SSRI: Pharmacology Update for ADPH Nurse Practitioners

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Faculty

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Serotonin

- **Serotonin (pronounced /ˌsɛrəˈtoʊnɨn/) or 5 - Hydroxytryptamine (5 - HT) is a monoamine neurotransmitter**
- **Biochemically derived from tryptophan, serotonin is primarily found in the gastrointestinal (GI) tract, platelets, and in the central nervous system (CNS) of humans and animals**

Serotonin

- **Modulation of serotonin at synapses is thought to be a major action of several classes of pharmacological antidepressants**

Serotonin

- **It is a well - known contributor to feelings of well - being; therefore it is also known as a happiness hormone**
- **20 % is synthesized in serotonergic neurons in the CNS where it has various functions**
  - **These include the regulation of mood, appetite, sleep, as well as muscle contraction**

Action of Serotonin

- **It plays an important role in postprandial satiety, anxiety, sleep, mood, obsessive - compulsive, and impulse control disorders**
- **Decreased serotonin activity (either by tryptophan depletion or serotonin antagonists) can contribute to an increased food intake**

Pharmacology

- Increase serotonin available in the brain
- Depression results when certain brain chemicals (neurotransmitters) get out of balance (low)

Mechanism of Action

- Not fully understood but it involves selective serotonin reuptake blockade at the neuronal membrane, thus enhancing serotonin (5 - HT) effects

Mechanism of Action

- Initially the availability of serotonin is increased in the somatodendritic area; however, during chronic use of SSRIs, serotonin auto receptors are down regulated and desensitized
  - This allows for an increase in serotonin release in the axon terminal synapses

Mechanism of Action

- Due to the increase of serotonin in the synapses, there is an increase in its neuronal impulses

Pharmacology

- Target Serotonin in Brain
  - SSRIs prevent reabsorption or reuptake back into the sending neuron
  - Therefore more serotonin between neurons in the brain

Pharmacology

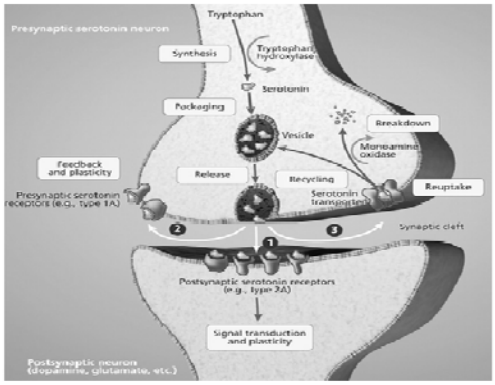
  - Equals greater reduction in depression
  - Differ from each other by degree of selectivity for the serotonin transporter
    - Share most indications

Pharmacology

- Inhibit reuptake of serotonin by serotonin transporters located on pre - synaptic neurons
  - Increases available serotonin in brain
  - Exact mechanism not known

Pharmacology

- Members of class differ in degree of selectivity for binding to the serotonin transporter
- Limited to activity in other receptors provides a more favorable adverse event profile compared with tricyclics



Pharmacology

- Which to use?
  - Drug interactions
    - Citalopram - QT prolongation - Not with drugs that do the same
  - Patient previous response
  - Patient specific characteristics
  - Metabolize or inhibit CYP450 isoenzyme

Advantages of SSRIs

- Newer (second generation) antidepressants
  - Fewer side effects than first generation
- First Generation Includes
  - Tricyclic antidepressants and MAOIs

Advantages of SSRIs

- Other second generation antidepressants include:
  - Buproprion (Wellbutrin and duloxetine(Cymbalta)

Advantages of SSRIs

- SSRIs are generally chosen as first - line antidepressants due to their safety in overdose and improved tolerability
- Work Well in most people
- Starter drug of choice in most people

Advantages of SSRIs

- Other first - line agents include SNRIs, bupropion and mirtazapine
- Treatment selection is based on individual patient characteristics
  - Co morbidities
  - Concomitant medication

Advantages of SSRIs

- Individual or strong family history of response to a particular medication
- Patient preference

Advantages of SSRIs

- Recommendations SSRIs as monotherapy for patients who are at Stage 1 depression
- Citalopram and fluoxetine should be avoided in patients with QT interval prolongation or in patients who are taking other drugs that increase the QT interval
- Not recommended with MAOI therapy

