ANTIDEPRESSANTS: SSRIs (p.1)

1. **Introduction**

SSRIs (Selective Serotonin Reuptake Inhibitors) were approved for use as antidepressants in the **mid 1980's** (**fluoxetine/Prozac**)

a whole new category of drugs, **must more selective** (just on 5HT transporter protein; no/little effect on NE or DA)

have both **antidepressant** and **anxiolytic** effects (no analgesic effects)

do not affect the post-synaptic RSs for 5HT directly…although could lead to 5HT RS down-regulation…?

generally 5HT regulates sleep, appetite, biorhythms, mood, aggression and anxiety

SSRIs have **no antiACh effects**…thus, lack many adverse SEs that the hetero-cyclics have

less toxic, safer in OD, safer in elderly pt., safer in cardiac pt.

2. **Major SSRIs**

fluoxetine/Prozac paroxetine/Paxil sertraline/Zoloft
fluvoxamine/Luvox citalopram/Celexa

3. **Effects on CNS**

block the presynaptic transporter proteins for 5HT --- leave more 5HT in synaptic cleft to affect the postsynaptic RSs…which could lead to down-regulation of these RSs

time course of antidepressant effects support down-regulation hypothesis…

probably stimulate the postsynaptic RSs more, 5HT#1, #2, & #3 RSs

5HT #1 --- less depression & less anxiety

5HT #2&#3 --- adverse SEs

#2s --- insomnia, anxiety, agitation, sexual dysfunction

#3s --- nausea

no/little effect on NE, DA, GABA, glutamate, ACh…hence term "selective"

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4. **Clinical Applications**

major depressive disorder
dysthymia
atypical depression
anxiety disorders: GAD, PA, OCD, PTSD, childhood anxiety
eating disorders: anorexia, bulimia
(morbid obesity)
aggression, rage, explosive personality, borderline personality
ETOH abuse & other addictions
premature ejaculation

5. **Adverse Side Effects**

GI discomfort: nausea, vomiting, diarrhea)
Headache (perhaps esp. in migraine/vascular headache prone Ss)
Agitation, nervousness, anxiety, insomnia
Increased sweating
Dizziness
Tremor
Sexual dysfunction (decreased erections, orgasm, delayed ejaculation)

6. "**Serotonin Syndrome**"

an especially bad effect, often due to **polypharmacy***
ataxia, muscle spasms, hyper reflexes
disorientation, confusion, hypomanic, agitation, restlessness
ANS dysfunction: fever, shivering, chills, sweating, diarrhea, tachycardia, HBP
seizures --- death

*caution necessary when switching pt. from an MAOI to an SSRI
must allow for a long enough "wash-out" period (3-4 weeks) before start SSRI
*caution when using other 5HT agonists (Valerian root, St. John's Wart, TCAs, central psychostimulants, L-tryptophan, ephedrine, decongestants, etc.)

no need for blood monitoring

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7. **Toxic Dose**

no need for blood monitoring in ordinary circumstances
no/little danger of toxic OD (high T.I.)
one "successful" suicide took 7000mg of SSRI (700x maximum dose, more than 3 month supply…)

8. **Dependence/Withdrawal**

S can become dependent on SSRI, i.e. will experience **some W/D Sxs** when D/C drug…about **60% of *Ss*** on SSRIs
W/D Sxs usually start **within a few days of D/C drug, last 3-4 weeks**
W/D effects are very **rare** in pts. on **Prozac**…why?

Sx of W/D:

dizziness, vertigo, ataxia
nausea, vomiting, diarrhea
flu-like Sxs (chills, fatigue, aches)
sensory disturbances (tingling, paresthesia)
sleep disturbances (insomnia, vivid dreams)
increased anxiety, agitation, depression
crying spells
irritability
confusion, decreased concentration, decreased memory, decreased cognitive abilities

which are signs of untreated/relapsing depression? which are signs of W/D?
not easy to say... all the above cease when SSRI is resumed…

9. **Pregnancy**

appear safe to use while pregnant or nursing
except perhaps **for citalopram/Celexa**

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10. Specific SSRIs: **fluvoxetine/Prozac**

the SSRI "grandparent" molecule…started it all, became available in 1988
considered a new line of drugs for tx of depression
almost the efficacy of imipramine/Tofranil with no cardiovas SEs ✍
more acceptable/fewer side effects --- greater compliance rates
allowed possibility of treating *Ss* with milder depression/dysthymia

Pharmacokinetics:

