX alone."
  - "Taking benefit and risk into account, we conclude that the combination of FLX and CBT appears superior to either monotherapy as a treatment for moderate to severe MDD in adolescents."

TADS Team, 2007: Long-term Effectiveness

- FLX & PBO treatment arms were unblinded after 12 weeks (recall that the CBT and COMB treatment arms were not blinded from the beginning of the study)
- Subjects in the FLX, CBT, and COMB groups continued with the same kind of treatment through 36 wks, but the intensity of treatment generally decreased in accordance with protocols for stages 2 (12-18 wks) and 3 (18-36 wks)
- Adjusted CGI-I response rates over time:
  - 12 wks: COMB (73%) = FLX (62%) > CBT (48%)
  - 18 wks: COMB (85%) > FLX (69%) = CBT (65%)
  - 24 wks: All 3 treatments converged
  - 36 wks: COMB (86%) = FLX (81%) = CBT (81%)

TADS Team, 2007: Long-term Safety

- Suicidal ideation over time:
  - 12 wks: FLX (19%) > COMB (9%) = CBT (6%)
  - 36 wks: FLX (14%) > CBT (4%) = COMB (3%)
  - No completed suicides

Reference: Emslie et al.

Fig. 1 Self-reported suicidal ideation (SIQ-Jr) total score. FLX = fluoxetine; COMB = combination treatment; CBT = cognitive behavioral therapy; PBO = placebo; SIQ-Jr = Suicidal ideation Questionnaire: Grades 7–9.

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Kennard et al., 2009: Remission & Recovery in TADS

• Remission rates in TADS over time:
  – 6 wks: COMB = FLX > CBT
  – 12 wks: COMB (39%) > FLX (24%) = CBT (19%) = PBO (19%)
  – 18 wks: COMB (56%) > FLX (37%) = CBT (27%)
  – 24 wks: All active treatments converged
  – 36 wks: CBT (64%) = COMB (60%) = FLX (55%)

• Residual symptoms at 12 weeks predicted failure to achieve remission at weeks 18 & 36

Curry et al, 2011
TADS 5-Year Follow-up

• By 2 years, majority had recovered
  – 96.2% of short-term treatment responders
  – 79.1% of partial responders or nonresponders
• 5 year follow-up of 45% of TADS sample
  – 96.4% recovered from their index episode of depression
  – 46.6% had a recurrence
  – Full or partial responders were less likely to have a recurrence (42.9%) than were nonresponders (67.6%) (P = .03)
  – Females were more likely to have a recurrence (57.0%) compared to males (32.9%) (P = .02)

Evidence That Conflicts with TADS: ADAPT

• “Adolescent Depression Antidepressant and Psychotherapy Trial,” conducted in the UK (Goodyer et al., 2007 & 2008)
• Pragmatic randomized controlled superiority trial comparing:
  1. Routine specialist care + fluoxetine 20-60 mg/day or other SSRIs (SSRI)
  2. Routine specialist care + SSRI as above + CBT for 19 sessions over 28 weeks (COMB)

ADAPT (cont.)

• Subjects were adolescents with moderate to severe MDD or probable MDD (N=208)
• Follow-up at 12 weeks (after acute treatment), and then at 28 weeks (maintenance phase)
• Key differences between ADAPT and TADS:
  – ADAPT included subjects with active suicidal intent, self-harm, depressive psychosis, or CD
  – ADAPT did not include a placebo group

ADAPT: Outcome Measures

• Primary:
  – Health of the Nation Outcome Scale at 12 weeks (assesses global impairment)
• Secondary:
  – Mood and Feelings Questionnaire
  – Children’s Depression Rating Scale-Revised
  – Children’s Global Assessment Scale
  – Clinical Global Impression Improvement Scale
  – Suicidality items from the K-SADS-PL depression section
ADAPT: Results

- 21% of participants improved with a brief initial intervention and were therefore withdrawn from the study
- No significant group differences for the primary or secondary outcome measures
- Much or very much improved at 28 weeks:
  - SSRI=61%, COMB=53%, overall=57%
- No response or worse at 28 weeks:
  - SSRI=17%, COMB=25%, overall=21%
- Suicidality:
  - On average, there was a ↓ in SI and self-harm
  - No evidence of a protective effect of CBT on SI or self-harm (unlike TADS)

ADAPT: Conclusions

- “Consideration of previous and current study data suggests that, for depressed patients referred from community settings, the addition of CBT adds little to specialist active clinical care in conjunction with an SSRI in the short term.”
- “Low attendance rates for CBT may have reduced response, despite the intensive efforts made to maintain therapeutic contact. This reflects the clinical realities of implementing treatment for severely depressed adolescents….”

ADAPT: Conclusions (cont.)

- “[F]or those presenting with moderate (6-8 symptoms) to severe depressions (>8 symptoms) and in those with either overt suicidal risk and/or high levels of personal impairment … the time allowed for response to psychosocial interventions should be no more than 2-4 weeks, after which fluoxetine should be prescribed.”

TORDIA Trial

- “Treatment of SSRI-Resistant Depression in Adolescents” (Brent et al., 2008)
- Federally funded, multi-site RCT in a clinical sample of 334 youth (12-18 years) with MDD who had not responded to 2-month initial treatment with an SSRI

TORDIA: Randomization

- Randomized to 12 weeks of:
  1. Switch to a second, different SSRI (PAR, CIT, or FLX)
  2. Second SSRI + CBT
  3. Switch to venlafaxine (VEN)
  4. VEN + CBT
- Medication assignment was double-blinded, and CBT was blinded to independent evaluators

TORDIA: Main Outcome Measures

- “Adequate clinical response,” defined as a CGI-Improvement score of “much” or “very much” improved and ≥50% ↓ in the Children’s Depression Rating Scale-Revised (CDRS-R)
- Change in CDRS-R over time
TORDIA: Efficacy Results

- Response rates:
  - CBT + switch to either medication regimen (55%) > medication switch alone (41%)
  - VEN (48%) = 2nd SSRI (47%)
- No differential treatment effects on change in the CDRS-R, CGAS, CGI-Severity Subscale, or self-rated depressive symptoms
- Remission from treatment associated with improvement in anxiety, ADHD and DBD
- Greater likelihood of response if also using sleep agents

TORDIA: Adverse Event Results

- No differences among treatments regarding:
  - Frequency of adverse events overall, serious adverse events, or removal from the study because of adverse events
  - Self-harm or suicide-related adverse events
- Psychiatric adverse events:
  - Sleep difficulties (5%) and irritability (5%) were the only psychiatric adverse events that occurred in ≥5% (no group differences)
  - Only 1 instance of hypomania during the first 12 wks
  - 18 suicide attempts in 17 participants, but no completed suicides

TORDIA: Adverse Events (cont.)

