Venlafaxine, Bupropion & Mirtazapine

Learning Objectives

1. Describe the evidence related to the efficacy of venlafaxine, mirtazapine, and bupropion in children and adolescents
2. Identify adverse effects, risks, and necessary precautions associated with these medications in children and adolescents
3. Explain how to initiate, titrate and monitor these medications in children and adolescents

Outline

• Topics to be covered for each medication:
  – Indications & clinical use
  – Pharmacodynamics & pharmacokinetics
  – Efficacy
  – Adverse effects
  – Contraindications & drug interactions
  – Monitoring
  – Dosing

**Interpretation of Efficacy Data**

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>MHRA</th>
<th>FDA</th>
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<td>Venlafaxine</td>
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<td>Mirtazapine**</td>
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**Negative on primary efficacy measure (trend), but positive on most secondary measures.

Indications and Clinical Use

• In adults, venlafaxine is approved for the treatment of MDD, GAD, and SP (Health Canada and FDA)
• In children and adolescents, venlafaxine has no approved indications (Health Canada and FDA)
• Clinically, venlafaxine has been used in pediatric populations as an antidepressant, an anxiolytic, and a treatment for ADHD

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Pharmacodynamics

- Inhibits reuptake of:
  - Serotonin
  - Norepinephrine
  - (Dopamine, to a lesser degree)
- Serotonergic reuptake is thought to be more prominent at lower doses (<150 mg/day [?])
- Noradrenergic reuptake is thought to be more prominent at higher doses (≥150 mg/day [?])
- No significant affinity for cholinergic, histaminic, or α1-adrenergic receptors

Pharmacokinetics

- Immediate release (IR) formulation of venlafaxine is not available in Canada
- Effexor XR (extended release):
  - $T_{\text{max}}$=6 hrs for venlafaxine and 9 hrs for active metabolite O-desmethylvenlafaxine (ODV) in adults
  - Rate of absorption is slower than rate of elimination; therefore, the effective adult elimination $T_{1/2}$ of 15 hours is actually the absorption $T_{1/2}$ rather than the true disposition $T_{1/2}$ (5 hrs for venlafaxine and 11 hrs for ODV) observed after administration of the IR formulation

Pharmacokinetics (cont.)

- Venlafaxine is metabolized by 2D6 and 3A4 to ODV (active metabolite)
- Weak inhibitor of 2D6
- Protein-binding of venlafaxine and ODV is about 30%
- Taking with food has negligible effects on absorption or metabolism

Efficacy: Depression

- Mandoki et al., 1997:
  - 33 subjects, 8-17 years old, with MDD
  - 6-week DBPC trial of venlafaxine+CBT vs. placebo+CBT
  - Venlafaxine dose range: 12.5-75 mg/day
  - Results:
    - Both groups improved, but no significant difference between groups
    - Venlafaxine was generally well tolerated
  - Limitations:
    - Short duration of treatment
    - Venlafaxine dose range may be too low

Efficacy: Depression (cont.)

- Emslie et al., 2007:
  - 2 DBPC trials of venlafaxine XR for up to 8 weeks in youth (7-17 years) with MDD
  - Total N=339
  - Mean daily dose=97.1 mg
    - Adolescents (12-17 years): 109.2 mg
    - Children (7-11 years): 80.4 mg
  - Primary outcome: change in the Children’s Depression Rating Scale-Revised (CDRS-R)

Emslie et al., 2007: Efficacy Results

- No significant differences between venlafaxine XR and placebo on the CDRS-R in either study
- Post-hoc age subgroup analysis of the pooled data:
  - Adolescents: VEN > PBO (-24 vs. -20; p=0.02)
  - Children: VEN = PBO
Emslie et al., 2007: Adverse Event Results

- **Common:**
  - anorexia, abdominal pain, dizziness

- **Notable:**
  - Suicide-related: VEN=11 vs. PBO=1
  - Hostility: VEN=7 vs. PBO=2
  - Hallucinations: VEN=2 vs. PBO=0

