

ANTIDEPRESSANT

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Introduction

Definition

Antidepressants :

- ♣ are drugs used for the treatment of MDD and other conditions, including dysthymia, anxiety disorders , obsessive compulsive disorder , eating disorders , chronic pain , neuropathic pain and, in some cases, dysmenorrhoea , snoring , migraine, attention deficit hyperactivity disorder (ADHD) , addiction , dependence, and sleep disorders .
- ♣ They may be prescribed alone or in combination with other medications.
- ♣ Fall into a wide variety of chemical classes

Introduction ...

- ♣ They have a wide range of neuro-pharmacological effects
- ♣ Grouped in based on the presumed primary action that leads to an antidepressant effect.
 1. drugs that inhibit the uptake of the monoamines noradrenaline, 5-HT, and dopamine into nerve endings
 2. drugs that inhibit monoamine oxidase and
 3. drugs with other primary actions that do not primarily involve inhibition of monoamine uptake or monoamine oxidase inhibition
- ♣ They correct chemical imbalances of neurotransmitters in the brain which probably cause changes in mood and behavior.

Introduction ...

Historical Background

- ♣ Antidepressants were initially developed in the 1950s.
- ♣ Before the 1950s, **opioids** and **amphetamines** were commonly used as antidepressants.
- ♣ Their use was later restricted due to their addictive nature and side effects.
- ♣ The antidepressant effect of a tricyclic, a three ringed compound, was first discovered in 1957 by **Roland Kuhn** in a Swiss psychiatric hospital.

Introduction ...

- ♣ Extracts from the herb **St John's wort** had been used as a "nerve tonic" to alleviate depression.
- ♣ Their use has become progressively more common over the last twenty years.
- ♣ In 1996 there were 13.3 million people using antidepressants in the United States.
- ♣ By 2010, the figure stood at 23.3 million people.

Introduction ...

- ❖ Researchers from Columbia University Medical Center, the New York State Psychiatric Institute, and the University of Pennsylvania added that rates remained low among racial and ethnic minorities.
- ❖ They believe antidepressant usage has become more common because:
 - There has been a broadening in the concepts of need for **mental health** treatment
 - Campaigns to promote mental health care have become more widespread
 - Mental health treatments have become more widely accepted by the public

Introduction ...

Types of antidepressants

♣ The most important classes of antidepressants are

1. the selective serotonin reuptake inhibitors (SSRIs),

2. serotonin-norepinephrine reuptake inhibitors (SNRIs),

3. tricyclic antidepressants (TCAs),
Classical

4. monoamine oxidase inhibitors (MAOIs),
antidepressant

5. reversible monoamine oxidase A inhibitors (rMAO-A inhibitors),

6. tetracyclic antidepressants (TeCAs)

Monoamine Oxidase Inhibitors

- ♣ MAOIs were the first class of approved antidepressant drugs, introduced in the late 1950s.
- ♣ **Isoniazid** was the first MAOI intended to be used as a treatment for tuberculosis, but its antidepressant properties were discovered by chance when some treated patients experienced elevation of mood during treatment.
- ♣ MAOIs are currently used **less frequently than other antidepressants**. This is b/c of -
 - the development of potentially lethal hypertension
 - potentially lethal dietary and drug interactions
 - introduction of the SSRIs and other new agents

Monoamine Oxidase Inhibitors...

- ♣ MAOIs are a group of drugs that inhibit MAO-A and MAO-B in the CNS and have antidepressant efficacy.
- ♣ The currently available MAOIs include
 - Phenelzine (Nardil),
 - Isocarboxazid (Marplan) ,
 - Tranylcypromine (Parnate) ,
 - Rasagiline (Azilect),
 - Moclobemide (Manerix), and selegiline (Eldepryl).
- ♣ Monoamine oxidase exists in two subtypes, A and B.
- ♣ Both forms are inhibited by the original MAO inhibitors, which are therefore nonselective.