- Nonpsychiatric adverse events:
  - Of nonpsychiatric adverse events that occurred in ≥5% of participants, only skin problems were significantly more common with VEN vs. a 2nd SSRI (8% vs. 2%)
  - Compared with a 2nd SSRI, VEN resulted in significantly greater ↑ in DBP (+3.3 vs. -1.6 mm Hg) and HR (+6.0 vs. -1.1 bpm)
  - CV changes associated with VEN were rarely clinically significant
  - Participants removed from the study for CV reasons: 4 for VEN vs. 1 for a 2nd SSRI (p=0.2)

TORDIA: Conclusions

- "For adolescents with depression not responding to an adequate initial treatment with an SSRI, the combination of CBT and a switch to another antidepressant resulted in a higher rate of clinical response than did a medication switch alone."
- "However, a switch to another SSRI was just as efficacious as a switch to venlafaxine and resulted in fewer adverse effects."

TASA Trial

- “Treatment of Adolescents Suicide Attempters Study” (Vitiello et al., 2009)
- Federally funded, multi-site trial in a clinical sample of 124 youth (12-18 years) with 90-day history of suicide attempt and current MDD diagnosis

TASA: Group Assignment

- Assigned to 6-months of:
  1. Antidepressant Medication
  2. CBT
  3. Antidepressant + CBT
- Either randomized or adolescent chose treatment arm (84%)
- 75% (N=93) received combination treatment

*Due to low recruitment
TASA: Main Outcome Measures

- Recurrence of suicide event as measured by the Scale for Suicidal Ideation (SSI)
- SSI scores were correlated with CDRS-R and both declined from baseline at week 12 and at week 24 (p<0.0001)
- 23 suicide events occurred in 15 subjects over the course of treatment
  - 35% occurred in first 4 weeks
  - 83% occurred in first 12 weeks

TASA: Conclusions

- "When vigorously treated with a combination of medication and psychotherapy, depressed adolescents who have recently attempted suicide show rates of improvement and remission of depression that appear comparable to those observed in non-suicidal depressed adolescents."

Other Findings from the Literature

- TORDIA
  - 59% of adolescents who completed study during the summer holidays improved compared to 41% who completed during school year (2011)
  - Anhedonia predicted poorer outcomes (depression free days, longer time to remission) (2012)
- Cheung et al. 2010
  - Comorbidities influences efficacy of fluoxetine in children and adolescents with depression

Efficacy: Pediatric OCD

Positive DBPC Trials of SSRIs for Pediatric OCD (Published)

- Fluoxetine:
  - Riddle et al., 1992
    - p = 0.01 on CGI-OCD, but p = 0.17 on CY-BOCS
  - Geller et al., 2001
- Paroxetine:
  - Geller et al., 2004
- Sertraline:
  - Open-label extension by Cook et al. (2001) was also positive
  - March et al., 1998
- Fluvoxamine:
  - Riddle et al., 2001

Effect size=0.2-0.7; NNT=2-6

Which SSRI for Pediatric OCD?

- Geller et al., 2003:
  - Meta-analysis of 12 studies (N=1044) of fluoxetine, fluvoxamine, paroxetine, sertraline, and clomipramine for pediatric OCD
  - Each medication examined was significantly better than placebo or comparator treatments
Geller et al., 2003 (cont.)

- Overall effect size for medication was **0.46** ("medium"):
  - Corresponds to a difference of about 4 points (out of 40) on the CY-BOCS between active treatment and placebo
- Overall, pharmacotherapy resulted in a 30-40% reduction in OCD symptoms

All SSRIs were comparably effective
- Although no studies of CIT were included in this meta-analysis, a subsequent RCT of FLX vs. CIT found no significant difference in efficacy (Alaghband-Rad & Hakimshooshtary, 2009)
- Clomipramine was significantly superior to each of the SSRIs
- However, the authors do NOT recommend clomipramine as the first-line medication for pediatric OCD, as it is associated with more frequent and serious adverse effects, particularly cardiac arrhythmias

SSRI vs. CBT for Pediatric OCD?

- Watson & Rees, 2008:
  - Meta-analysis of RCTs for pediatric OCD:
  - Includes 10 pharmacotherapy (N=1016) & 5 CBT (N=161) trials
  - Medications studied in the pharmacotherapy trials include FLX, SER, PAR, FLV, & CMI
  - Effect sizes:
    - Pharmacotherapy: **0.48**
    - CBT: **1.45**

Watson & Rees, 2008 (cont.)

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</table>

Note: n = number of studies, NA = not applicable
*Results were not pooled due to lack of multiple studies.

POTS

- Pediatric OCD Treatment Study (POTS Team, JAMA, 2004)
- Federally funded, multisite RCT conducted in the U.S.
- Subjects were 112 youth (7-17 years) with moderate to moderately severe OCD

POTS: Randomization

- 4 treatment groups (12 weeks):
  1. Sertraline up to 200 mg/d (SER)*
  2. CBT (CBT)**
  3. Sertraline up to 200 mg/d + CBT (COMB)**
  4. Placebo (PBO)*

*Blinded **Unblinded
POTS: Interventions

- CBT:
  - 14 1-hour sessions, including 3 conjoint parent and youth sessions
- Sertraline:
  - Fixed-flexible upward titration from 25 to 200 mg/day over 6 weeks
  - Mean highest dose of SER/PBO:
    - SER: 170 mg/day
    - COMB: 133 mg/day
    - PBO: 176 mg/day

POTS: Main Outcome Measures

- Change in CY-BOCS (Children’s Yale-Brown Obsessive-Compulsive Scale)
- Rate of clinical remission defined as a CY-BOCS score ≤ 10

POTS: Efficacy Results

- Change in CY-BOCS:
  - COMB > CBT = SER > PBO
- Rate of clinical remission:
  - COMB (54%) = CBT (39%)
  - COMB (54%) > SER (21%) = PBO (4%)
  - CBT (39%) > PBO (4%)
  - But... CBT (39%) = SER (21%)

POTS: Efficacy Results (cont.)