- **“Serious”:**
  - VEN=12 (7%) vs. PBO=3 (2%)
  - No completed suicides

Efficacy: Resistant Depression

- **Recall the TORDIA Study:**
  - “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 \( \geq 50\% \) ↓ 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%) = 2\textsuperscript{nd} SSRI (47%)

- **No differential treatment effects on change in the CDRS-R, CGAS, CGI-Severity Subscale, or self-rated depressive symptoms**

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 \( \geq 5\% \) (no group differences)
    - Only 1 instance of hypomania during the first 12 wks
    - 18 suicide attempts in 17 participants, but no completed suicides

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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."

Efficacy: GAD

• Rynn et al., 2007:
  – 2 DBPC trials of venlafaxine XR for 8 weeks in youth (6-17 years) with GAD
  – Total N=313
  – Daily dose range: 37.5 to 225 mg
  – Primary outcome: change in score on 9 items of the GAD section of the K-SADS

Rynn et al., 2007: Efficacy Results

• Study 1:
  – VEN > PBO on the primary outcome measure
  – VEN > PBO on all 8 secondary outcome measures
  – VEN > PBO on response rate using primary outcome measure (38% vs. 17%)

• Study 2:
  – Trend towards VEN > PBO (p=0.06) on the primary outcome measure
  – VEN > PBO on only 3 of 8 secondary outcome measures
  – VEN = PBO on response rate using primary outcome measure

• Pooled analysis:
  – VEN > PBO on the primary outcome measure

Efficacy: Social Phobia

• March et al., 2007:
  – DBPC trial of venlafaxine XR for 16 weeks in youth (8-17 years) with social anxiety disorder
  – N=293 across 48 (!) sites
  – VEN or PBO was titrated from 37.5 mg/day to a maximum of 225 mg/day
  – Primary outcome measures:
    • Social Anxiety Scale (child or adolescent version)
    • Clinical response defined as "much" or "very much" improved on the CGI-I

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March et al., 2007: Efficacy Results

• Social Anxiety Scale:
  – VEN > PBO (p=0.001)
    • VEN: 59.5 @ week 1 → 40.6 @ week 16
    • PBO: 61.3 @ week 1 → 47.7 @ week 16
  – Effect size=0.46
• Clinical response:
  – VEN (56%) > PBO (37%) (p=0.001)
  – NNT=5

March et al., 2007: Adverse Event Results

• Adverse events: VEN=90%, PBO=81%
  – Most common AEs associated with VEN: asthenia, anorexia, nausea, weight loss, abnormal behaviour, pharyngitis, mydriasis
• AEs during tapering: VEN=41%, PBO=23%
  – Most common taper-emergent AEs in the VEN group: nausea, headache, dizziness, and nervousness
• No suicides, suicide attempts, or hostility
• Suicidal ideation: VEN=3, PBO=0 (NNH=47)
• VEN was associated with ↑ in HR (4 bpm) and DBP, and 2 patients (1%) on VEN experienced sustained hypertension

Adverse Effects

• Nausea, abdominal pain
• Anorexia, weight loss
• ↑ appetite
• Behavioural activation
• Insomnia
• Sedation
• Irritability, hostility
• Asthenia
• Dizziness
• Dry mouth
• Nasal congestion
• Skin problems

Adverse Effects (cont.)

