Management of SSRI Induced Sexual Dysfunction

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Serotonin Reuptake Inhibitors*

- fluoxetine (Prozac)
- clomipramine (Anafranil, a TCA)
- sertraline (Zoloft)
- paroxetine (Paxil, Paxil CR)
- fluvoxamine (Luvox)
- venlafaxine (Effexor, IR XR)
- citalopram (Celexa, Lexapro)
- duloxetine (Cymbalta)

*In order of U.S.A. market entry.
Adapted from Table 2: “Incidence of Sexual Dysfunction With Antidepressants Assessed by the Psychotropic-Related Sexual Dysfunction Questionnaire” (N=1022)

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Mg mean dose</th>
<th># with SD</th>
<th>% with SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>66</td>
<td>28.7</td>
<td>48</td>
<td>72.7</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>208</td>
<td>23.4</td>
<td>147</td>
<td>70.7</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>55</td>
<td>159.5</td>
<td>37</td>
<td>67.3</td>
</tr>
<tr>
<td>Sertraline</td>
<td>159</td>
<td>90.4</td>
<td>100</td>
<td>62.9</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>77</td>
<td>115.7</td>
<td>48</td>
<td>62.3</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>279</td>
<td>24.5</td>
<td>161</td>
<td>57.7</td>
</tr>
</tbody>
</table>


COMMON SEXUAL SIDE EFFECTS OF ANTIDEPRESSANTS

- Decreased Libido
- Decreased Arousal/Excitation
  - Decreased penile engorgement
  - Decreased clitoral engorgement
  - Decreased vaginal lubrication
  - Genital numbing (decreased sensitivity)
- Orgasmic/Ejaculation Dysfunction
  - Difficulty with orgasm
  - Anorgasmia
  - Delayed ejaculation
  - Inability to ejaculate
Unusual Sexual Side Effects Of Antidepressants

- Penile Priapism
- Clitoral Priapism
- Painful Ejaculation
- Retrograde ejaculation
- Increased Libido
- Spontaneous Orgasm With Yawning

Putative Etiology of SSRI Induced Sexual Dysfunction

- Central elevation of serotonin
- Spinal cord elevation of serotonin
- Anticholinergic side effect
  - paroxetine
- Nitric Oxide Synthase inhibition
  - paroxetine
- Prolactin elevation
  - fluoxetine, paroxetine, fluvoxamine, citalopram
- Other
### Potency of Antidepressants for Blocking Monoamine Transporters

<table>
<thead>
<tr>
<th>Drug</th>
<th>NE Transporter</th>
<th>5-HT Transporter</th>
<th>DA Transporter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>+++</td>
<td>+++++</td>
<td>-</td>
</tr>
<tr>
<td>Citalopram</td>
<td>-</td>
<td>+++++</td>
<td>0</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>+++</td>
<td>++++++</td>
<td>-</td>
</tr>
<tr>
<td>Desipramine</td>
<td>+++++</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Doxepin</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>+++</td>
<td>++++++</td>
<td>+</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>++</td>
<td>+++++</td>
<td>-</td>
</tr>
<tr>
<td>Imipramine</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>+++</td>
<td>++++++</td>
<td>+</td>
</tr>
<tr>
<td>Sertraline</td>
<td>+</td>
<td>++++++</td>
<td>+++</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>+</td>
<td>+++</td>
<td>-</td>
</tr>
</tbody>
</table>

Richelson, E; J Clin Psychiatry; 2003; 64 (suppl 13); page 6.

### Protein Binding and Urinary Excretion of SRIs

<table>
<thead>
<tr>
<th>Drug</th>
<th>% Protein Bound</th>
<th>% Urinary Excretion</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluoxetine</td>
<td>94</td>
<td>&lt;2.5</td>
<td>14 days</td>
</tr>
<tr>
<td>S-sertraline</td>
<td>98</td>
<td>&lt;1</td>
<td>26 hours</td>
</tr>
<tr>
<td>R-paroxetine</td>
<td>95</td>
<td>&lt;2</td>
<td>21 hours</td>
</tr>
<tr>
<td>fluvoxamine</td>
<td>77</td>
<td>&lt;5</td>
<td>15 hours</td>
</tr>
<tr>
<td>venlafaxine</td>
<td>27</td>
<td>4.6</td>
<td>5 hours</td>
</tr>
<tr>
<td>D-M-venlafaxine</td>
<td>30</td>
<td>29</td>
<td>11 hours</td>
</tr>
<tr>
<td>citalopram</td>
<td>80</td>
<td>10.5</td>
<td>35 hours</td>
</tr>
<tr>
<td>S-citalopram</td>
<td>56</td>
<td>18*</td>
<td>29 hours</td>
</tr>
</tbody>
</table>

The Pharmacological Basis of Therapeutics; Goodman & Gilman; 10th Edition; 2001

*From Physician’s Desk Reference; 2004; page 1302.
Serotonin Discontinuation Syndrome