- Effect sizes (using the CY-BOCS):
  - COMB: 1.4
  - CBT: 0.97
  - SER: 0.67
- NNT for clinical remission:
  - COMB: 2
  - CBT: 3
  - SER: 6

POTS: Adverse Event Results

- POTS treatments were generally well tolerated
- Medication-related adverse events (≥25% of patients treated with SER and ≥2x the rate seen in patients treated with PBO): ↓ appetite, diarrhea, enuresis, motor overactivity, nausea, stomachache
- No serious adverse events
- No patient had SI or made a suicide attempt
- No episodes of mania, hypomania, or depression

POTS: Conclusion

- “Children and adolescents with OCD should begin treatment with the combination of CBT plus a selective serotonin reuptake inhibitor or CBT alone.”
POTS Secondary Analysis
• March et al., 2007:
  – Stratified analysis:
    • OCD without chronic tic disorder (N=95)
    • OCD with chronic tic disorder (N=17)
  – Outcome measure: change in CY-BOCS
  – Results:
    • OCD without chronic tic disorder:
      = COMB > CBT > SER > PBO
    • OCD with chronic tic disorder:
      = COMB > CBT > PBO; SER = PBO

POTS Secondary Analysis
• Garcia et al., 2010:
  – Moderators and predictors of outcomes
  – Better outcomes for youth with:
    • Lower OCD severity
    • Less OCD-related functional impairment
    • Greater insight
    • Fewer co-morbid externalizing symptoms
  – Family history of OCD associated with more than 6x decrease in effect size in CBT monotherapy

POTS II
• Pediatric OCD Treatment Study II
  (Franklin et al., 2011)
• CBT augmentation study
• Federally funded, multisite RCT conducted in the U.S.
• Subjects were 124 youth (7-17 years) with moderate to moderately severe OCD who partially responded to treatment with SSRI

POTS II: Randomization
• 3 treatment groups (12 weeks):
  1. Medication only
  2. Medication + instructions in CBT
  3. Medication + CBT (14 sessions)

POTS II: Main Outcome Measures
• Change in CY-BOCS (Children’s Yale-Brown Obsessive-Compulsive Scale)
• Rate of clinical response defined as a decrease in CY-BOCS score by 30%

POTS II: Efficacy Results
• Percentage of subjects with clinical response:
  – COMB (69%) > CBT instruction (34%) > Medication alone (30%)
  – COMB > CBT instruction and Medication alone
  – But CBT instruction not better than Medication alone
POTS II: Efficacy Results (cont.)

- Effect sizes (using the CY-BOCS):
  - COMB: 0.85
  - CBT instruction: 0.16
- NNT for clinical response:
  - COMB: 3
  - CBT instruction: 25

POTS II: Adverse Event Results

- POTS II treatments were generally well tolerated
- No differences in medication-related adverse events seen between groups
- One patient (medication alone) made a suicide attempt and one patient (CBT instruction) had SI

POTS II: Conclusion

- Children and adolescents with OCD and partial response to SSRI should begin treatment with CBT

Efficacy: Pediatric Non-OCD Anxiety Disorders

- Positive DBPC Trials of SSRIs for Pediatric Non-OCD Anxiety (Published)
  - Fluoxetine:
    - Birmaher et al., 2003 (SAD, GAD, SP)
    - Beidel et al., 2007 (SP)
  - Paroxetine:
    - Wagner et al., 2004 (SP)
  - Sertraline:
    - Rynn et al., 2001 (GAD)
    - CAMS, 2008 (SAD, GAD, SP)
  - Fluvoxamine:
    - RUPP Anxiety Study Group, 2001 (SAD, GAD, SP)

  *Effect size = 0.4-1.9; NNT = 1-4*

CAMS

- “Child-Adolescent Anxiety Multimodal Study” (Walkup et al., NEJM, 2008)
- Federally funded, multisite RCT in 488 youth (7-17 yrs) with a primary diagnosis of a non-OCD anxiety disorder (separation anxiety disorder, generalized anxiety disorder, or social phobia)
CAMS: Randomization

- 4 treatment groups (12 weeks):
  1. Sertraline up to 200 mg/day (SER)*
  2. CBT**
  3. Combination of SER up to 200 mg/day + CBT (COMB)**
  4. Placebo (PBO)*

*Blinded    **Unblinded

CAMS: Main Outcome Measures

- Treatment response defined as a CGI-Improvement score of “much” or “very much” improved
- Pediatric Anxiety Rating Scale (PARS)

CAMS: Interventions

- CBT:
  - 14 60-minute sessions based on the Coping Cat program
- Sertraline:
  - Fixed-flexible upward titration from 25 to 200 mg/day over 8 weeks
  - Mean dose of SER/PBO at final visit:
    • SER: 134 mg/day
    • COMB: 146 mg/day
    • PBO: 176 mg/day

CAMS: Efficacy Results

- Response rates (CGI):
  - COMB (81%) > CBT (60%) = SER (55%) > PBO (24%)
- PARS results revealed a similar ordering of outcomes:
  - COMB > SER = CBT > PBO
- Remission rates (based on loss of dx):
  - COMB (46% to 68%) > SER (34% to 46%), CBT (20% to 46%) > PBO (15% to 27%)

CAMS: Efficacy Results (cont.)

- Effect sizes and NNT:
  - COMB: ES=0.86, NNT=1.7
  - SER: ES=0.45, NNT=3.2
  - CBT: ES=0.31, NNT=2.8

CAMS: Efficacy Results (cont.)