• ↑ HR and BP (especially DBP)
• Suicidality:
  – RR compared to placebo=4.97 (95% CI=1.09-22.72) (Hammad et al., 2006)
• (?) Suppression of growth in height:
  – Rynn et al., 2007: after 8 weeks, VEN ↑ 0.3 cm vs. PBO ↑ 1.0 cm (p<0.001)
• (?) ↑ cholesterol:
  – Rynn et al., 2007
• (?) Priapism:
  – Case report in a 16-year-old (Samuel, 2000)

Contraindications

• Hypersensitivity to venlafaxine
• Concurrent MAOI (wait ≥2 weeks between stopping one and starting the other)
• Caution if history of hypertension

Drug Interactions

• MAOIs (serotonin syndrome)
• Inhibitors/inducers of 2D6 and 3A4
• Venlafaxine will modestly increase levels of 2D6 substrates
• Combination of venlafaxine 150 mg/day (steady-state) and haloperidol 2 mg (single dose) resulted in a 70% increase in haloperidol AUC and an 88% increase in venlafaxine C\text{max} (T\text{1/2} unchanged)
  – The mechanism that accounts for this finding is unknown

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Monitoring

- Blood pressure (especially diastolic)
- Suicidality
- Because of venlafaxine’s association with ↑ DBP and its prominent noradrenergic activity at higher doses, some authorities recommend that EKG monitoring be considered for some patients

Dosing: General Info

- No official guidelines for dosing venlafaxine in children and adolescents
- Pharmacokinetic data obtained by Derivan et al. (1997 [abstract]) suggest that to achieve similar blood levels as in adults, children and adolescents need weight-adjusted venlafaxine doses approximately 1.5 times higher

Dosing: General Info (cont.)

- Effexor XR is generally dosed once daily in the morning
- Effexor XR capsules must be swallowed whole (do not cut or chew)
- Taking the medication with food may reduce nausea, but has negligible pharmacokinetic effects

Dosing Specifics (Suggested)

- Start with 37.5 mg po qam
- Gradually titrate up by 37.5-75 mg/day, waiting at least a week between dose increases
- As with all antidepressants, clinical response generally takes 4-6 weeks at a given dose
- In adults, maximum recommended daily dose is 225 mg (HC and FDA)
- Note that the IR formulation of venlafaxine has been studied in adults at doses up to 375 mg/day

Dosing Schedule Used in Study by Rynn et al., 2007

<table>
<thead>
<tr>
<th>Week</th>
<th>25-39.5 kg</th>
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<td>1</td>
<td>17.5 mg</td>
<td>22.5 mg</td>
<td>27.5 mg</td>
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<tr>
<td>2-4</td>
<td>35 or 70 mg</td>
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<tr>
<td>4+6</td>
<td>35 or 70 mg</td>
<td>75 or 105 mg</td>
<td>75 or 105 mg</td>
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</table>

*All patients received 37.5 mg the first week. 2 doses thereafter were increased on the basis of response to treatment and as indicated for each body weight range.

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**Indications and Clinical Use**

- Bupropion is approved by HC and the FDA for depression and smoking cessation in adults.
- Bupropion is not approved by HC or the FDA for any indication in children or adolescents.
- Clinically, bupropion is used in children and adolescents for the following indications:
  - 4th-line medication for ADHD
  - Occasionally for depression after serotonergic agents have failed
  - Occasionally for smoking cessation in adolescents

**Pharmacodynamics**

- Mechanism of action remains unclear
- Blocks NE and DA reuptake
- Major metabolite, hydroxybupropion, is present at levels 10-20 times higher than bupropion itself and blocks only NE reuptake

**Pharmacokinetics**

- Bupropion is rapidly and extensively metabolized in the liver to three active metabolites, the most important of which is hydroxybupropion.
- The metabolism of bupropion to hydroxybupropion is catalyzed primarily by CYP 2B6.
- Bupropion inhibits (but is not metabolized by) CYP 2D6.

**Pharmacokinetics (cont.)**

- Taking bupropion with food has no clinically significant effect.
- Protein-binding is 84% for bupropion and similar for hydroxybupropion.
- Only the SR and XL formulations are available in Canada, and both have linear kinetics in adults and in youths.