Advantages of SSRIs

- I would not use SSRIs as monotherapy in patients who have bipolar disorder, due to the increased likelihood of precipitation of a mixed / manic episode
- Avoid SSRI therapy in patients who have closed - angle glaucoma, because SSRIs may result in increased intraocular pressure

Antidepressants vs Placebo

- Most studies that evaluate antidepressants have done so in the secondary setting rather than the primary setting

Antidepressants vs Placebo

- In primary care, there is a 12 - month depression prevalence of 18.1%
- Patients with depression in the primary care setting often present with somatic symptoms, including gastrointestinal, skeletal muscle, and cardiovascular complaints

Wolters Kluwer Health

SSRI	Half-Life (h)	Metabolite Half-Life	Peak Plasma Level (h)	% Protein Bound	Bioavailability (%)	Initial Dose
Citalopram (CeleXA)	35	S-desmethyl-citalopram: 59 hours	4	80	80	20 mg qAM
Escitalopram (Lexapro)	27-32	S-desmethyl-citalopram: 59 hours	5	56	80	10 mg qAM
FLUoxetine (PROzac, PROzac Weekly, Sarafem, Selfemra)	Initial: 24-72 Chronic: 96-144	Norfluoxetine: 4-16 days	6-8	95	72	10-20 mg qAM
FluvoxaMINE (Luvox CR)	16	N/A	3	80	53	50 mg qhs
PARoxetine (Paxil, Paxil CR, Pexeva)	21	N/A	5	95	>90	10-20 mg qAM
Sertraline (Zoloft)	26	N-desmethyl-sertraline: 62-104 hours	5-8	98	88	25-50 qAM

Indications	Citalopram Hydrobromide	Escitalopram	Fluoxetine HCL	Fluvoxamine Maleate	Paroxetine HCL	Paroxetine Mesylate	Sertraline HCL
Impairment Dosing Adjustment	Yes		Yes		Yes	Yes	
Hepatic Impairment Dosing Adjustment	Yes		Yes	Yes	Yes	Yes	
social phobia (social anxiety disorder)	Yes†	Yes†	Yes†	Yes	Yes	Yes	Yes
premenstrual dysphoric disorder (PMDD)	Yes†		Yes	Yes†	Yes	Yes	Yes
premature ejaculation			Yes†		Yes†	Yes†	Yes†
posttraumatic stress disorder (PTSD)	Yes†		Yes†	Yes†	Yes	Yes	Yes
panic disorder	Yes†	Yes†	Yes	Yes†	Yes	Yes	Yes
obsessive-compulsive disorder (OCD)	Yes†		Yes	Yes	Yes	Yes	Yes
hot flashes	Yes†		Yes†		Yes	Yes	Yes†
generalized anxiety disorder (GAD)		Yes		Yes†	Yes	Yes	Yes†
depression	Yes	Yes	Yes	Yes†	Yes	Yes	Yes

Yes – Labeled

Yes+ - Off-label, Recommended

NR – Off-label, Not Recommended

List SSRIs

Generic Name	Brand Name
citalopram	Celexa
escitalopram	Lexapro
fluoxetine	Prozac
fluvoxamine	Luvox
paroxetine	Paxil
sertraline	Zoloft
vilazodone	Viibryd

List SSRIs / SNRI

Generic	Brand
Desvenlafaxine	Pristiq
Duloxetine	Cymbalta
Levomilnacipran	Fetzima
Milnacipran	Savella
Venlafaxine	Effexor

Other Uses

- Anxiety disorders - Panic, OCD, General anxiety disorder, PTSD, social anxiety disorder
  - None are superior to another
  - May be used continuously or during luteal phase
  - Premature ejaculation
  - Hot flashes

Uses Discussion

- **SSRIs not preferentially recommended over SNRIs or other second generation antidepressants**
- **Choice based on**
  - **Adverse event profile**
  - **Drug interactions**
  - **Prior Hx of response**
  - **Cost**