Monoamine Oxidase Inhibitor

- ♣ The A form metabolizes the neurotransmitter monoamines most closely linked to depression (serotonin and norepinephrine).
- ♣ The A form also metabolizes the amine most closely linked to control of blood pressure (norepinephrine).
- ♣ MAO A inhibition is linked both to antidepressant action and to the troublesome hypertensive side effects of the MAO inhibitors

Monoamine Oxidase Inhibitor CONT'D

- ♣ The B form is thought to convert some amine substrates, called **protoxins**, into toxins that may cause damage to neurons.
- ♣ Inhibition of MAO B is linked to prevention of neurodegenerative processes, such as those in Parkinson's disease.
- ♣ A newer class of MAO inhibitors, which has entered clinical practice for the treatment of depression, is known as reversible inhibitors of MAO A (RIMAs).
 - This is a very welcome development in new drug therapeutics for depression, because it has the potential of making MAO A inhibition for the

PHARMACOLOGIC ACTIONS

♣ Phenelzine , tranylcypromine , and isocarboxazid :

- are readily absorbed after oral administration and reach peak plasma concentrations within 2 hours.
- their plasma half-lives are in the range of 2 to 3 hours,
- their tissue half-lives are considerably longer.
- Because they irreversibly inactivate MAOs, the therapeutic effect of a single dose of irreversible MAOIs may persist for as long as 2 weeks.

Monoamine Oxidase Inhibitors...

♣ RIMA moclobemide

- rapidly absorbed and has a half-life of 0.5 to 3.5 hours.
- has a much briefer clinical effect after a single dose than do irreversible MAOIs.
- ♣ The MAO enzymes are found on the outer membranes of mitochondria and they degrade cytoplasmic and extraneuronal monoamine neurotransmitters such as nor-epinephrine, serotonin, dopamine, epinephrine, and tyramine.
- ♣ MAOIs act in the CNS, the sympathetic nervous system, the liver, and the GI tract.

Monoamine Oxidase Inhibitors...

- ♣ There are two types of MAOs, **MAOA** and **MAO B**.
- ♣ MAOA primarily metabolizes norepinephrine, serotonin, and epinephrine.
- ♣ dopamine and tyramine are metabolized by both MAOA and MAOB.
- ♣ The structures of phenelzine and tranylcypromine are-
 - Similar to those of amphetamine and have similar pharmacologic effects in that they increase the release of dopamine and norepinephrine with attendant stimulant effects on the brain.

Monoamine Oxidase Inhibitors...

THERAPEUTIC INDICATIONS

- Depression - Atypical depression , bipolar depression
- panic disorder and social phobia
- bulimia nervosa ,
- post traumatic stress disorder (PTSD)
- anginal pain
- atypical facial pain
- migraine
- attention-deficit/hyperactivity disorder (ADHD)
- idiopathic orthostatic hypotension
- depression associated with traumatic

Monoamine Oxidase Inhibitors...

- ♣ MAOIs are more effective than TCA for Atypical depression , especially phenelzine is more effective than TCAs in depressed patients or pts with a constellation symptoms of atypical depression such as
 - mood reactivity,
 - extreme sensitivity to interpersonal loss or rejection,
 - prominent anergia
 - hyperphagia , and hypersomnia
- └ MAOIs are more effective than TCAs as a treatment for bipolar depression.

Monoamine Oxidase Inhibitors...

PRECAUTIONS AND ADVERSE REACTIONS

♣ The most frequent adverse effects of MAOIs are -

- orthostatic hypotension
- insomnia
- weight gain
- edema
- sexual dysfunction

♣ **Orthostatic hypotension** can lead to dizziness and falls.

└ Thus, cautious upward tapering of the dosage should be used to determine the

Monoamine Oxidase Inhibitors...

- ♣ Treatment for **orthostatic hypotension** includes:
 - avoidance of caffeine
 - intake of 2L of fluid per day
 - addition of dietary salt or adjustment of antihypertensive drugs (if applicable)
 - support stockings
 - in severe cases , treatment with fludrocortisone (Florinef), a mineralocorticoid, 0.1 to 0.2 mg a day.
- ♣ Orthostatic hypotension associated with **tranylcypromine** use can usually be relieved by dividing the daily dosage.

Monoamine Oxidase Inhibitors...

♣ **Insomnia** can be treated -

- by dividing the dose,
- not giving the medication after dinner
- using trazodone (Desyrel) or a benzodiazepine hypnotic if necessary.