**Pharmacokinetics (cont.)**

- Bupropion SR:
  - $T_{\text{max}}$:
    - Adults: 3 hrs for bupropion SR; 6 hrs for hydroxybupropion
    - Youths: 3 hrs for bupropion SR; (?) for hydroxybupropion
  - $T_{1/2}$:
    - Adults: 21 hrs for bupropion SR; up to 37 hrs for active metabolites
    - Youths: 12 hrs for bupropion SR; up to 35 hrs for active metabolites

- Bupropion XL:
  - $T_{\text{max}}$:
    - Adults: 5 hrs for bupropion XL; 7 hrs for hydroxybupropion
    - Youths: 5 hrs for bupropion XL; (?) for hydroxybupropion
  - $T_{1/2}$:
    - Adults: CPS and PDR give the same values for bupropion XL as for bupropion SR
    - Youths: 17 hrs for bupropion XL; (?) for active metabolites
Efficacy: ADHD

- 4 controlled trials in *children* showing superiority of bupropion over placebo:
  - Casat et al., 1987
  - Clay et al., 1988
  - Casat et al., 1989
  - Conners et al., 1996 (n=109)

Efficacy: ADHD (cont.)

- 1 small (n=15) controlled trial in *children and adolescents* (Barrickman et al., 1995):
  - Bupropion vs. MPH crossover (no placebo group)
  - Bupropion and MPH were both effective and did not differ significantly, but nearly all the rating scales trended in favour of MPH
  - Low doses of both drugs were used (MPH mean dose was 0.7 mg/kg/day; bupropion mean dose was 3.3 mg/kg/day or 140 mg/day
  - After the study, more patients stayed on MPH

Efficacy: ADHD (cont.)

- 3 controlled trials in *adults* showing superiority over placebo:
  - Wilens et al., 2001
  - Kuperman et al., 2002 (trend towards superiority, but not statistically significant)
  - Wilens et al., 2005

Efficacy: ADHD (cont.)

- Effect size: “small” in both children and adults
- Thus, bupropion does not, on average, improve ADHD symptoms as much as stimulants, atomoxetine, or TCAs

Efficacy: Depression

- No **controlled** trials of bupropion for pediatric depression have been reported
- 2 **open** trials in *adolescents* found that bupropion improved both depressive and ADHD symptoms (Daviss et al., 2001; Soltakhah et al., 2005)
- 1 **open** trial in *children* found that bupropion improved depressive, ADHD, and other psychiatric symptoms (Simeon et al., 1986)

Efficacy: Depression

- Daviss et al., 2001
  - Depressive response > ADHD response
  - Depressive response (CGI-I≤2): 88%
  - ADHD response (CGI-I≤2): 63%
  - Response in both disorders: 58%
- Daviss et al., 2006
  - Depressive response associated with blood levels
Efficacy: Smoking Cessation

• Muramoto et al., 2007:
  – DBPC trial in 312 adolescent smokers with no other current major psychiatric diagnosis
  – BUP 150 mg/d vs. BUP 300 mg/d vs. PBO for 6 weeks (then discontinued), plus weekly brief individual counseling
  – Abstinence rates after “quit date” (beginning of BUP/PBO trial):
    • At 6 weeks: PBO=6%, 150 mg=11%, 300=15% (p=0.03 for 300 mg vs. PBO)
    • At 26 weeks: PBO=10%, 150 mg=3%, 300 mg=14% (p=0.05 for 150 mg vs. PBO, p=0.3 for 300 mg vs. PBO)
  – Abstinence rates were lower than those reported for adults, with rapid relapse after medication discontinuation

Efficacy: Smoking Cessation (cont.)

• Monuteaux et al., 2007:
  – DBPC trial of BUP for the prevention of smoking in 57 nonsmoking youth (9-18 years) with ADHD
  – 6 trials involving 816 adolescents
  – Few adverse events but no impact on short or mid-term abstinence

Efficacy: Smoking Cessation (cont.)