- 24-36 Week Outcome
  - Responders (active arms) had 6 monthly booster sessions
  - Combination remain superior to monotherapy of Sertraline or CBT
  - However, concomitant treatment common and may explain convergence
CAMS: Other Findings

- **CAMS**
  - Having more severe and impairing anxiety, greater caregiver strain, and a principal diagnosis of social phobia were associated with less favorable outcomes (2014)
  - Naturalistic follow-up at 6 years (59% of sample) - 50% were in remission Acute responders more likely to be in remission (OR = 1.83) (2014)

CAMS: Adverse Event Results

- 3 subjects had serious adverse events during the study period:
  - 1 was considered to be possibly related to sertraline
  - The other 2 were considered unrelated to a study treatment
- There were no completed or attempted suicides in the study

CAMS: Adverse Events (cont.)

- There were significantly more reports of the following adverse events in the SER group than in the CBT group: insomnia (8% vs. 1%), fatigue (6% vs. 0%), sedation (5% vs. 0%), and restlessness or fidgeting (4% vs. 0%)
- However, no physical, psychiatric, or harm-related adverse event was significantly more frequent in the SER group than in the PBO group

CAMS: Conclusions

- CBT and sertraline each brought about a similar reduction in anxiety in children with non-OCD anxiety disorders
- A combination of CBT and sertraline had a superior response rate than either treatment alone
- “[All three of the treatment options may be recommended, taking into consideration the family’s treatment preferences, treatment availability, cost, and time burden.”

Robb et al., 2011

DBPC trial of PTSD

- Children and adolescents (6-17 years old) with PTSD
- 131 subjects randomized to 10 weeks of sertraline (50-200 mg/day) or placebo
- Primary efficacy measure was the University of California, Los Angeles Post-Traumatic Stress Disorder Index for DSM-IV (UCLA PTSD-I)
- No difference between sertraline and placebo in the UCLA PTSD-I score
- Attrition was higher on sertraline (29.9%) compared to placebo (17.7%)
- Discontinuation due to adverse events:
  - Sertraline 7.5%
  - Placebo 3.2%

Do SSRIs Work Better for Anxiety, or Does Placebo Just Work Better for MDD?

- Cohen et al., 2008:
  - Compared PBO response rates in pharmacological trials for pediatric MDD (23 trials), OCD (7), and non-OCD anxiety disorders (10)
  - Pooled PBO response rate was found to be significantly higher (p=0.002) for MDD than for OCD or non-OCD anxiety:
    - MDD: 50%
    - OCD: 31%
    - Non-OCD anxiety: 40%
  - Children showed a nonsignificantly higher PBO response rate than adolescents, and differences were similar (about 10%) in each of the 3 diagnostic categories
SSRIs: Adverse Effects

- GI symptoms (vomiting in particular is more common in younger children)
- Headaches
- Dizziness
- Activation (especially in younger children)
- Triggering of manic symptoms in individuals with a bipolar diathesis
- Akathisia
- Mania
- Increased Prolactin

SSRIs: Adverse Effects (cont.)

- Irritability
- Insomnia
- Somnolence (less common in children)
- Appetite decrease or increase
- Diaphoresis
- Sexual dysfunction
- Serotonin syndrome
- Flu-like symptoms during discontinuation
- Suicidality

SSRI & Suicide Controversy

- Hammad et al., 2006:
  - FDA meta-analysis of 24 placebo-controlled trials (4582 subjects) of 2nd-generation antidepressants (SSRIs, venlafaxine, mirtazapine, nefazodone, and bupropion) for the treatment of pediatric MDD (N=16), OCD (N=4), GAD (N=2), SP (N=1), or ADHD (N=1)
  - Objective: To investigate the relationship between antidepressant drugs and suicidality in pediatric patients

Hammad et al., 2006 (cont.)

- Results:
  - The risk ratio for suicide-related events (SREs) for all trials and indications was 1.95 (95% CI: 1.28-3.98)
  - The risk difference for all trials and indications was 2% (95% CI: 1-3%)
  - The risk ratio for SSRIs in depression trials was 1.66 (95% CI: 1.02-2.68)

Risk of SREs with Each Individual Antidepressant
Hammad et al., 2006 (cont.)

- Bottom line:
  - No suicides occurred in these trials
  - Overall, the average risk of SREs was 4% on drug, compared with 2% on placebo

FDA Public Health Advisory (2004):

- FDA include black box warnings that recommend close observation of adult and pediatric patients treated with antidepressants for worsening of depression or the emergence of suicidality (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram, bupropion, venlafaxine, nefazodone, and mirtazapine).
- Risk is doubled on antidepressant treatment

FDA Public Health Advisory (cont.)

- “at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.”
- Monitoring schedule removed 1 year later
- In December 2006, the FDA voted to extend its “black box” warning regarding the risk of suicidality with antidepressants up to age 25


- “Patients of all ages taking (SSRIs and other new antidepressants) may experience behavioural and/or emotional changes that may put them at increased risk of self-harm or harm to others.”
- “Patients, their families and caregivers should note that a small number of patients taking drugs of this type may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts that could involve self-harm or harm to others.”

Health Canada Advisory (cont.)

- “It is important to note that Health Canada has not authorized these drugs for use in patients under 18 years of age.”
- “Off-label use of these drugs in children is acknowledged to be an important tool for doctors.”
- “Doctors are advised to carefully monitor patients of all ages for emotional or behavioural changes that may indicate potential for harm, including suicidal thoughts and the onset or worsening of agitation-type adverse events.”

SSRI & Suicide Controversy, Revisited

- Bridge et al., 2007:
  - Meta-analysis of 27 DBPC trials (5310 subjects) of 2nd-generation antidepressants (SSRIs, venlafaxine, mirtazapine, and nefazodone) for treatment of pediatric MDD, OCD, or non-OCD anxiety disorders
  - 2 objectives:
    1. Assess efficacy of the antidepressants
    2. Assess risk of suicidality of the antidepressants
Bridge et al., 2007: Efficacy Results

• Pooled risk differences in rates of primary study-defined measures of responder status significantly favoured antidepressants over placebo for MDD, OCD, and non-OCD anxiety disorders

• However, the strength of the effect varied by treatment indication

Bridge et al., 2007: Efficacy Results (cont.)

