OPTIMIZING TREATMENT OF DEPRESSION AND ANXIETY WITH SSRI: FROM BASIC TO CLINICAL ASPECTS
Marcus Debiasi, PMHNP-BC

LEARNING OBJECTIVES

1. The nurse practitioner will understand basic principles of neurobiochemistry and mechanisms of action of common serotonergic agents used to treat anxiety and depression.
2. The nurse practitioner will understand how different pharmacokinetic profiles of common serotonergic agents to treat anxiety and depression will impact response, substitution taper schedules and discontinuation schedules of these agents.
3. The nurse practitioner will understand the importance of incorporating the patient environmental factors not only when diagnosing and treating mental illness, but also when evaluating responses to psychopharmacological interventions.

"HOLISTIC" CONSIDERATIONS

- SADNESS / GRIEF
- ADJUSTMENT DISORDERS WITH DEPRESSED MOOD
- ADJUSTMENT DISORDERS WITH ANXIETY
NEUROTRANSMISSION

AFFECTIVE / COGNITIVE FUNCTIONS OF SEROTONIN

- Fear processing
- Modulation of anxiety in response to stress
- Learning and memory
- Aggression and impulsivity
- Social Reward
- Selection of salient stimuli
PHARMACODYNAMICS: THE SEROTONIN REUPTAKE PUMP

SOMATIC FUNCTIONS OF SEROTONIN

- Pain
- Motor adaptation
- Gastric motility
- Emesis
- Regulation of vascular tone
- Regulation of sleep

IF INCREASING SEROTONIN DECREASES DEPRESSIVE / ANXIOUS SYMPTOMS, WHY DO WE HAVE TO WAIT 4 WEEKS FOR A RESPONSE?
NEUROADAPTATION

• REM sleep significant decreased in FLUOXETINE group of cats
• Increased irritability in FLUOXETINE group of cats
• REM sleep back to normal 2 weeks into treatment

INHIBITION OF REM SLEEP BY FLUOXETINE, A SPECIFIC INHIBITOR OF SEROTONIN UPTAKE

I. H. Slater, G. T. Jones and R. A. Moore

- REM sleep significant decreased in FLUOXETINE group of cats
- Increased irritability in FLUOXETINE group of cats
- REM sleep back to normal 2 weeks into treatment
RESPONSE TO INCREASED SEROTONERGIC ACTIVITY

- IMMEDIATE
- DELAYED
- LATENT

TYPICAL UNDESIRABLE EFFECTS TO SSRI:
IMMEDIATE

- GI disturbances
- Increased anxiety / dysphoria
- Akathisia
- Insomnia

TYPICAL UNDESIRABLE EFFECTS TO SSRI:
DELAYED / LATENT

- Emotional blunting
- Sexual problems
- Loss of response
- Persistent fatigue
"THE TRIAD OF SEROTONIN SYNDROME"
[Considerations for Excessive Dosing]

• Autonomic hyperactivity
• Altered mental status
• Neuromuscular hyperactivity

DISCONTINUATION SYNDROME

• Agents with shorter half-lives tend to produce DS of higher severity and quicker onset
• Do not represent true baseline state without the agent
• Dizziness, HAs, "electric shock / rushing in the head", nausea

PHARMACOKINETICS

• ABSORPTION
• DISTRIBUTION
• METABOLISM
• EXCRETION

PHARMACODYNAMICS

• TARGETED MOLECULES [wanted and unwanted]
• RESPONSE AND SIDE-EFFECTS
HEROIN AND HYDROCODONE ARE THE SAME DRUG

PAROXETINE AND FLUOXETINE THE SAME DRUG

PHARMACOKINETICS

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (mg)</th>
<th>t½ (days)</th>
<th>Tmax (hr)</th>
<th>Cmax (ng/mL)</th>
<th>Same</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine</td>
<td>20-40</td>
<td>1-3</td>
<td>2-4</td>
<td>50</td>
<td>Yes</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20-40</td>
<td>2-3</td>
<td>1-2</td>
<td>30</td>
<td>Yes</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50-100</td>
<td>1-2</td>
<td>1-2</td>
<td>20</td>
<td>Yes</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Citalopram</td>
<td>20-60</td>
<td>2-3</td>
<td>1-2</td>
<td>30</td>
<td>Yes</td>
<td>CYP2C19</td>
</tr>
</tbody>
</table>