Daily Dose Chart

Dosage Chart SSRI	Dosage Chart SSRI
Drug	Dosage
Citalopram	20 - 40 mg / day
Escitalopram	10 - 20 mg / day
Fluoxetine	20 - 80 mg / day
Fluvoxamine	50 - 300 mg / day
Paroxetine	20 - 60 mg / day
Sertraline	50 - 200 mg / day
Vilazodone	10 mg / day; increase to target of 40 mg / day

Drugs to Avoid

- **These are General Guidelines**
- **Have to be evaluated based on drug information and individual Hx**
- **Some interactions may not be severe – adjust each accordingly**
- **Check with Physician or Pharmacist**
  - **Many Pharmacists provide MTM Consultations**

Drugs To Avoid

- **Ideally MTM consultation prior to taking**
- **Can contribute to Serotonin Syndrome**
- **Patient should let MD know all meds patient is taking**
  - **Include OTC, herbs, all other possible interactors**
- **Not all drugs in each category interact**

Drugs To Avoid

Alcohol	Allergy / Cold Meds
Antidepressants – other	Antidiabetic meds
Antipsycotic medications	Asthma medications
Blood pressure meds	Detoxification meds
Heart medications	L – tryptophan
Migraine medications	Seizure medications
Theophylline	Tranquilizers
Tremor medications	Warfarin

Increase Serotonin Activity

- **Nefazodone (Serzone)**
- **Trazodone(Desyrel)**
- **Venlafaxine (Effexor)**

Increase Serotonin Activity

- **Natural Products - Possible Interaction**
  - **5 - hydroxytryptophan (5 - HTP) - Migraine - Risk SS**
  - **S - adenosylmethionine (SAMe) - Osteoarthritis and depression - Risk SS**
  - **St John's Wort - Depression**
  - **Folate - May be beneficial**

Side Effects

- **Note: Not all SSRIs produce all of the listed side effects**
- **Not every one who takes the SSRIs have Side Effects - some do not have any**
- **Some side effects dissipate or disappear quickly**
- **Some side effects continue throughout Tx**

General Side Effects

- **Elderly may be more sensitive to them**
- **If severe or not tolerable - contact physician**
- **If not sure side effects are from meds - contact Physician**
- **MTM Consultation**

Bothersome Side Effects

Apathy	Appetite Loss
Body aches	Constipation
Diarrhea	Dizziness
Dry mouth	Headache
Insomnia	Nausea
Nervousness	Rash
Sexual dysfunction	Stomach upset
Sweating	Tingling
Tiredness	Tremors
Weakness	

SSRI Top 20 Adverse Reactions / Side Effects Table

Adverse reaction/side effect	Citalopram HBr	Escitalopram	Fluoxetine HCl	Fluvoxamine Maleate	Paroxetine HCl	Paroxetine Mesylate	Sertraline HCl
nausea	21%	15 - 18%	12 - 29%	34 - 40%	4.3 - 26%	4.3 - 26%	25%
insomnia	15%	9 - 12%	10 - 33%	21 - 35%	8 - 24%	8 - 24%	21%
ejaculation dysfunction	6.1%	12%	2 - 7%	8 - 11%	13 - 28%	13 - 28%	>14%
drowsiness	18%	6 - 13%	5 - 17%	22 - 27%	9 - 24%	9 - 24%	13%
asthenia	Reported	Reported	7 - 21%	14 - 26%	12 - 22%	12 - 22%	>1%
diarrhea	8%	8%	8 - 18%	11 - 18%	6 - 18%	6 - 18%	20%
anxiety	4%	Reported	6 - 15%	5 - 8%	2 - 5%	2 - 5%	4%
dizziness	2%	5%	9%	11 - 15%	6 - 14%	6 - 14%	12%
tremor	8%	Reported	3 - 13%	5 - 8%	4 - 11%	4 - 11%	8%
libido decrease	1.3 - 3.8%	3 - 6%	1 - 11%	4 - 6%	3 - 12%	3 - 12%	6%
hyperhidrosis	11%	4 - 5%	2 - 8%	6 - 7%	6 - 11%	6 - 11%	7%
yawning	2%	2%	1 - 11%	2 - 5%	4 - 5%	4 - 5%	>1%
dyspepsia	5%	3%	6 - 10%	8 - 10%	2 - 5%	2 - 5%	8%
impotence (erectile dysfunction)	2.8%	2%	1 - 7%	2%	4 - 10%	4 - 10%	>1%
headache		24%	21%	22 - 35%	6.3 - 27%	6.3 - 27%	25%
xerostomia	20%	6 - 9%	4 - 12%	10 - 14%	3 - 18%	3 - 18%	
anorexia	4%		4 - 17%	6 - 14%	1 - 9%	1 - 9%	6%
constipation		3 - 5%	5%	4 - 10%	5 - 16%	5 - 16%	6%
fatigue	5%	5 - 8%		Reported	<4.9%	<4.9%	12%
pharyngitis			3 - 10%	6%	1 - 4%	1 - 4%	pharyngitis