♣ **Weight gain, edema , and sexual dysfunction**

-
- often do not respond to any treatment
- may warrant switching to another agent
- When switching from one MAOI to another, the clinician should taper and stop use of the first drug for 10 to 14 days before beginning use of the second drug

Monoamine Oxidase Inhibitors...

- ♣ Paresthesias, myoclonus, and muscle pains are occasionally seen in persons treated with MAOIs.
- ♣ Paresthesias may be secondary to **MAOI-induced pyridoxine deficiency** :
 - respond to supplementation with pyridoxine, 50 to 150 mg orally each day.
- ♣ Occasionally, persons complain of feeling drunk or confused, perhaps indicating that the dosage should be **reduced and then increased gradually**.

Monoamine Oxidase Inhibitors...

- ♣ The hydrazine MAOIs are associated with hepatotoxic effects are relatively uncommon.
- ♣ MAOIs are **less cardiotoxic and less epileptogenic** than are the tricyclic and tetracyclic drugs.
- ♣ The most common adverse effects of the RIMA moclobemide are :
 - dizziness
 - nausea
 - insomnia or sleep disturbance

Monoamine Oxidase Inhibitors...

- ❖ RIMAs cause fewer GI adverse effects than do SSRIs.
- ❖ **Moclobemide** does not have adverse anti-cholinergic or cardiovascular effects, and it has not been reported to interfere with sexual function.
- ❖ MAOIs should be used with caution by persons with **renal disease, cardiovascular disease** , or **hyperthyroidism**.
- ❖ MAOIs may alter the dosage of a hypoglycemic agent required by persons with diabetes.

Monoamine Oxidase Inhibitors...

- ♣ MAOIs have been particularly associated with **induction of mania** in persons in the depressed phase of bipolar I disorder and **triggering of a psychotic decompensation** in persons with schizophrenia .
- ♣ MAOIs are **contraindicated during pregnancy**, although data on their teratogenic risk are minimal.
- ♣ MAOIs **should not be taken by nursing women** because the drugs can pass into the breast milk.

Monoamine Oxidase Inhibitors...

Tyramine-Induced Hypertensive Crisis

- ♣ Is the most worrisome side effect of MAOIs

Mechanism of Action

1. The amino acid tyramine is normally transformed via GI metabolism.



2. MAOIs inactivate GI metabolism of dietary tyramine



3. Allowing intact tyramine to enter the circulation.



4. A hypertensive crisis may subsequently occur as a result of a powerful pressor effect of the amino acid.

Monoamine Oxidase Inhibitors...

- ♣ Tyramine - containing foods should be **avoided for 2 weeks** after the last dose of an irreversible MAOI to allow resynthesis of adequate concentrations of MAO enzymes.
- ♣ Foods rich in tyramine or other sympathomimetic amines, such as ephedrine, pseudoephedrine (Sudafed), or dextromethorphan (Trocadol), should be avoided by persons who are taking irreversible MAOIs.

Monoamine Oxidase Inhibitors...

- ♣ Patients should be advised to continue the dietary **restrictions for 2 weeks** after they stop MAOI treatment to allow the body to resynthesize the enzyme.
- ♣ Bee stings may cause a hypertensive crisis.
- ♣ In addition to severe hypertension , other symptoms may include headache ,stiff neck, diaphoresis, nausea and vomiting.
- ♣ A patient with these symptoms should seek **immediate medical treatment.**

Monoamine Oxidase Inhibitors...

Treatment of MAOI-induced hypertensive crisis

- ♣ Should be treated with α -adrenergic antagonists
 - for example, phentolamine (Regitine) or chlorpromazine (Thorazine).
 - These drugs lower blood pressure within 5 minutes.
- ♣ IV furosemide (Lasix) can be used to reduce fluid load,
- ♣ a β -adrenergic receptor antagonist can control tachycardia
- ♣ A sublingual 10-mg dose of nifedipine

Monoamine Oxidase Inhibitors...

N.B : MAOIs should not be used by persons with thyrotoxicosis or pheochromocytoma.

♣ The risk of tyramine-induced hypertensive crises is relatively low for persons who are taking RIMAs, such as moclobemide and befloxatone.