• Pooled risk differences (antidepressants vs. placebo) in responder status by indication:
  – MDD: 11% (61% vs. 50%)
    • Corresponds to NNT=10 (similar to the result of Tsapakis et al., 2008)
    • For children <12 yrs, only fluoxetine showed benefit over placebo
  – OCD: 20% (52% vs. 32%)
    • Corresponds to NNT=6
  – Non-OCD anxiety: 37% (69% vs. 39%)
    • Corresponds to NNT=3

Bridge et al., 2007: Suicidality Results

• There was a significantly increased risk difference of suicidal ideation/attempt for antidepressants ACROSS all trials and indications: 0.7%
  – Corresponds to NNH=143
  – Lower than the 2% reported by Hammad et al., 2006

• The pooled risk differences WITHIN each indication were not statistically significant
• There were no completed suicides

Bridge et al., 2007: Conclusions

• “Relative to placebo, antidepressants are efficacious for pediatric MDD, OCD, and non-OCD anxiety disorders”

• Benefit of antidepressants:
  - Non-OCD anxiety > OCD > MDD
  - “Benefits of antidepressants appear to be much greater than risks from suicidal ideation/attempt across indications”

But Not Everyone Agrees…

• Wallace et al., 2006:
  – “Cumulative meta-analyses of 7 RCTs for efficacy and 11 RCTs for safety suggest an adverse safety/efficacy profile for SSRIs overall [for pediatric depression].”
  – “Fluoxetine and citalopram appear to offer favorable risk to benefit profiles, while shorter-acting agents pose greater risks and provide marginal benefit.”

SSRIs & Suicidality: Not Just Kids?

 enlarged slide appended

Epidemiological Perspective

- 12-month incidence of suicide or suicide-related events in youth aged 15-19:
  - Suicide: 0.008% (Anderson, 2002)
  - Suicidal ideation: 15% (Grunbaum et al., 2007)
  - Suicide attempt: 7% (Grunbaum et al., 2007)
- Only 2% of youth who commit suicide are receiving medication at the time of suicide (Leon et al., 2004; Isacsson et al., 2005)
- Some evidence indicates that rates of youth suicide correlate inversely with the number of antidepressant prescriptions for youth (Olfson et al., 2003; Gibbons et al., 2006)

Meta-analysis of Observational Studies of SSRIs & Suicide Attempt/Completion

What About Differences By Class?

- Cooper et al., 2014:
  - Medicaid population aged 6-18 years old
  - No difference found in rates of medically treated suicidality between SSRI's and SNRI's
- Gibbons et al., 2005
  - No significant relationship between antidepressant medication prescription and suicide rate
  - SSRIs and other new-generation non-SSRI antidepressants are associated with lower suicide rates

Consequences of Recent Warnings Regarding SSRIs and Suicidality

- Libby et al., 2007 (using a U.S. national database):
  - From 1999 to 2004, pediatric diagnoses of depression ↑ from 3 to 5 per 1,000, but after the FDA advisory about the risk of suicidality in youth taking SSRIs for depression (October 2003), they ↓ to 1999 levels
  - Among patients with depression, the proportion receiving no antidepressant ↑ to 3x the rate predicted by the pre-advisory trend, and SSRI prescription fills were 58% lower than predicted by the trend
  - No evidence of a significant ↑ in the use of treatment alternatives (psychotherapy, atypical antipsychotics, and anxiolytics)
- Libby et al., 2007 (cont.):
  - Conclusions:
    - “The FDA advisory was associated with significant reductions in aggregate rates of diagnosis and treatment of pediatric depression.”
    - “The results of our study suggest a need for public health interventions to ease unintended but predictable changes in treatment patterns that may increase ‘the risk of doing nothing.’”

But on the Other Hand…

- Olfson et al., 2008 (also using a U.S. national database):
  - Objective was to characterize associations of antidepressant use with two FDA warnings regarding SSRIs and the risk of suicidal behavior:
    - June 2003: FDA recommended that paroxetine (PAR) not be used in youth
    - Oct 2004: FDA issued a “black box” warning concerning all antidepressants for youth

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Olfson et al., 2008 (cont.)

• Results:
  – During the prewarning study period, there was a 36%/year ↑ in total youth antidepressant use
  – After the PAR warning, there was a significant absolute ↓ in PAR use by youth, but not significant ↓ in use of other antidepressants by youth
  – Following the black box warning, there was a statistically nonsignificant ↓ in antidepressant treatment of youth, including a significant deceleration in the rate of treatment with SSRIs other than PAR
  – Changes in antidepressant use were less pronounced in adults than in youth

Conclusions:

– “Concern has been expressed that the FDA advisories may have resulted in excessive declines in antidepressant prescribing, thereby putting depressed youth at increased risk. Our report indicates that the absolute rate of overall antidepressant treatment of youth did not significantly decrease during the period of FDA regulatory activity.”
– “The paroxetine and black box warnings had modest and relatively targeted effects on the intended populations. These changes, which were greatest for youth, were broadly consistent with the FDA warnings and the scientific literature.”

More data in 2012…

• Chen et al., 2012
  – Examined rates of prescribing pre-FDA and post-FDA warning in US national surveys
  – Overall decrease in depression visits and antidepressant prescribing for ages 5 to 17
  – Depressive visits and antidepressant prescribing unchanged if it was for Major Depressive Disorder
  – No changes in adults

Completed Suicide Data: Gibbons et al., 2007

• After warnings were issued in 2003 and 2004 about antidepressants and suicidality, SSRI prescriptions for youth ↓ by 22% in both the Netherlands and the U.S.
• In the Netherlands, the youth suicide rate ↑ by 49% from 2003 to 2005, showing a significant inverse association with SSRI prescriptions
• In the U.S., the youth suicide rate ↑ by 14% from 2003 to 2004, the largest year-to-year change since suicide data started to be collected in 1979

What About Canada?