Rare But Serious ADRs

Serotonin Syndrome	**All SSRIs**
Prolonged QT interval	**Citalopram, fluoxetine**
Stroke	**Citalopram**
Worsening depression, suicidal thoughts, suicide	**All SSRIs**
Mania	**Fluoxetine, sertraline**
Erythema multiforme	**Fluoxetine**
SJS, Toxic Epidermal Necrolysis (TEN)	**Fluvoxamine, paroxetine, sertraline (SJS only)**
Hyponatremia	**Fluoxetine, fluvoxamine, sertraline**
Abnormal bleeding	**Fluoxetine, fluvoxamine**
Agranulocytosis	**Fluvoxamine**
Acute hepatitis	**Paroxetine**
Seizure	**Fluoxetine, fluvoxamine, paroxetine, sertraline**
Anaphylaxis	**Sertraline**
Rhabdomyolysis	**Sertraline**

Serious Side Effects

- Chest pain
- Palpitations or irregular heartbeat
- Vision disturbances
- Confusion
- Tremor
- Muscle Spasm
- Fever
- Serotonin Syndrome

Side Effects Discussion

- QT interval prolongation
  - Citalopram associated with dose - related QT interval prolongation
  - Torsade de pointes has been reported

Side Effects Discussion

- GI – most common first two weeks
  - Nausea - transient and mild
  - Diarrhea, dry mouth, constipation, vomiting also
  - Sertraline - higher incidence

Side Effects Discussion

- Sexual dysfunction
  - Men - ejaculatory delay, decreased libido and ED
  - Women - decreased libido and orgasm dysfunction
  - Paroxetine – highest rate

Side Effects Discussion

- Bleeding - Impaired platelet aggregation due to serotonin depletion - may increase bleeding risk
  - Epistaxis most common
  - GI bleeding - Combo with other antiplatelet drugs i.e. aspirin

Side Effects Discussion

- Hyponatremia - from inappropriate antidiuretic hormone secretion
  - serum sodium levels less than 110 mmol / L

Side Effects Discussion

- Dermatologic – Rare
  - Severe cutaneous, Stevens - Johnson syndrome, toxic epidermal necrolysis and erythema multiforme reported

Side Effects Discussion

- Neonatal abstinence syndrome
  - Poor feeding, hypoglycemia, hypothermia, lethargy or irritability, vomiting, etc.) have been reported in infants exposed to SSRIs in utero

Side Effects Discussion

- When treating a pregnant woman with an SSRI during the third trimester, the physician should carefully consider the potential risks and benefits of treatment
  - If clinically feasible, and taking the drug half - life into consideration, tapering of the serotonergic agent prior to delivery may be considered as an alternative. [50547]

Drug Interactions

- All agents interact with MAOIs, triptans, linezolid and tramadol which can increase the risk of serotonin syndrome
- Fluoxetine and fluvoxamine interact with alprazolam - there is an increase in plasma concentrations and half - life of alprazolam

Drug Interactions

- Fluoxetine, fluvoxamine, and paroxetine interact with beta - blockers, which results in increased BB concentration (heart block, bradycardia)
- Fluoxetine and fluvoxamine interact with carbamazepine, causing an increase in carbamazepine concentrations

Drug Interactions

- MAO inhibitors - SSRIs are contraindicated in patients receiving MAO inhibitors or within two weeks of their discontinuation
- SSRIs, SNRIs, and other serotonergic drugs