-These drugs have relatively little inhibitory activity for MAOB and because they are reversible , normal activity of existing MAOA returns within 16 to 48 hours of the last dose of a RIMA.

Monoamine Oxidase Inhibitors...

- ♣ The dietary restrictions are less stringent for RIMAs, applying only to foods containing high concentrations of tyramine, which need be avoided for 3 days after the last dose of a RIMA.
- ♣ A reasonable dietary recommendation for persons taking RIMAs is to avoid eating tyramine-containing foods **1 hour before and 2 hours after** taking a RIMA.
- ♣ Spontaneous, nontyramine-induced hypertensive crisis is **a rare occurrence**, usually shortly after the first exposure of a MAOI.

Monoamine Oxidase Inhibitors...

Withdrawal

- ♣ Abrupt cessation of regular doses of MAOIs may cause a self-limited discontinuation syndrome consisting of arousal, mood disturbances, and somatic symptoms.
- ♣ To avoid these symptoms when discontinuing use to a MAOI, dosages should be gradually tapered over several weeks.

Monoamine Oxidase Inhibitors...

Overdose

- ♣ There is often an asymptomatic period of 1 to 6 hours after a MAOI overdose before the occurrence of the symptoms of toxicity.
- ♣ MAOI overdose is characterized by agitation that can progress to coma with hyperthermia , hypertension, tachypnea , tachycardia, dilated pupils, and hyperactive deep tendon reflexes.
- ♣ Involuntary movements may be present, particularly in the face and the jaw.

Monoamine Oxidase Inhibitors...

- ♣ Acidification of the urine markedly hastens the excretion of MAOIs, and dialysis can be of some use.
- ♣ Phentolamine or chlorpromazine may be useful if hypertension is a problem.
- ♣ Moclobemide alone in over dosage causes relatively mild and reversible symptoms.

Monoamine Oxidase Inhibitors...

DRUG INTERACTIONS

- ♣ Most antidepressants as well as precursor agents should be avoided.
- ♣ Persons should be instructed to tell any other physicians or dentists who are treating them that they are taking a MAOI.
- ♣ MAOIs may potentiate the action of CNS depressants, including alcohol and barbiturates.
- ♣ MAOIs should not be co-administered with serotonergic drugs, such as SSRIs and clomipramine (Anafranil), because this combination can trigger a serotonin

Monoamine Oxidase Inhibitors...

- ♣ Use of lithium or tryptophan with an irreversible MAOI may also induce a serotonin syndrome.
- ♣ Initial symptoms of a serotonin syndrome can include tremor, hypertonicity, myoclonus, and autonomic signs, which can then progress to hallucinosis, hyperthermia, and even death.
- ♣ Fatal reactions have occurred when MAOIs were combined with meperidine (Demerol) or

Monoamine Oxidase Inhibitors...

Drugs to be Avoided During Monoamine Oxidase Inhibitor Treatment

Never use

- antiasthmatics
- antihypertensives (methyldopa, guanethidine, reserpine)
- Buspirone
- Levodopa
- opioids
- Cold, allergy, sinus medications
- SSRIs, clomipramine, venlafaxine
- Sympathomimetic
- L-tryptophan

Monoamine Oxidase Inhibitors...

Use carefully

- Anticholinergics
- antihistamines
- Disulfiram
- Bromocriptine
- Hydralazine
- Sedative hypnotics
- Terpin hydrate with codein
- Tricyclic and tetracyclics (avoid clomipramine)

Monoamine Oxidase Inhibitors...

- ♣ When switching from an irreversible MAOI to any other type of antidepressant drug, persons should wait **at least 14 days** after the last dose of the MAOI before beginning use of the next drug to allow replenishment of the body's MAOs.
- ♣ When switching from an antidepressant to an irreversible MAOI, persons should wait **10 to 14 days** (or 5 weeks for fluoxetine [Prozac]) before starting use of the MAOI to avoid drug-drug interactions.

Monoamine Oxidase Inhibitors...