Hiemke & Härtter, 2000
**FLUOXETINE [Prozac]**

**FDA approval**
- MDD
- OCD
- Bulimia Nervosa
- Panic Disorder [with or without agoraphobia]

**FLUOXETINE [Prozac]**
- Longest ½ life of all SSRIs: 7-14 days - good option for poor compliance; steady state > 4 weeks
- Lowest affinity for the serotonin transporter [KDa=14]
- Non-linear kinetics
- Significant NET inhibition [*the activating SSRI*]
- May take months to achieve a steady state
- Virtually "tapers itself off"
- Long "wash-out" period before switching to another SSRI
PAROXETINE [Paxil]
FDA Approval
- MDD
- OCD
- Panic Disorder [with or without agoraphobia]
- Social Anxiety Disorder
- Panic Disorder
- Generalized Anxiety Disorder
- PTSD

PAROXETINE [Paxil]
- Shorter ½ life of commonly used SSRIs [21 hours]; steady state 1-2 weeks.
- Highest affinity for serotonin transporter [kDa=0.7]
- Start “low” to avoid paradoxical reactions.
- May have to be dosed twice daily on fast metabolizers.
- Anticholinergic effects comparable to that of TCAs [HS dosing]
- Significant withdrawal syndrome [may use “bridge” SSRI when stopping]

CITALOPRAM [Celexa]
- Linear kinetics
- Half-life ~36h; steady state 6-10 days
- Moderate affinity for SERT [kDa=2.6]
- Mild anti-histaminergic effects
- Potential for prolonging QTc interval
ESCITALOPRAM [Lexapro]
FDA Approval
- FDA approval: MDD and Generalized Anxiety Disorder
- Allosteric modulator serotonin transporter
- Highly selective for serotonin transporter
- High affinity for SERT ($K_d=1.1$)
- Linear pharmacokinetics
- Half-life: 27-32 h
- Statistically provides the best response and tolerability

SERTRALINE [Zoloft]
FDA Approval
- MDD
- OCD
- Panic Disorder
- PTSD
- Social Anxiety Disorder
- Pre-Menstrual Dysphoric Disorder [continuous or intermittent]

SERTRALINE [Zoloft]
- Half-life ~ 26 hours; steady state 5-7 days
- Linear kinetics
- Moderate affinity for serotonin transporter ($K_d=3.4$)
- Weak dopaminergic/noradrenergic effects
- Antagonizes sigma-1 receptors [anxiolytic?]
FLUOXAMINE [Luvox]

- FDA approval for OCD
- Moderate affinity for SERT \([K_D=6.2]\)
- Antagonistic properties for sigma-1 receptors
- Half-life ~ 15 h; steady state 10 days
- Often dosed twice daily
- Sedation is common [poorly tolerated]

IMPLICATIONS FOR STARTING

- Potency of agent
- Typical profile of agent vs. predominant symptoms
- Time of dosing
- Fluctuation of effects / adverse effects
- Risk of paradoxical reaction

IMPLICATIONS FOR SWITCHING

- Long vs. short half-lives
- Daytime vs. nighttime dosing
- Affinity for SERT
- Characteristics of each drug
- Neuroadaptation: reducing vs. increasing
IMPLICATIONS FOR STOPPING

- Long vs. Short half-lives
- Differentiating between discontinuation syndrome and baseline state
- Adjustment of taper schedule [consider patient's level of functionality].

LIVER CLEARANCE: GENETIC TESTING

"AS TIME GOES BY"

- "It was a little rough the first two weeks but then I got used to it".
"AS TIME GOES BY"

- "I felt panicky; like my anxiety / depression got much worse".

- "I felt nothing".

- "It worked for a while but now it quit working".
"AS TIME GOES BY"

"It worked for a while but now I feel like I'm losing my mind".

QUESTIONS?