

OPTIMIZING TREATMENT OF  
DEPRESSION AND ANXIETY  
WITH SSRI: FROM BASIC TO  
CLINICAL ASPECTS

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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

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LEARNING OBJECTIVES

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.

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LEARNING OBJECTIVES

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.

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"HOLISTIC" CONSIDERATIONS

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

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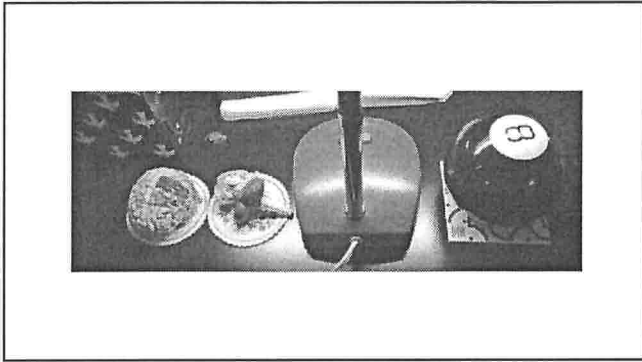
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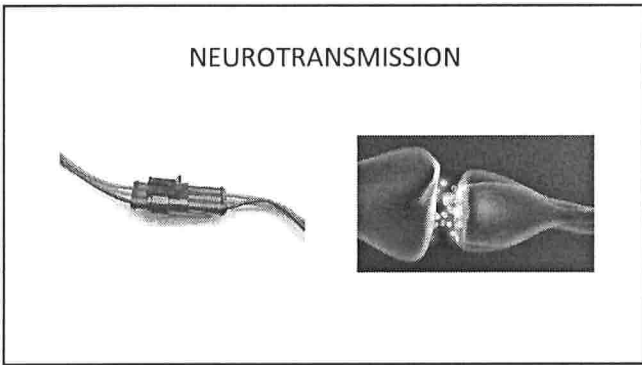
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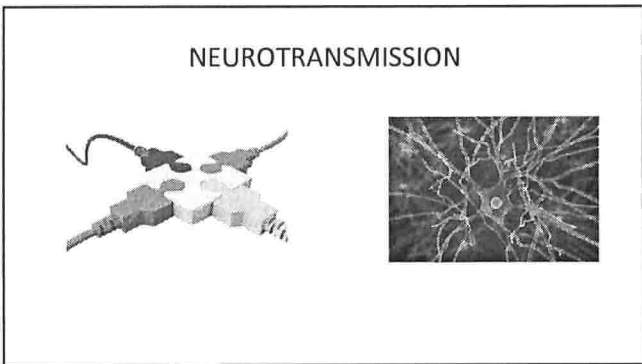
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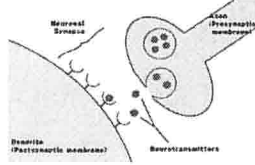
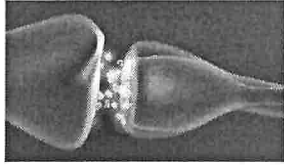
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### NEUROTRANSMISSION



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### AFFECTIVE / COGNITIVE FUNCTIONS OF SEROTONIN

- Fear processing [Boccio, M et al, 2016]
- Modulation of anxiety in response to stress [Lowry, CA, 2005]
- Learning and memory [Ballaz SJ, 2007]
- Aggression and Impulsivity [O'Dell LE & Parsons LH, 2004]
- Social Reward [Dolen G et al, 2013]

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### SEROTONIN: THE PARADOXICAL NEUROTRANSMITTER



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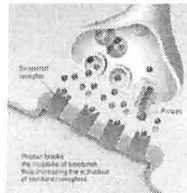
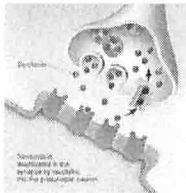
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### PHARMACODYNAMICS: THE SEROTONIN REUPTAKE PUMP



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### SOMATIC FUNCTIONS OF SEROTONIN

- Pain [Haleem, 2018]
- Motor adaptation [Okamoto, 2016]
- Gastric motility [Crowell, 2004]
- Emesis [Higgins, 1989]
- Regulation of vascular tone [Skop and Brown, 1996]
- Regulation of sleep [Slater et al, 1979]

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

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### NEUROADAPTATION



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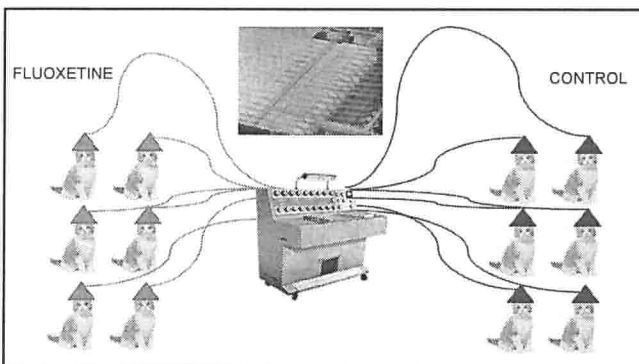
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#### INHIBITION OF REM SLEEP BY FLUOXETINE, A SPECIFIC INHIBITOR OF SEROTONIN UPTAKE\*