• Somatic symptoms
  – Disequilibrium, dizziness, unsteadiness, vertigo
  – Feeling “spacey”, confusion, memory dysfunction
  – Flu-like symptoms (myalgia, chills, fatigue, nausea)
  – Sensations of electric shocks, paresthesia, tremor
  – Insomnia, overactivity, vivid dreams
• Psychological symptoms
  – Agitation, anxiety, irritability
  – Mood lability, crying spells
  – Cognitive fog

“Don’t Ask/Don’t Tell” Approach is Countertherapeutic and Can Create More Dysfunction

• An informed patient is more likely to remain medication compliant
• Onset of uninformed sexual dysfunction can create:
  – Relationship stress with significant other
  – Self-judgment and increased depression
  – Confusion as to source of sexual dysfunction
• Can compromise the therapeutic alliance
• Awareness of availability of “antidotes” enhances compliance
Treatment Strategies For The Sexual Side Effects Of Antidepressants

- Decrease the dose
- Switch antidepressants
- Wait for a decrease or disappearance of the side effect
- Augment treatment with a second agent
- Add an “antidote” for prn use
- Avoid drug holidays

“Antidotes” to Serotonin-Induced Sexual Dysfunction
“Antidotes” For The Sexual Dysfunction Side Effects Of Antidepressant Medications

<table>
<thead>
<tr>
<th>ANTIDOTE</th>
<th>COMMONLY EFFECTIVE DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>100-200 mg prn</td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>300-400mg/day (given BID)</td>
</tr>
<tr>
<td>Buspirone</td>
<td>15-60 mg/day (given BID)</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>4-16 mg prn</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>10-20 mg prn</td>
</tr>
<tr>
<td>Ginkgo Biloba</td>
<td>80mg TID</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>10-20 mg prn</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>100-400mg qhs</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>0.125-1.5mg/day prn</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>25-100mg qd prn</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>2.7-16.2 mg prn or 5.4 mg TID</td>
</tr>
</tbody>
</table>

Amantadine

- Effective dosage range 100-200 mg prn
- Putative mechanism:
  - Release dopamine and norepinephrine??
  - Inhibit reuptake of dopamine and norepinephrine??
- One placebo controlled study showed improvement no greater than placebo
Bupropion SR

- Effective dosage range 300-400mg/day
  - Give BID, 200mg/dose max, 6-8 hours apart
- Useful in augmentation of depression:
  - Improves energy, decreases hypersomnia, improves cognition and motivation
- May be used as primary “antidote”
- Mechanism of action:
  - dopamine and norepinephrine reuptake inhibitor
- Contraindicated in patients with seizure hx

Buspirone

- Effective dosage range 15-60 mg/day
  - Give BID
- Mechanism of action
  - Serotonin 5HT-1A partial agonist
- One placebo controlled study showed improvement no greater than placebo
- Seems to work better in women than men
Psychostimulant
Dopamine Agonists

- Dextroamphetamine  10-20 mg/day or prn
- Methylphenidate    10-20 mg/day or prn
- Contraindicated in substance abusers
- Side effects include:
  - insomnia, anxiety
- Mechanism of action:
  - dopamine reuptake inhibition
  - presynaptic dopamine and norepinephrine release

Anti-Parkinsonian
Dopamine Agonists

- Mirapex (pramipexole)  0.125-1.5mg/day prn
- Requip (ropinirole)    0.25-3mg qd prn
- Mechanism of action:
  - Dopamine agonist D3>D2
- Very little clinical experience to date
- Await more peer reviewed research literature
**Cyproheptadine**

- Effective dose 4-16 mg qd prn
- Mechanism of action
  - Serotonin receptor antagonist
  - Likely action at spinal cord
- Antihistaminic sedation
- DO NOT use daily – will reverse SSRI effect
- May reverse antidepressant effect of SSRIs
- RARE incidence of retroperitoneal fibrosis

**Ginkgo Biloba**

- Effective dose 80mg TID
- Onset of action delayed up to 14 days
- Sold as a food supplement/herbal remedy
- No accountability re quality control
- Putative mechanism of action is vasodilation
- Increases blood flow to genitals and brain
- Double benefit:
  - Improves sexual functioning
  - Remember they had sex the next day
Nefazodone

- Effective dose 100-400mg qhs
- New black box warning re liver disease
- Baseline LFTs, and follow closely first 6 months
- Mechanism of action 5HT-2A antagonist
- Will also treat residual anxiety and insomnia
- Antihistaminic sedation
- Weight neutral
- Drug interactions at Cytochrome P450-3A4

Yohimbine

- Effective dose 2.7-16.2 mg prn or 5.4 mg TID
- Anxiety, panic attacks and agitation are common side effects
- Available prior to 1938
- natural Yohimbe is a tree bark which contains yohimbine
  - Sold OTC as a dietary supplement for body building and "enchanced male performance"; reports of renal failure, seizures and death.
- Mechanism of action
  - Central alpha-2-receptor antagonist
  - Increase in sympathetic drive secondary to an increase in norepinephrine release
Sildenafil (Viagra)
The “Gold Standard”

- Effective dose 25-100mg qd prn
- Effective in men and women
- Contraindications in women same as in men with addition of pregnancy & breast feeding
- Take one hour before sexual activity
- True kamikaze effect – does the job and leaves in four hours
- cyclicGMP Phosphodiesterase Type 5 inhibitor