• Kurdyak et al., 2007:
  – Studied whether 5 advisories (1 UK, 3 US, 1 CAN) about the possible ↑ risk of suicidality during AD therapy had an effect on AD prescription trends in Ontario (limited to those on assistance or >65 years of age)
  – Results:
    • Rate of new PAR prescriptions in patients <20 yrs (but not in other age groups) ↓ by 54% immediately after the first warning for PAR was issued in the UK (June 2003)
    • However, the rate of new prescriptions for SSRIs as a group did not change after any AD warning in any age group
Manitobans Must Have More Respect for Authority

• Katz et al., 2008:
  – Studied the rates of antidepressant prescription, use of health services, and outcomes in youth and young adults (5-24 yrs) in Manitoba during 2 periods:
    1. The 9 years before the Health Canada warning about antidepressants and suicide risk (June 2004)
    2. The 2 years after the Health Canada warning

Katz et al., 2008: Results

• Following the Health Canada warning:
  – Rate of antidepressant prescriptions ↓ significantly among youth and among young adults
  – Ambulatory visits because of depression ↓ significantly among youth and among young adults
  – Rate of completed suicides ↑ significantly among youth (0.04/1000 before the warning vs. 0.15/1000 after the warning), but not among young adults

Katz et al., 2008: Conclusions

• “Health advisories and warnings issued by regulatory bodies may have unintended consequences on the provision of care, delivery of health services and clinical outcomes.”
• “Given the potentially devastating consequences of some health warnings, greater attention must be paid to optimal dissemination strategies for health advisories and warnings.”
Why did Practices Change?

• Cheung et al., 2008
  – Survey of pediatricians in Canada (n=670)
  – 80% changed practice due to warnings
  – 32% followed patients more closely
  – 7% stopped treatment in at least one patient
  – 25% referred back to psychiatrist for care
  – 8% reported patients stopping medications on their own
  – Experience with worsening symptoms affected more likely to stop treatment

SSRI & Suicide Controversy: Questions & Discussion

Contraindications

• Hypersensitivity to the SSRI

• Treatment with an MAOI
  – Wait at least 14 days between stopping one (SSRI or MAOI) and starting the other, except for fluoxetine, which must be stopped for at least 5 weeks before starting an MAOI

Drug Interactions

• Beware of CYP 450 interactions

• Protein binding competition (e.g., with warfarin, phenytoin, and valproic acid)

• MAOIs (serotonin syndrome)

Monitoring

• Improvement in target symptoms (standardized rating scales are useful)

• Emergence of manic symptoms or SI

• Akathisia and activation

• Other adverse effects

• No labs required, but some suggest monitoring CBC, LFTs, and electrolytes

Choosing an SSRI

• FLX is generally the first medication choice for pediatric depression because:
  – FDA approval for MDD (as well as OCD) in youth
  – Has the most evidence to support efficacy for pediatric MDD, especially in children <12 years
  – Long half-life is an advantage if non-adherence is a concern
  – Long half-life minimizes the risk of withdrawal
  – Unlike the other SSRIs, it’s available as an oral solution (liquid) in Canada
  – Recommended as “the antidepressant of choice” in the CMAP algorithm (Hughes et al., 2007)
Choosing an SSRI (cont.)

- Reasons for choosing CIT/ECIT or SER instead of FLX for pediatric MDD (Hughes et al., 2007):
  - Potential drug interactions with FLX
  - Wish to avoid a long-acting agent because the patient has risk factors for bipolar disorder
  - Family resistance to FLX
  - Prior poor response to an adequate trial of FLX
  - (?) Family history of poor response to FLX, or good response to CIT/ECIT or SER
- For pediatric OCD and other anxiety disorders, “the antidepressant of choice” is arguably SER, as it has FDA approval for OCD and was studied in both POTS and CAMS

Dosing Considerations

- SSRI dosing is not well established in children
- In general, pediatric doses are similar to adult doses, but most suggest starting lower and going slower
  - This may be open to debate given the titration schedules used in POTS and CAMS, and how well tolerated SER was in these trials
- Because of children’s increased rate of drug metabolism, some recommend BID dosing at lower dosages of all SSRIs except FLX to minimize the risk of daily withdrawal symptoms

Suggested Dosing

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<th>Usual Dose Range (mg/day)</th>
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<td>2.5-10</td>
<td>10-80</td>
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</tr>
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<td>Sertraline</td>
<td>25-50</td>
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<td>• The FDA has recommended that PAR not be used in youth</td>
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<tr>
<td>Citalopram</td>
<td>5-10</td>
<td>10-60</td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>2.5-5</td>
<td>5-20</td>
<td>• Reportedly 4 times as potent as citalopram</td>
</tr>
</tbody>
</table>

Discontinuing an SSRI (Pine, 2002)

1. For children who achieve marked reduction in anxiety or depressive symptoms on an SSRI, consider recommending a medication-free trial
2. When indicated, this medication-free trial should coincide with the first low-stress period (e.g., summer vacation) occurring after 1 year of continuous SSRI treatment
3. SSRI treatment should be reinitiated in children who exhibit signs of relapse during this medication-free trial

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Should young people be given antidepressants?

Andrew Cotgrove clinical director, Pine Lodge Young People’s Centre, Cheshire and Wirral Partnership NHS Foundation Trust, Chester CH2 1AW andy.cotgrove@cwpnt.nhs.uk

Sami Timimi consultant child and adolescent psychiatrist, Lincolnshire Partnership NHS Trust, Skeffold, Lincolnshire NG34 8QA stimimi@talk21.com

**YES**

Depression and obsessive-compulsive disorder cause considerable distress in young people. These disorders affect emotional, educational, and social development. To deny these vulnerable groups the possibility of receiving antidepressants would be to withhold one of the few evidence based treatments available to them.

**NOT**

The medical profession had endorsed the use of selective serotonin reuptake inhibitors (SSRIs) well before any of the big studies in children were published.¹ Now that studies have been done, the evidence is clear: the drugs are not effective in young people and can increase suicidal behaviour. Continuing to use SSRIs in young people is not good value for money, dangerous, and ethically unsound.