• Kim et al., 2011:
  – Meta-Analysis of DBPC trial of BUP for smoking cessation in adolescents aged 12-20 years with ADHD
  – Duration of follow-up ranged from 4 to 168 weeks
  – Trend (p~0.1) for subjects treated with BUP to be about 2x more likely to initiate or continue smoking
  – However, secondary post hoc analyses revealed that concurrent stimulant treatment was significantly associated with lower rates of smoking initiation and continuation

Adverse Effects

• Headache
• Constipation
• Dry mouth
• Insomnia
• Dizziness
• Tremor
• Tinnitus
• Agitation
• Nausea & vomiting
• Tic exacerbation

Adverse Effects (cont.)

• Seizure:
  – 0.1% in adults treated with bupropion SR 100-300 mg/day
  – 0.4% in adults treated with bupropion SR 400 mg/day or bupropion IR 300-450 mg/day
  – Almost 4% in adults treated with bupropion IR 450-600 mg/day
• Open trials in depression showed less potential for suicidality

Contraindications

• Hypersensitivity to bupropion
• Seizure disorder
• Risk factors for seizure, for example:
  – Eating disorders (a higher incidence of seizures was found in patients treated for bulimia with bupropion IR)
  – Alcohol or benzodiazepine withdrawal
  – Concurrent medications that lower seizure threshold
• Caution in patients with a predisposition to psychosis
• Concurrent MAOI
Drug Interactions

• Bupropion levels are increased by 2B6 inhibitors
• Bupropion increases levels of 2D6 substrates
• Carbamazepine, phenytoin, and phenobarbital:
  – All induce the metabolism of bupropion, resulting in lower bupropion levels

Drug Interactions (cont.)

• Levodopa and amantadine:
  – Higher incidence of neuropsychiatric adverse effects when combined with bupropion (e.g., confusion, agitation, delirium, tremor, ataxia, dizziness)
• Nicotine patch:
  – Increase in BP (need to monitor)
• MAOIs:
  – Increase risk of acute bupropion toxicity

Monitoring

• Suicidal ideation and related emotional and behavioural changes (as required for all antidepressants in youth)
• BP in patients using a nicotine patch

Dosing: General Comments

• Not approved for use in children, so no clear dosing algorithm
• Published reports have used 1.4 to 7.1 mg/kg/day or 50-300 mg/day
• Need to wait several weeks for full response at a given dose

Dosing: General Comments (cont.)

• Because of risk of seizure:
  – Do not exceed recommended maximum doses
  – When dosing bupropion SR twice daily, give doses ≥8 hours apart
• CPS indicates that neither SR nor XL tablets should be cut, crushed, or chewed; however, some say that the SR tablet can be cut as long as the pieces are used within 48 hours of cutting

Dosing Specifics: Bupropion SR

• Suggested pediatric dosing algorithm:
  – Start at 50-100 mg QAM for one week
  – Then add a second dose at least 8 hours after the first
  – If response is inadequate after 6 weeks and the child is tolerating the medication, increase by 50 mg/dose to a maximum of 7 mg/kg/day or 300 mg/day (150 mg/dose), whichever is less
• In adults, usual target dose is 100-150 mg QAM per HC, but 150 mg BID per FDA
• In adults, maximum dose is 300 mg/day (150 mg/dose) per HC, but 400 mg/day (200 mg/dose) per FDA
Dosing Specifics: Bupropion XL

- Suggested pediatric dosing algorithm for bupropion XL (Daviss et al., 2006):
  - Algorithm designed for children ≥ 30 kg, although the lightest child in the study was 49 kg
  - Start at 150 mg QAM for at least 2 weeks
  - If response is inadequate after 6 weeks and the child is tolerating the medication, increase to a maximum of 300 mg QAM
  - Optimal dose is 3.3 mg/kg/day (Daviss et al., 2005; Daviss et al., 2006)
- In adults, usual target dose is 150-300 mg QAM
- In adults, maximum dose is 300 mg QAM per HC, but 450 mg QAM per FDA