- ♣ The effects of the MAOIs on hepatic enzymes are poorly studied.
- ♣ Tranylcypromine inhibits CYP2C19.
- ♣ Moclobemide inhibits CYP2D6, CYP2C19, and CYP1A2 and is a substrate for 2C19.
- ♣ Cimetidine(Tagamet) and fluoxetine significantly reduce the elimination of moclobemide.
- ♣ Modest doses of fluoxetine and moclobemide administered concurrently may be well tolerated, with no significant pharmacodynamic or pharmacokinetic interactions.

Monoamine Oxidase Inhibitors...

LABORATORY INTERFERENCES

- ♣ MAOIs may lower blood glucose concentrations.
- ♣ MAOIs artificially raise urinary metanephrine concentrations and may cause a false-positive test result for pheochromocytoma or neuroblastoma.
- ♣ MAOIs have been reported to be associated with a minimal false elevation in thyroid function test results.

Monoamine Oxidase Inhibitors...

DOSAGE AND CLINICAL GUIDELINES

- ♣ There is no definitive rationale for choosing one irreversible MAOI over another.
- ♣ Phenelzine use should begin with a test dose of 15 mg on the first day.
 - The dosage can be increased to 15 mg three times daily during the first week and increased by 15 mg a day each week thereafter until the dosage of 90 mg a day, in divided doses, is reached by the end of the fourth week.

Monoamine Oxidase Inhibitors...

- ♣ Tranylcypromine and isocarboxazid use should begin with a test dosage of 10 mg and may be increased to 10 mg three times daily by the end of the first week.
- ♣ Many clinicians and researchers have recommended upper limits of 50 mg a day for isocarboxazid and 40 mg a day for tranylcypromine.
- ♣ Administration of tranylcypromine in multiple small daily doses may reduce its hypotensive

Monoamine Oxidase Inhibitors...

- ♣ Even though co administration of MAOIs with TCAs, SSRIs, or lithium is generally contraindicated, these combinations have been used successfully and safely to treat patients with refractory depression.
 - they should be used with extreme caution.
- ♣ Hepatic transaminase serum concentrations should be monitored periodically because of the potential for hepatotoxicity, especially with phenelzine and isocarboxazid.

Monoamine Oxidase Inhibitors...

- ❖ Elderly persons may be more sensitive to MAOI adverse effects than are younger adults.
- ❖ MAO activity increases with age, so MAOI dosages for elderly persons are the same as those required for younger adults.
- ❖ The use of MAOIs for children has had minimal study.
- ❖ Studies have suggested that transdermal selegiline has antidepressant properties.

Although selegiline is a type B inhibitor at low doses, it becomes less selective as the dose is increased.

Typical Dosage Forms and Recommended Dosages for Currently Available MAOIs

Drug	Usual dose (mg/day)	Max dose (mg/day)	Dosage (oral) Formulation
Isocarboxazid (Marplan)	20-40	60	10- mg Tablets
Phenelzine (Nardil)	30-60	90	15-mg Tablets
Tranylcypromine	20-60	60	10-mg Tablets
Rasagiline	0.5- 1	1	0.5 or 1 -mg Tablets
Selegiline (eldepryl)	10	30	5-mg Tablets
Moclobemide (Manerix)	300-600	600	100 or 150mg Tablets

Drugs that inhibit MA reuptake at the synapse

- ♣ The drugs with **secondary amine structures**:
 - desipramine, nortriptyline, and protriptylene
 - predominantly noradrenaline uptake inhibitors with little effect on 5-HT uptake.
- ♣ **older drugs** imipramine ,amitriptyline and clomipramine inhibits both noradrenaline and 5-HT uptake.
- ♣ Drugs with **a tertiary amine** structure tend to produce more antagonism on α_1 -adrenergic, histamine and muscarinic cholinergic receptors

TRICYCLIC ANTIDEPRESSANTS (TCAS)