Drug Interactions

- Meperidine, triptans, most antidepressants, amphetamines, ergot alkaloids, dopamine antagonists, St. John's wort, and others
- Do not co - administer SSRIs with an SNRI or another SSRI as the risk for serotonin syndrome or neuroleptic malignant syndrome is greatly increased
- Monitor Close for SS

Drug Interactions

- Antithrombotic drugs
  - Anticoagulants, antiplatelet drugs, nonsteroidal anti - inflammatory drugs, and aspirin should be administered with caution
  - Especially with elderly

Drug Interactions

- Monitor for signs and symptoms of bleeding while taking an SSRI with an anticoagulant medication and to promptly report any bleeding events to the practitioner

Drug Interactions

- CYP 450 isozymes
- Fluoxetine and Paroxetine inhibit CYP2D6 - increasing drug levels
- Fluvoxamine - inhibit CYP2C19, CYP1A2, CYP3A4 interact - tricyclic antidepressants, antipsychotics, propranolol and warfarin

Drug Interactions

- QT Interval Prolongation
  - Citalopram - Fluoxetine - Current use with drugs that prolong QT interval not recommended
- CYP2C19 inhibitors, the maximum recommended daily dose is 20 mg due to the risk of QT interval prolongation

Safety Issues

- X – Contraindicated
- X-BBW – Contraindicated and Black Box Warning
- BBW – Black Box Warning, Not Contraindicated
- Yes – REMS or MedGuide is available

Safety Issue	Citalopram Hbr	Escitalopram	Fluoxetine Hcl	Fluvoxamine Maleate	Paroxetine HCl	Paroxetine Mesylate	Sertraline HCl
REMS							
MedGuide	Yes	Yes	Yes	Yes	Yes	Yes	Yes
citalopram hypersensitivity	X	X					
MAOI therapy	X	X		X	X	X	X
children	BBW	BBW	BBW	BBW	BBW	BBW	BBW
suicidal ideation	BBW	BBW	BBW	BBW	BBW	BBW	BBW
pregnancy					X	X	

Safety Issues

- Increased Risk of suicide
  - All antidepressants - Children and young adults, especially the first few months of therapy
  - AACP- Risk benefit ratio favorable with close monitoring
  - Careful monitoring for all patients on initiation of therapy with SSRI

Safety Issues

- QT Prolongation - Citalopram can prolong
  - Not recommended in patients with congenital long QT syndrome, bradycardia, or uncorrected electrolyte disturbances or using other drugs that prolong QT

Safety Issues

- Poor metabolizers of CYP2C19 - max dose 20mg / d
- Frequent monitoring indicated if mandatory concurrent use

Safety Issues

- Pregnancy
  - Paroxetine Category D
  - Most Category C
  - Some studies show septal heart defects when mothers taking sertraline or citalopram in early pregnancy

Safety Issues

- Persistent pulmonary hypertension of newborn with maternal use after 20 weeks
- 3rd trimester use associated with neonatal abstinence syndrome after delivery

Safety Issues

- Breast feeding - benefits weighed against risk
  - Sertraline, paroxetine and nortriptyline may be preferred due to low concentrations

Safety Issues

- Abrupt discontinuation
  - Avoid if possible
  - Flu - like symptoms
  - Gradual tapering recommended
  - Paroxetine - withdraw 2 weeks
  - Fluoxetine - lowest rate due to slow metabolism

Safety Issues

- Bipolar Disorder
- Precipitation of mania in patients with bipolar disorder can occur and should be considered when selecting drug therapy

Efficacy Monitoring

- Patients will show substantial improvement during the first 2 weeks of treatment, but a maximum improvement may not be evident for 4 or more weeks
- A similar delayed pattern (4 to 6 weeks) of therapeutic response is similar among all antidepressant agents

Efficacy Monitoring

- Baseline and periodic electrolyte measurements in patients at risk for significant electrolyte disturbances
- ECG for QT interval prolongation

Efficacy Monitoring

- Monitor for serotonin syndrome
  - Signs / symptoms include mental status changes, tachycardia, in coordination, nausea, vomiting and diarrhea

Major Counseling Points

- Avoid activities requiring mental alertness of coordination until drug effects are realized
- Report use of a MAOI within the last 14 days prior to initiation of drug