Indications and Clinical Use

- In adults, mirtazapine is approved for the treatment of depression (Health Canada and FDA)
- In children and adolescents, mirtazapine has no approved indications (Health Canada and FDA)
- Clinically, mirtazapine has been used in pediatric populations as an antidepressant, an anxiolytic, a hypnotic, and an appetite stimulant

Pharmacodynamics

- “NaSSA”: Noradrenergic and Specific Serotonergic Antidepressant
  - Like venlafaxine, mirtazapine is more serotonergic at lower doses and more noradrenergic at higher doses

Pharmacodynamics (cont.)

a) Antagonism of presynaptic α2-autoreceptors on noradrenergic neurons
   - This inhibits negative feedback, which in turn leads to increased release of NE
   - ↑ release of NE results in ↑ firing of postsynaptic noradrenergic neurons
   - ↑ release of NE also results in ↑ firing of postsynaptic serotonergic neurons, because of NE’s activity on α1-adrenoreceptors on the cell body of these neurons

Pharmacodynamics (cont.)

b) Antagonism of presynaptic α2-heteroreceptors on serotonergic neurons
   - This inhibits negative feedback, which in turn leads to increased release of 5-HT

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Pharmacodynamics (cont.)

**c)** Potent antagonism of postsynaptic 5-HT\textsubscript{2} and 5-HT\textsubscript{3} receptors, but little effect on postsynaptic 5-HT\textsubscript{1} receptors

- This biases the activation of serotonin receptors in favour of 5-HT\textsubscript{1} receptors and against 5-HT\textsubscript{2} and 5-HT\textsubscript{3} receptors
- Activation of postsynaptic 5-HT\textsubscript{1} receptors is thought to reduce anxiety and depressive symptoms
- Antagonism of postsynaptic 5-HT\textsubscript{2} and 5-HT\textsubscript{3} receptors is thought to reduce anxiety and depressive symptoms and also to reduce nausea
  - Note: Activation of postsynaptic 5-HT\textsubscript{2} and 5-HT\textsubscript{3} receptors (e.g., by SSRIs) may cause anxiety, insomnia, nausea, and sexual dysfunction

**d)** Low affinity for D\textsubscript{1} and D\textsubscript{2} receptors

**e)** Potent histaminergic (H\textsubscript{1}) antagonist

- Results in sedation and weight gain

**f)** Moderate α\textsubscript{1}-antagonist

- Moderate BP-lowering effect

**g)** Moderate muscarinic (M\textsubscript{1}) antagonist

- Moderate anticholinergic side effects

Clinical Pearl

Given mirtazapine's pharmacodynamic profile and common side effects, think of using it for:

**a)** Children with ADHD on stimulants who have:

- Appetite suppression
- Initial insomnia
- Comorbid anxiety/depression

Clinical Pearl (cont.)

**b)** Medically ill children who may be experiencing:

- Nausea
- Decreased appetite
- Insomnia, agitation
- Anxiety/depression

Pharmacokinetics

- Well absorbed (taking with food reduces the rate but not the extent of absorption)
- \( T_{\text{max}} = 2 \) hrs (adults)
- \( T_{1/2} = 20-40 \) hrs (adults) with substantial individual variation, but generally longer for women (mean=37 hrs) than men (mean=26 hrs)
- Extensively metabolized by the liver and eliminated via urine (75%) and feces (25%)
Pharmacokinetics (cont.)
- Metabolism involves demethylation and oxidation followed by conjugation
- Substrate for 2D6, 3A4, and 1A2
- Does not inhibit or induce any of the CYP450 systems
- Only one active metabolite, desmethyl-mirtazapine, which has a similar pharmacokinetic profile as the parent compound
- Protein-binding is approximately 85%