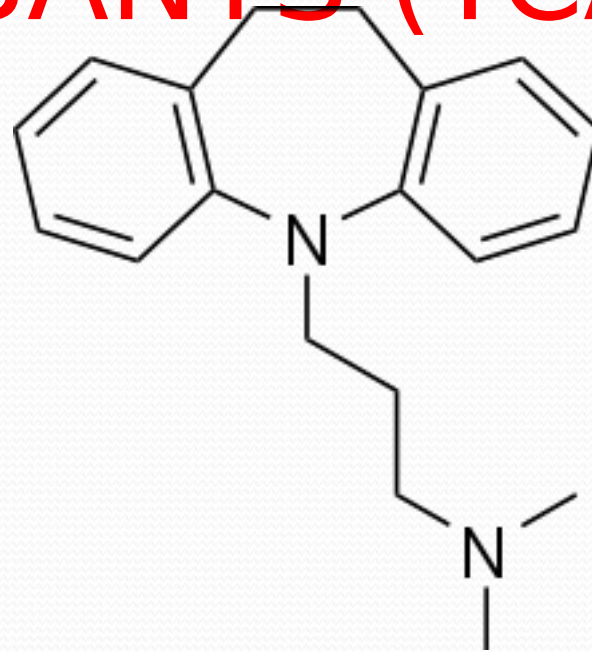
History

Imipramine

Current Drugs

Mechanism of Action

Side Effects



Imipramine

TRICYCLIC ANTIDEPRESSANTS (TCAS)

Historical background

- ♣ The observation in 1957 that **imipramine** (**Tofranil**) had antidepressant effects led to the development of a new class of antidepressant compounds, the tricyclics (TCAs).
- ♣ After the introduction of imipramine, several other antidepressant compounds were

TCA..

- ❖ **Amitriptyline** and **imipramine** were the two most commonly prescribed antidepressants in the United States
- ❖ Because of their anticholinergic and antihistaminic side effects, their use declined and **nortriptyline** and **desipramine** became more popular.
- ❖ The introduction of newer antidepressant agents with more selective actions on neurotransmitters or with unique mechanisms of action has sharply reduced the prescribing of TCAs and tetracyclic.

TCA..

Tertiary tricyclic drugs

Amitriptyline (Elavil)
Clomipramine (Anafranil)
Doxepin (Sinequan)
Imipramine (Tofranil)
Trimipramine

Secondary tricyclic drugs

Desipramine (Norpramin, Pertofrane)
Nortriptyline (Aventyl, Pamelor)
Protriptyline (Vivactil)

Tetracyclic drugs

Amoxapine (Asendin)
Moprotiline (Ludiomil)

Tricyclic and Tetracyclic Drug Preparations

DRUGS	TABLETS(mg)	Capsules (mg)	Parenteral (mg/ml)	Solution
Imipramine	10 , 25 , 50	75,100,125,150	12.5	-----
Desipramine	10,25,50,75,100,150	-----	-----	-----
Trimipramine	-----	10, 50, 100	-----	-----
Amitriptyline	10,25,50,75,100,150	-----	10	-----
Nortriptyline	-----	10,25,50,75	-----	10mg/5 ml
protriptyline	5,10	-----	-----	-----
Amoxapine	25,50,100,150	-----	-----	-----
Maprotiline	25,50,75	-----	-----	-----
5/29/2020 Clomipramine	Asmare B. (PHO, MSc) -----	25,50, 75	-----	----- 50

TCA..

PHARMACOLOGIC ACTIONS

- ♣ The absorption of most TCAs is complete after oral administration, and there is significant metabolism from the first-pass effect.
- ♣ Peak plasma concentrations occur within 2 to 8 hours,
- ♣ the half-lives of the TCAs vary from 10 to 70 hours
- ♣ **Nortriptyline, maprotiline** and particularly **protriptyline** can have longer half-lives.

- ♣ The long half-lives allow all the compounds to be given once daily
- ♣ 5 to 7 days is needed to reach steady-state plasma concentrations.
- ♣ The TCAs undergo hepatic metabolism by the CYP450 enzyme system.

TCA..

- ❖ Plasma TCAs level elevated when Clinically relevant drugs interactions can result in competition for enzyme CYP 2D6
 - drugs that compete for CYP2D6 quinidine, cimetidine (Tagamet), fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), phenothiazines, carbamazepine, antiarrhythmic drugs.
- ❖ The dosage of the TCA may need to be adjusted to correct changes in the rate of hepatic TCA metabolism.
- ❖ genetic variations in the activity of CYP 2D6 may

TCA..