Major Counseling Points

- Report worsening depression, suicidal ideation, agitation, irritability, or unusual changes in behavior, especially at initiation of therapy or with dose changes

Major Counseling Points

- Immediately report any symptoms of QT prolongation (CP, SOB, syncope, palpitations, dizziness), especially with citalopram and fluoxetine
- May cause sexual dysfunction
- Symptomatic improvement may not be seen for a few weeks

Major Counseling Points

- Report signs / symptoms of serotonin syndrome (high fever, agitation, confusion, hallucinations, hyperreflexia, n / v / d)
  - Concurrent use of serotonergic agents (Triptans, tryptophan), linezolid, lithium, tramadol, or St. John's wort may increase risk

Major Counseling Points

- Report signs of hyponatremia (HA, difficulty concentrating, confusion, memory impairment, and weakness / unsteadiness that may lead to falls), especially with fluoxetine, fluvoxamine and sertraline
- Report decreased appetite and weight loss

Major Counseling Points

- Report skin rash, with or without systemic symptoms (fever, edema, pulmonary effects)
- Consult healthcare professional prior to new drug use, including OTC and herbal drugs

Major Counseling Points

- Advise against sudden discontinuation due to significant withdrawal symptoms
- Avoid or minimize consumption of alcohol while on this drug
- Concomitant use of ASA, NSAIDs, warfarin, or other anticoagulants may increase the risk of bleeding

Instructions for Administration

- Citalopram, escitalopram, fluoxetine
  - May be taken in the morning or evening without regard to food
- Fluvoxamine
  - Take at bedtime
  - Do not crush or chew extended - release capsules

Instructions for Administration

- Divide total daily doses > 100 mg of immediate - release tablets into 2 doses
  - If 2 doses of unequal size are to be taken daily, the larger dose should be taken at bedtime

Instructions for Administration

- Paroxetine
  - Administer as a single dose without regard to food usually in the morning
  - Suspension: Shake well before using
  - Controlled - release tablets: Do not crush or chew tablet; swallow whole

Instructions for Administration

- Sertraline
  - Oral concentrate: Dilute in 4 ounces (one - half cup) using only water, ginger ale, lemon - lime soda, lemonade or orange juice; dilute immediately before use - do not mix in advance

Serotonin Syndrome (SS)

- Neuromuscular effects
- Autonomic effects
- Mental status changes

Serotonin Syndrome (SS)

- Occurrence - Central and peripheral serotonin receptors are over stimulated through action of medications or drugs of abuse
- Incidence unknown but uncommon
- Symptoms non specific diagnostic criteria vary
- Mild symptoms may be ignored

SS Signs and Symptoms

- Hallmark sign - clonus - involuntary rapid muscle contraction and relaxation or tremor
- Mental Status changes
  - Pressured speech
  - Hypomania
  - Hypervigilance

SS Signs and Symptoms

- Hyperactivity
- Hallucinations
- Delirium
- Confusion
- Agitation

SS Signs and Symptoms

- Automomic changes
  - Diarrhea
  - Mydriasis
  - Fever
  - Flushing
  - Increased bowel sounds
  - Respiratory rate
  - Tearing

SS Signs and Symptoms

- Neuromuscular
  - Hyperreflexia
  - Increased muscle tone
  - Restlessness
  - Rhabdomyolysis
  - Rigidity

SS Signs and Symptoms

- Shivering
- Spontaneous, inducible or ocular clonus
- Tremor

SS Signs and Symptoms

- Occur typically after increase in dose or overdose or addition of other serotonergic drug
- 67 % symptoms within 6 hours
- 75 % symptoms within 24 hours

SS Signs and Symptoms

- Mild SS
  - May not be recognized
  - Patients with increased temperature and muscle rigidity should be considered medical emergency
  - Multiorgan failure within hours

SS Signs and Symptoms

- SS can occur after discontinuance of long acting medications
  - Prozac, Sarafem
  - MAOI - Marplan Phenelzine, etc.