Efficacy: Depression
- 2 unpublished DBPC trials of mirtazapine for depression in children and adolescents were negative (FDA website, 2001)
- Response rates:
  - Study A (N=126): MIR (60%) = PBO (57%)
  - Study B (N=124): MIR (54%) = PBO (42%)

Adverse Effects
- Sedation (>50% of adults)
- ↑ appetite, weight gain
- Orthostatic hypotension, dizziness
- Anticholinergic side effects (e.g., dry mouth, constipation)
- Transient increases in LFTs (2% of adult patients)

Adverse Effects (cont.)
- Suicidality:
  - RR compared to placebo=1.58 (95% CI=0.06-38.37) (Hammad et al., 2006)
- Neutropenia/agranulocytosis:
  - Pre-marketing (adult):
    - 1.5% neutropenia (generally mild)
    - 0.1% agranulocytosis (3 cases)
  - Postmarketing: 6 cases of agranulocytosis reported out of >3 million treated
  - All patients recovered after drug discontinuation

Contraindications
- Hypersensitivity to mirtazapine
- Concurrent MAOI (wait ≥2 weeks between stopping one and starting the other)

Drug Interactions
- MAOIs (serotonin syndrome)
- Inhibitors/inducers of 2D6, 3A4, and 1A2
- Synergistic depressant effects on motor and cognitive performance when used in conjunction with benzodiazepines or alcohol (Kuitunun, 1994)
Monitoring

- Suicidality
- HR and BP
- For adults, no routine lab monitoring is required, but...
  - If patient develops clinical evidence of infection, check CBC to assess for neutropenia/agranulocytosis
  - If patient develops clinical evidence of liver toxicity, check LFTs

Monitoring (cont.)

- For children, no official guidelines for lab monitoring exist, but...
  - Some recommend CBC at baseline, after 2 months, and then every 6-12 months
  - Consider baseline and repeat LFTs as well
  - As with adults, if child develops clinical evidence of infection or liver toxicity, check CBC and LFTs, respectively

Dosing: General Info

- No official guidelines for dosing in children and adolescents
- Generally given once daily at HS
- Purportedly causes greater sedation and appetite increase at lower doses
- Remeron RD (fruit-flavoured, orally disintegrating tablets) may be useful for children who have trouble swallowing pills
- Remember that mirtazapine has a relatively long half-life, especially in females; consequently, it may take 1-2 weeks to reach steady state

Dosing Specifics (Suggested)

- Start 7.5-15 mg or 0.8 mg/kg QHS
- If child is ≥40 kg, consider starting with 30 mg QHS to minimize sedation and appetite increase
- Titrate to initial target dose of 0.8 mg/kg/day
- If no response after 4-6 weeks and WBC is stable, can ↑ to 1 mg/kg/day or maximum of 45 mg QHS
TABLE 1. Schedule for Daily Dose of Extended-Release Venlafaxine for Pediatric Generalized Anxiety Disorder in Two Placebo-Controlled Trials, by Patient Body Weight$^a$

<table>
<thead>
<tr>
<th>Week</th>
<th>25–39 kg</th>
<th>40–49 kg</th>
<th>≥50 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37.5 mg</td>
<td>37.5 mg</td>
<td>37.5 mg</td>
</tr>
<tr>
<td>2</td>
<td>37.5 or 75 mg</td>
<td>75 mg$^b$</td>
<td>75 mg$^b$</td>
</tr>
<tr>
<td>3–4</td>
<td>37.5 or 75 mg</td>
<td>75 or 112.5 mg</td>
<td>75 or 150 mg</td>
</tr>
<tr>
<td>4–8</td>
<td>37.5, 75, or 112.5 mg</td>
<td>75, 112.5, or 150 mg</td>
<td>75, 150, or 225 mg</td>
</tr>
</tbody>
</table>

$^a$ All patients received 37.5 mg/day during week 1; doses thereafter were increased on the basis of response to treatment and as indicated for each body weight range.

$^b$ The dose increase during week 2 was mandatory per protocol.