- ♣ The TCAs block the transporter site for **norepinephrine** and **serotonin**, thus increasing synaptic concentrations of these neurotransmitters.
- ♣ Each drug differs in its affinity for each of these transporters
 - Clomipramine being the most serotonin selective
 - Desipramine the most norepinephrine selective of the TCAs.

TCA..

- ❖ Secondary effects of the TCAs include antagonism at the **muscarinic acetylcholine, histamine H1, and α 1- and α 2-adrenergic receptors.**
- ❖ The potency of these effects on other receptors largely determines the side effect profile of each drug.
- ❖ Amoxapine, nortriptyline, desipramine, and maprotiline have the least anticholinergic activity;
- ❖ doxepin has the most antihistaminergic activity.

TCA..

- ♣ TCAs are more likely to cause constipation, sedation, dry mouth, or light headedness than the SSRIs,
- ♣ the TCAs are less prone to cause sexual dysfunction, significant long-term weight gain, and sleep disturbances than the SSRIs.
- ♣ The half-lives and plasma clearance for most TCAs are very similar.

THERAPEUTIC INDICATIONS

- Major Depressive Disorder
- Panic Disorder with Agoraphobia
- Generalized Anxiety Disorder
- Obsessive-Compulsive Disorder
- Pain
- Childhood enuresis - is often treated with **imipramine**
- Peptic-ulcer disease - can be treated with **doxepin**
- narcolepsy, nightmare disorder, and PTSD
- ADHD, sleep walking disorder, separation anxiety disorder
- sleep terror disorder
- premature ejaculation, movement disorders, and compulsive behavior in children with autistic

TCA..

ADVERSE REACTIONS

→Psychiatric Effects

- ♣ The TCAs can induce a switch to mania or hypomania in susceptible individuals
- ♣ TCAs may also exacerbate psychotic disorders in susceptible persons.
- ♣ At high plasma concentrations (levels above 300 ng/mL), the anti-cholinergic effects of the TCAs can cause confusion or delirium.

→Anticholinergic Effects

- ♣ Anticholinergic effects often limit the tolerable dosage to relatively low ranges .

TCA..

- ♣ Some persons may develop a tolerance for the anticholinergic effects with continued treatment.
- ♣ Anticholinergic effects include dry mouth, constipation, blurred vision, delirium, and urinary retention.

Sugarless gum, candy, or fluoride lozenges can alleviate dry mouth.

- ♣ Bethanechol (Urecholine) , 25 to 50 mg three or four times a day, may reduce urinary hesitancy and may be helpful in erectile dysfunction when the drug is taken 30 minutes before sexual intercourse.

- ♣ Narrow-angle glaucoma can also be aggravated by anticholinergic drugs, and the precipitation of glaucoma requires emergency treatment with a

TCA..

- ♣ The TCAs should be avoided in persons with narrow-angle glaucoma , and SSRI should be substituted.
- ♣ Severe anticholinergic effects can lead to a CNS anticholinergic syndrome with confusion and delirium, especially if the TCAs are administered with dopamine receptor antagonists (DRAs) or anticholinergic drugs.
- ♣ **IM or IV physostigmine (Antilirium, Eserine)** is used to diagnose and treat anticholinergic delirium.

→ Cardiac Effects

- ♣ When administered in their usual therapeutic dosages, the TCAs may cause tachycardia, flattened T waves, prolonged QT intervals, and depressed ST segments in the electrocardiographic (EKG) recording.

TCA..

- ♣ **Imipramine** has a quinidine-like effect at therapeutic plasma concentrations and may reduce the number of premature ventricular contractions.
- ♣ Because the drugs prolong conduction time, their use in persons with preexisting conduction defects is contraindicated.
- ♣ In persons with a history of any type of heart disease :
 - the TCAs should be used only after SSRIs or other newer antidepressants have been found ineffective,
 - If used, they should be introduced at Low dosages, with gradual increases in dosage and monitoring of cardiac functions

TCA..

- ♣ All of the TCAs can cause tachycardia , which may persist for months and is one of the most common reasons for drug discontinuation, especially in younger persons.
- ♣ At high plasma concentrations, as seen in overdoses, the drugs become arrhythmogenic .