SS Causative Agents

- Causes
  - Increased serotonin production
  - Inhibition of serotonin reuptake
  - Inhibition of serotonin metabolism
  - Increased serotonin release
  - Stimulation of serotonin receptors

SS Causative Agents

- Administration of two or more drugs that affect the serotonin system through different mechanisms
  - Increased serotonin production
  - Inhibition of serotonin metabolism
  - Increased serotonin release
  - Stimulation of serotonin receptors
  - Multiple mechanisms

SS Causative Agents

- Increased serotonin production
  - L- tryptophan - serotonin precursor
- Inhibition of serotonin reuptake
  - Chlorpheniramine (Chlortirmeton), SSRIs, St. John's wort, tramadol (Ultram), Trazodone (Desyrel), tricyclic antidepressants (clomipramine imipramine)

SS Causative Agents

- Dextromethorphan (Robitussin DM, etc.)
- Meperidine (Demerol)
- Methadone
- Pentazocine (Talwin)
- Venlaxafine (effexor)

SS Causative Agents

- **Inhibition of serotonin metabolism**
  - **MAOI inhibitors - isocarboxazid (Marplan), phenelzine (Nardil), selegiline (eldepryl), and tranylcypromine (Parnate)**

SS Causative Agents

- **Increased serotonin release**
  - **Dextromethorphan, meperidine, methadone, methylenedioxymethamphetamine (MDMA, ecstasy), Mirtazapine (Remeron)**

SS Causative Agents

- **Stimulation of serotonin receptors**
  - **Buspirone, lysergic acid diethylamide (LSD), meperidine, lithium, metoclopramide (reglan), dihydroergotamine (DHE 45) and triptans (sumatriptan etc.)**

SS Causative Agents

- **Alteration of the elimination of a serotonergic drug - some SSRIs can inhibit metabolism of tramadol by CYP2D6 inhibition - increase serotonergic activity**

SS Causative Agents

- **Occurrance - Elimination of a serotonergic drug which is altered**
  - **SSRIs can inhibit tramadol by CYP2D6 inhibition - increasing serotonergic activity**
    - **See Interaction Chart**

SS Causative Agents

Inhibition of Serotonin Reuptake	
Generic Name	Brand
Chlorpheniramine	Chlortrimeton
Dextromethorphan	Robitussin
Hypericum perforatum	St. John's wort
Cyclobenzaprine	Flexeril
Meperidine	Demerol
Methadone	Dolophine

SS Causative Agents

Inhibition of Serotonin Reuptake	
Generic Name	Brand
Sibutramine	Meridia
Tramadol	Ultram
Trazodone	Desyrel
Tricyclics (clomipramine, imipramine)	numerous
Venlafaxine	Effexor

SS Causative Agents

Increased Serotonin Release:	
Generic	Brand
Dextromethorphan	Robitussin, Delsym
Meperidine	
Methadone	
Methylenedioxymethamphetamine	MDMA, ecstasy
Mirtazapine	Remeron

SS Causative Agents

Stimulation of Serotonin Receptors	
Generic	Brand
Buspirone	Buspar
Lysergic acid diethylamide	LSD
Meperidine	
Lithium	
Metoclopramide	Reglan
Dihydroergotamine	D.H.E. 45
Triptans	Sumatriptan etc.

SS Treatment

- **Treatment - Discontinue offending drug**
  - **Supportive care**
  - **Mild to moderate cases resolve in 24 - 72 hours**
  - **Severe cases longer**

SS Treatment

- **Mild cases - Benzodiazepines (reduce hypertonicity and neurologic excitability)**
- **Severe cases - Sedation, paralyzation, intubation**

SS Treatment

- **Fever - Caused by excessive muscular activity, not a change in hypothalamic temperature set point - antipyretic therapy not recommended**
- **Serotonin antagonists have been recommended**
  - **Cyproheptadine (periactin)**
  - **Chlorpromazine (Thorazine)**

SS Commentary

- Relatively few patients get SS
- Fatalities rare
- Improvement seen with supportive care
- No way to predict

SS Commentary

- Some combinations more problematic
  - Tramadol and other antidepressants
    - Avoid if possible, alter doses

SS Commentary

- Linezolid - monitor- may reduce antidepressant dose during Tx
- MAOI - 50 %
  - Avoid adding up to 2 weeks
  - 5 weeks for fluoxetine