Reference: British Medical Journal, 13 October 2007, Volume 335

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TADS: Adverse Event Results

• Emslie et al., 2006:
  – *Non*psychiatric medication-related AEs (≥2% of patients on FLX and ≥2x the rate seen in patients on PBO): sedation, insomnia, vomiting, upper abdominal pain
  – Psychiatric AEs *besides* suicide-related events:

<table>
<thead>
<tr>
<th>TABLE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneously Reported Psychiatric Adverse Events</td>
</tr>
<tr>
<td>Symptom</td>
</tr>
<tr>
<td>Mania spectrum</td>
</tr>
<tr>
<td>Irritability</td>
</tr>
<tr>
<td>agitation spectrum</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Event rate</td>
</tr>
</tbody>
</table>

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Figure 2. Adjusted mean Children’s Depression Rating Scale–Revised (CDRS-R) total scores. A, intention-to-treat (ITT) analysis. B, and observed case (OC) (B) analyses. CBT indicates cognitive behavior therapy.

Table 3. Magnitude of the Effect of Combination Therapy and Fluoxetine Relative to CBT

<table>
<thead>
<tr>
<th>Week</th>
<th>Contrast</th>
<th>ITT Population</th>
<th>OC Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Effect Size, Hedges $g$</td>
<td>CDRS-R</td>
<td>RAD5</td>
</tr>
<tr>
<td>12</td>
<td>Combination-CBT</td>
<td>0.71</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>FLX-CBT</td>
<td>0.48</td>
<td>0.39</td>
</tr>
<tr>
<td>18</td>
<td>Combination-CBT</td>
<td>0.55</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>FLX-CBT</td>
<td>0.38</td>
<td>0.33</td>
</tr>
<tr>
<td>36</td>
<td>Combination-CBT</td>
<td>0.07</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>FLX-CBT</td>
<td>-0.01</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Abbreviations: CBT, cognitive behavior therapy; CDRS-R, Children’s Depression Rating Scale–Revised; CGI-I, Clinical Global Impressions–Improvement; FLX, fluoxetine hydrochloride therapy; ITT, intention-to-treat; NNT, number needed to treat; OCs, observed cases; RADS, Reynolds Adolescent Depression Scale.
TADS Team, 2007: Long-term Safety

- Suicidal ideation over time:
  - **12 wks**: FLX (19%) > COMB (9%) = CBT (6%)
  - **36 wks**: FLX (14%) > CBT (4%) = COMB (3%)
  - No completed suicides

### Table 5. ORs and Treatment Contrasts for Suicidal Events

<table>
<thead>
<tr>
<th>Planned Contrast</th>
<th>ITT Population</th>
<th>OC Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \chi^2 ) Test</td>
<td>( P ) Value</td>
</tr>
<tr>
<td>Stage 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination-CBT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.0</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>FLX-CBT</td>
<td>3.3</td>
<td>.07</td>
</tr>
<tr>
<td>FLX-combination</td>
<td>3.0</td>
<td>.08</td>
</tr>
<tr>
<td>Stages 1-3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination-CBT</td>
<td>0.4</td>
<td>.55</td>
</tr>
<tr>
<td>FLX-CBT</td>
<td>4.1</td>
<td>.04</td>
</tr>
<tr>
<td>FLX-combination</td>
<td>2.1</td>
<td>.15</td>
</tr>
</tbody>
</table>

Abbreviations: CBT, cognitive behavior therapy; CI, confidence interval; FLX, fluoxetine hydrochloride therapy; ITT, intention-to-treat; OCs, observed cases; OR, odds ratio.

<sup>a</sup>Unless otherwise indicated, \( P \) values were calculated using \( 2 \times 2 \chi^2 \) test results.

<sup>b</sup>Fisher exact test was used to calculate the \( P \) value owing to 25% of the cells having expected counts less than 5.

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### Table 4: Pooled effect sizes of OCD symptom severity for treatment approach compared to control

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pooled ES</th>
<th>95% CI</th>
<th>$I^2$(%)</th>
<th>Test for overall effect (z, p)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT</td>
<td>1.45</td>
<td>.68, 2.22</td>
<td>76.0</td>
<td>3.69, $p = .0002$</td>
<td>5</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>.48</td>
<td>.36, .61</td>
<td>0</td>
<td>7.5, $p &lt; .00001$</td>
<td>10</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>.85</td>
<td>.32, 1.38</td>
<td>37.2</td>
<td>3.21, $p = .0018$</td>
<td>2</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>.51</td>
<td>.18, .84</td>
<td>0</td>
<td>3.02, $p = .0026$</td>
<td>3</td>
</tr>
<tr>
<td>Fluvoxamine*</td>
<td>.31</td>
<td>-.05, .67</td>
<td>NA</td>
<td>1.71, $p = .09$</td>
<td>1</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>.44</td>
<td>.24, .64</td>
<td>0</td>
<td>4.36, $p &lt; .0001$</td>
<td>2</td>
</tr>
<tr>
<td>Sertraline</td>
<td>.47</td>
<td>.21, .73</td>
<td>0</td>
<td>3.61, $p = .0003$</td>
<td>2</td>
</tr>
<tr>
<td>Any treatment</td>
<td>.72</td>
<td>.48, .96</td>
<td>68.2</td>
<td>5.92, $p &lt; .0001$</td>
<td>15</td>
</tr>
</tbody>
</table>

*Notes: n = number of studies, NA = not applicable

*aResults were not pooled due to lack of multiple studies.
Risk of SREs with Each Individual Antidepressant

Table 3. Summary of the Overall Risk Estimates of the Primary Outcome by Drug Across All Indications and in MDD Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>MDD Trials</th>
<th>All Trials, All Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>1.37 (0.53-3.50)</td>
<td>1.37 (0.53-3.50)</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>No MDD trials</td>
<td>5.52 (0.27-112.55)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>2.15 (0.71-6.52)</td>
<td>2.65 (1.00-7.02)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>1.53 (0.74-3.16)</td>
<td>1.52 (0.75-3.09)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>2.16 (0.48-9.62)</td>
<td>1.48 (0.42-5.24)</td>
</tr>
<tr>
<td>Venlafaxine (extended release)</td>
<td>8.84 (1.12-69.51)</td>
<td>4.97 (1.09-22.72)</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>1.58 (0.06-38.37)</td>
<td>1.58 (0.06-38.37)</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>No events</td>
<td>No events</td>
</tr>
<tr>
<td>Bupropion</td>
<td>No MDD trials</td>
<td>No events</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; MDD, major depressive disorder.