I. H. SLATER, G. T. JONES and R. A. MOORE  
(1979)

- 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

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RESPONSE TO INCREASED SEROTONIN

- IMMEDIATE
- DELAYED
- LATENT

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TYPICAL  
UNDESIRABLE EFFECTS TO SSRI:  
IMMEDIATE

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

Goethe JW et al,(2009); Stahl S,(1998)

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TYPICAL  
UNDESIRABLE EFFECTS TO SSRI:  
DELAYED / LATENT

- Emotional blunting
- Sexual problems
- Loss of response
- Persistent fatigue

Goethe JW et al,(2009); Stahl S,(1998)

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"THE TRIAD OF SEROTONIN SYNDROME"  
[Considerations for Excessive Dosing]

- Autonomic hyperactivity
- Altered mental status
- Neuromuscular hyperactivity

[Sun-Edelstein, 2008]

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DISCONTINUATION SYNDROME

- Agents with shorter half-lives tend to produce DS of higher severity and quicker onset [Oliver JS, 1999]
- Do not represent true baseline state without the agent [Young A, 2000]
- Dizziness, HAs, "electric shock / rushing in the head", nausea [Warner CH, 2006]

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HEROIN AND HYDROCODONE ARE THE  
SAME DRUG



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**PHARMACOKINETICS**

- ABSORPTION
- DISTRIBUTION
- METABOLISM
- EXCRETION

**PHARMACODYNAMICS**

- TARGETED MOLECULES [wanted and unwanted]
- RESPONSE AND SIDE-EFFECTS

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**PAROXETINE AND FLUOXETINE THE SAME DRUG**




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**PHARMACOKINETICS**

Table 1  
Pharmacokinetic parameters of SSRIs and clinically relevant interactions with CYP isoenzymes

SSRI	Daily dose (mg)	t <sub>1/2</sub>	Time to reach steady state	t <sub>1/2</sub> (h)	Linear kinetics	CYP inhibition
Fluoxetine	20-60	1-4 days	1-4 weeks	20-43	No	2D6
Nefazodone	125-300	15 hr	10 days	8	No	2D6, 3A4
Paroxetine	20-60	20 hr	7-14 days	7-17	No	2D6, CYP
Sertraline	50-150	26 hr	3-7 days	20	Yes	Mixed
Citalopram	10-60	35 hr	6-10 days	14-16	Yes	Not relevant

Hiemke & Hirtler, 2000

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FLUOXETINE [Prozac]  
FDA approval

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

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FLUOXETINE [Prozac]

- Longest 1/2 life of all SSRIs: 7-14 days -good option for poor compliance]
- 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

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PAROXETINE [Paxil]  
FDA Approval

- MDD
- OCD
- Panic Disorder [with or without agoraphobia]
- Social Anxiety Disorder
- Panic Disorder
- Generalized Anxiety Disorder
- PTSD

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**PAROXETINE [Paxil]**

- Shorter ½ life of commonly used SSRIs [21 hours].
- 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]

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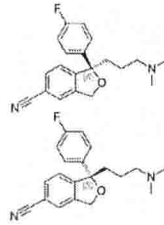
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**CITALOPRAM [Celexa]**

- Linear kinetics
- Half-life ~36h
- Moderate affinity for SERT [kDa=2.6]
- Mild anti-histaminergic effects
- Potential for prolonging QTc interval




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**ESCITALOPRAM [Lexapro]  
FDA Approval**

- FDA approval: MDD and Generalized Anxiety Disorder
- Allosteric modulator serotonin transporter
- Highly selective for serotonin transporter
- Linear pharmacokinetics
- Half-life: 27-32 h
- Statistically provides the best response and tolerability

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SERTRALINE [Zoloft]  
FDA Approval

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

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SERTRALINE [Zoloft]

- Half-life ~ 26 hours
- Linear kinetics
- Moderate affinity for serotonin transporter [kDa=3.4]
- Weak dopaminergic / noradrenergic effects
- Antagonizes sigma-1 receptors [anxiolytic?]

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FLUVOXAMINE [Luvox]

- FDA approval for OCD
- Moderate affinity for SERT [kDa=6.2]
- Antagonistic properties for sigma-1 receptors
- Half-life ~ 15 h
- Often dosed twice daily
- Sedation is common [poorly tolerated]

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"AS TIME GOES BY"

. "It was a little rough the first two weeks but then I got used to it".

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"AS TIME GOES BY"

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

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"AS TIME GOES BY"

. "I felt nothing".

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"AS TIME GOES BY"

. "It worked for a while but now it  
quit working".

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"AS TIME GOES BY"

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

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