SS Commentary

- Triptans - FDA alert
  - Use with SSRS or SNRIs
  - Incidence low
  - Patients should be educated about problem if unavoidable

SS Commentary

- Avoid unnecessary combinations
  - Counsel patients on problems
  - Contact prescriber for even mild symptoms
  - DC and get help if severe symptoms occur

SSRIs and Pregnancy

- SSRIs most prescribed
- Risks weighed against benefits
- Preterm birth rates not clearly defined

SSRIs and Pregnancy

- Congenital malformations
  - Paroxetine cardiac risk about 2 %
  - 1 % in all infants
- Autism
  - Not clearly defined by studies

SSRIs and Breast Milk

- Risks and benefits
  - Need by mother
  - Potential effects on milk production
  - Amount of drug excreted into human milk
  - Extent of oral absorption by breastfeeding infant
  - Potential adverse effects on the breastfeeding infant

SSRIs and Breast Milk

- Risks and Benefits
  - Most often in two months and younger
  - Rare in six months or older
  - Pharmacogenetics emerging guidance may help individualize decisions

SSRIs and Breast Milk

- Database Recommended
  - LactMed - http://toxnet.nlm.nih.gov
  - There's an APP for that!
  - Recommended reference for up to date information

SSRIs and Breast Milk

SSRIs Exceeding 10% of Maternal Plasma Concentration	Reference
Citalopram	Weissman 2004
Fluoxetine	Weissman 2004, 20 product labeling
Fluvoxamine	Weissman 2004
Sertraline	Hendrick 2001, Stowe 2003
Venlafaxine	Newport 2009

SSRIs Pediatric Depression

- Most common antidepressant in children and adolescents
- Fluoxetine most used - Starting dose 10 to 20 mg once daily
  - Graduating dose
- Citalopram and Sertraline – Not FDA approved yet
- All available in liquid formulations

SSRIs Pediatric Depression

- Escitalopram
  - FDA approved for adolescents
  - Starting dose 10 mg up to 20 mg once daily

SSRIs Pediatric Depression

- Citalopram and Sertraline
  - Evidence of use
  - Sertraline 25 mg once daily increased to 50 mg once daily, increased every two weeks up to 200 mg once daily
  - Citalopram initial dose - 10 mg once daily increased to 20 mg once daily after a week, maximum dose 40 mg once daily

SSRIs Pediatric Depression

- Follow up
  - Weekly for 4 weeks
  - Every 2 weeks for 4 weeks
  - At week 12 then as indicated
  - Continue for at least 6 - 12 months
  - Taper when DC'd

SSRIs Pediatric Depression

- Side effects
  - Dose dependent - resolve with time
  - Rule out bi - polar disorder
  - Monitor for agitation, disinhibition and suicidal thoughts
  - Common side effects include
    - Headache, sleepiness or disturbance

SSRIs Pediatric Depression

- Abrupt discontinuation - Avoid
  - May cause worsening depression and suicidality
  - Fluoxetine lowest risk due to long half - life

SSRIs Pediatric Depression

- QT prolongation
  - Don't use citalopram
  - Use with caution in patients with congenital heart disease, liver disease or arrhythmias

SSRIs Pediatric Depression

- Suicidality
  - Mentioned in MedGuide
  - Dispensed with prescriptions
  - Weigh benefits vs. risks
  - Monitor for

SSRIs and the Elderly

- First line treatment in elderly
- Little evidence as opposed to tricyclics

SSRIs and the Elderly

- Weigh benefits vs. risk
- Advantages - Fewer anticholinergic effects, benign cardiovascular profile, ease of use and safety in overdose
- Few differences in different forms

SSRIs and the Elderly

- Adverse effects in elderly
  - Falls, hyponatremia, weight loss, sexual dysfunction and drug interactions
- Patient monitoring important
- Titrate slowly
- Use caution for interacting drugs

Dispensing Role of Nurses

- Nurses in Health Department Statutorily allowed to dispense
  - Counseling Patient in Dispensing
    - Uses of drug
    - Dosage to take
    - Side effects

Dispensing Role of Nurses

- Interactions - Check for and counsel
- Inform patient about their drug
- PILs

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