PO, absorbed through GI tract
peak plasma levels in 6-8 hours
about 94% protein bound
metabolized by liver, **inhibits P-450 enzymes**
½ life is 2-3 days (long!), has an **active metabolite (norfluoxetine) with 7-15 day ½ life!**
thus, can be given once a week!
takes weeks (4-6) to reach steady state & have an effect on depression
excretion is mainly through the kidneys/urine

note**: implications for length of "wash out" period**

Side-effects:

anxiety, agitation, insomnia
anorexia, decreased appetite, weight loss
jitteriness, tremors
impaired sexual functioning (50-60% of pts)
headaches
rare – seizures, suicidal "manic" state

few antiACh or antiH effects--- no blurred vision, no constipation, no weight gain, no sedation, no dry mouth, no cardiovas effects
low risk of toxicity in OD

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11. Specific SSRI: **sertraline/Zoloft**

2nd SSRI introduced

even more specific in its effect on NS than Prozac in deceasing 5HT reuptake

shorter ½ life (1 day) than Prozac, reaches steady state in 4-7 days ("rule of 5")

very effective in tx of pts. with major depression, OCD, PA, anxiety

SEs – diarrhea

mild/few antiACh or antiH effects, no cardiovas SEs

low risk of toxicity in OD

appears safe during pregnancy & nursing

12. Specific SSRI: **paroxetine/Paxil**

3rd SSRI introduced

most **potent** of all the SSRIs

like Zoloft, is a very selective 5HT reuptake inhibitor

reaches steady state in 7 days, ½ life is 1 day

relatively inactive metabolites

very effective in tx of depression and anxiety

now the 1st choice in tx of **PAs**

also used for PTSD, OCD, social phobia, PMS (premenstrual dysphoric disorder), & chronic migraine headaches

SEs – drowsiness, dry mouth

13. Specific SSRIs: **fluvoxamine/Luvox**

a derivative of fluvoxetine/Prozac

effective antidepressant

also used for PTSD, dysphoria/dysthymia, PAs, OCD, social phobia

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14. Specific SSRIs: **citalopram/Celexa**

steady state reached in 7 days
maximum effects seen in 5-6 weeks (like Prozac)
metabolized by liver --- **3 active metabolites** (although all are less active & less potent than parent molecule)
½ life is 33 hours (1 ½ days)
need to **reduce dose levels by 33-50% in elderly** (have reduced liver enzymes)
is **less of a liver enzyme inhibitor** than is fluoxetine/Prozac --- fewer drug interactions
may help to decrease ETOH consumption in ETOH abuse pts.
useful in tx of anxiety disorders as well as depression
note: may have a **teratogenic effect** at high doses
do see **SEs in infants** nursing on mothers who take this drug (sedation, decreased feeding, slower weight gain)
SEs – at high doses see more serious toxicities
EKG abnormalities, convulsions, & rare fatalities
thus, is not the first choice amongst the SSRIs

15. **Dual-Action "SSRIs":**

these are less-specific SSRIs, block 5HT transporter protein & a 2nd NT system
sometimes called "**SNRIs**" (serotonin & norepinephrine reuptake inhibitors)

nefazodone/Serzone

blocks 5HR2A RS
blocks transporter protein for both 5HT and NE
--- down regulation of postsynaptic 5HT & NE RSs

mirtazine/Remeron

blocks presynaptic NEalpha2 autoreceptors --- increased release of NE
blocks postsynaptic NEalpha2 RSs (displayed on surface of a 5HT releasing neuron) --- increases release of 5HT
both effects lead to **down regulation of postsynaptic NE&5HT RSs**
also blocks 5HT#2 & 5HT#3 RSs --- fewer typical SSRI-like SEs
potent antiH SEs --- drowsiness, increased appetite, weight gain

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15. **Dual-Action "SSRIs"** (cont.)

clomipramine/Anafranil

structurally similar to TCAs, is sometimes classified as a "2nd generation" drug
SNRI (mixed 5HT & NE reuptake inhibition)
parent molecule blocks reuptake of 5HT
active metabolite (desmethly clomipramine) blocks reuptake of NE
used especially to treat OCD
40-75% of pts improved markedly on Anafranil
also used to tx depression, PAs, and phobic disorders
but…one especially serious SE: **agranulocytosis**

venlafaxine/Effexor

another mixed 5HT & NE reuptake inhibitor
also slightly reduces the reuptake of DA
lacks antiACh and antiH SEs
actually improves motor performance & cognitive functions
not sedating
at high doses can --- **HBP**
in an extended release form is used to tx. GAD

reboxetine/Vestra

selective NE reuptake inhibitor