(Hammad et al., 2006)
SSRIs & Suicidality: Not Just Kids?

Risk Varies by Age

An FDA analysis of data from 372 clinical trials of 11 antidepressant medications in nearly 100,000 adults revealed that the risk of suicidal thoughts and behaviors was significantly increased for those under the age of about 25, compared with those taking placebo. For those aged 25 to 64, the risk was the same for both groups. However, for those over the age of 65, the risk was significantly reduced for the antidepressant group.

Source: Mark Levenson, Ph.D., Chris Holland, M.S., FDA, December 2006
Meta-analysis of **Observational Studies** of SSRIs & Suicide Attempt/Completion

<table>
<thead>
<tr>
<th>Group; study</th>
<th>Age, yr</th>
<th>Odds ratio (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adolescents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olsson et al.</td>
<td>6–18</td>
<td>11.26 (0.97–130.70)</td>
<td>0.14–0.85</td>
</tr>
<tr>
<td>Olsson et al.</td>
<td>6–18</td>
<td>1.91 (0.90–4.07)</td>
<td></td>
</tr>
<tr>
<td>Sondergard et al.</td>
<td>10–17</td>
<td>4.47 (0.95–20.96)</td>
<td>0.30–0.58</td>
</tr>
<tr>
<td>Tihonen et al.</td>
<td>10–19</td>
<td>1.91 (1.43–2.55)</td>
<td>0.44–1.73</td>
</tr>
<tr>
<td>Valuck et al.</td>
<td>12–18</td>
<td>1.59 (0.89–2.82)</td>
<td>0.74–1.38</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.92 (1.51–2.44)</td>
<td>0.57 (0.47–0.70)</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gibbons et al.</td>
<td>18–25</td>
<td>0.35 (0.14–0.85)</td>
<td></td>
</tr>
<tr>
<td>Gibbons et al.</td>
<td>26–45</td>
<td>0.44 (0.29–0.65)</td>
<td></td>
</tr>
<tr>
<td>Gibbons et al.</td>
<td>46–65</td>
<td>0.42 (0.30–0.58)</td>
<td></td>
</tr>
<tr>
<td>Olsson et al.</td>
<td>19–64</td>
<td>0.87 (0.44–1.73)</td>
<td></td>
</tr>
<tr>
<td>Olsson et al.</td>
<td>19–64</td>
<td>0.80 (0.74–1.38)</td>
<td></td>
</tr>
<tr>
<td>Sondergard et al.</td>
<td>56*</td>
<td>0.58 (0.50–0.66)</td>
<td></td>
</tr>
<tr>
<td>Tihonen et al.</td>
<td>38*</td>
<td>0.76 (0.57–1.10)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.57 (0.47–0.70)</td>
<td>0.57 (0.47–0.70)</td>
</tr>
<tr>
<td><strong>Elderly</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gibbons et al.</td>
<td>≥ 65</td>
<td>0.38 (0.16–0.91)</td>
<td></td>
</tr>
<tr>
<td>Rahme et al.</td>
<td>75*</td>
<td>0.53 (0.27–1.06)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.46 (0.27–0.79)</td>
<td>0.46 (0.27–0.79)</td>
</tr>
</tbody>
</table>

**Figure 2:** Random-effect meta-analysis of the risk of suicide attempt and completion associated with the use of selective serotonin reuptake inhibitors compared with no exposure to any antidepressants. *Mean age. Note: CI = confidence interval.

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Figure 1: Crude annual prevalence of antidepressant prescriptions per 1000 children (5–11 years), adolescents (12–17 years) and young adults (19–24 years) in the province of Manitoba, by fiscal year, before and after Health Canada issued a warning about antidepressant use in children and adolescents (date indicated by red line). People aged 18 years were excluded because of an unclear impact of the warning on prescribing in this age group. The dates are indicated for similar warnings issued in the United Kingdom (dashed line) and the United States (dotted line).

Katz et al., 2008
Figure 2: Crude annual prevalence of fluoxetine prescriptions per 1000 children (5–11 years), adolescents (12–17 years) and young adults (19–24 years) in the province of Manitoba, by fiscal year, before and after Health Canada issued a warning about antidepressant use in children and adolescents (date indicated by red line). People aged 18 years were excluded because of an unclear impact of the warning on prescribing in this age group. The dates are indicated for similar warnings issued in the United Kingdom (dashed line) and the United States (dotted line).
Figure 3: Crude annual rates of completed suicide per 1000 children and adolescents (8–17 years) and young adults (19–24 years), by year, before and after Health Canada issued a warning about antidepressant use in children and adolescents (date indicated by red line). People aged 18 years were excluded because of an unclear impact of the warning on prescribing in this age group. Data for years with fewer than 6 suicides, although included in the outcome analysis, are not portrayed in the figure for confidentiality purposes. The dates are indicated for similar warnings issued in the United Kingdom (dashed line) and the United States (dotted line).
# Suggested Dosing

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting Dose (mg/day)</th>
<th>Usual Dose Range (mg/day)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>2.5-10</td>
<td>10-80</td>
<td>• Long half-life is a disadvantage if the patient may have a bipolar diathesis</td>
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<td>Paroxetine</td>
<td>5-10</td>
<td>10-60</td>
<td>• The FDA has recommended that PAR not be used in youth</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Withdrawal may be particularly problematic</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>25-50</td>
<td>50-300</td>
<td>• BID dosing is generally recommended to minimize side effects</td>
</tr>
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<td>5-10</td>
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