→ Other Autonomic Effects

- ♣ **Orthostatic hypotension**
 - is the most common cardiovascular autonomic adverse effect
 - the most common reason TCAs are discontinued
 - It can result in falls and injuries in affected persons

- **Nortriptyline** may be the drug least likely to cause

♣ **Treatment of Orthostatic hypotension**

- avoidance of caffeine
- intake of at least 2L of fluid per day
- addition of salt to the diet unless the person is being treated for hypertension.
- In persons taking antihypertensive agents, reduction of the dosage may reduce the risk of orthostatic hypotension

♣ **other possible autonomic effects**

- Profuse sweating
- palpitations
- increased blood pressure (BP)

TCA..

- ♣ some persons respond to **fludrocortisone (Florinef)**, **0.02 to 0.05 mg** twice a day, substitution of an SSRI is preferable to addition of potentially toxic mineralocorticoid such as fludrocortisone.
- ♣ The TCAs' use should be discontinued several days before elective surgery because of the occurrence of hypertensive episodes during surgery in persons receiving TCAs.

→ Sedation

- ♣ Sedation is a common effect of the TCAs and may be welcomed if sleeplessness has been a problem.
- ♣ The sedative effect of the TCAs is a result of anticholinergic and antihistaminergic activities.

TCA..

- ❖ Amitriptyline, trimipramine, and doxepin are the most sedating agents
- ❖ imipramine, amoxapine, nortriptyline, and maprotiline are less sedating
- ❖ desipramine and protriptyline are the least sedating agents

→ Neurologic Effects

- ❖ A fine, rapid tremor may occur.
- ❖ Myoclonic twitches and tremors of the tongue and the upper extremities are common
- ❖ Rare effects include speech blockage, paresthesia, peroneal palsies, and ataxia.

TCA..

♣ Amoxapine

- is unique in causing parkinsonian symptoms, akathisia , and even dyskinesia because of the dopaminergic blocking activity of one of its metabolites.
- may also cause neuroleptic malignant syndrome in rare cases.

♣ Maprotiline may cause seizures when the dosage is increased too quickly or is kept at high levels for too long.

♣ Clomipramine and amoxapine may lower the seizure threshold more than other drugs in the class

♣ As a class, however, the TCAs have a relatively low risk for inducing seizures except in persons

TCA..

- ♣ Although the TCAs can still be used by such persons, the initial dosages should be lower than usual, and subsequent dosage increases should be gradual.
- Allergic and Hematologic Effects
 - ♣ **Exanthematous rashes** are seen in 4 to 5 percent of all persons treated with maprotiline.
 - Jaundice is rare.
 - Agranulocytosis , leukocytosis, leukopenia, and eosinophilia are rare complications of TCA treatment.
 - a person who has a sore throat or a fever during the first few months of TCA treatment should have a **complete blood count (CBC)** done immediately.

TCA..

→ Hepatic Effects

- ♣ Mild and self-limited increases in serum transaminase concentrations may occur and should be monitored.
- ♣ The TCAs can also produce a fulminant acute hepatitis in 0.1 to 1 percent of persons.
 - This can be life threatening, and the antidepressant should be discontinued.

→ Other Adverse Effects

- Modest weight gain is common.
- Amoxapine exerts a DRA effect and may cause Hyperprolactinemia, impotence, galactorrhea, anorgasmia, and ejaculatory disturbances.

TCA..

- ❖ Other TCAs have also been associated with gynecomastia and amenorrhea .
- ❖ The syndrome of inappropriate secretion of antidiuretic hormone has also been reported with TCAs.
- ❖ Other effects include nausea , vomiting, and hepatitis.

→ Teratogenicity and Pregnancy-Related Risks

- ❖ A definitive link between the tricyclic compounds and tetracyclic compounds and teratogenic effects has not been established, but isolated reports of morphogenesis have been reported.
- ❖ TCAs cross the placenta, and neonatal drug withdrawal can occur.
 - This syndrome includes tachypnea , cyanosis, irritability, and poor sucking reflex.

Precautions

- ♣ The TCAs may cause a withdrawal syndrome in newborns consisting of tachypnea, cyanosis, irritability, and poor sucking reflex.
- ♣ The drugs do pass in to breast milk but at concentrations that are usually undetectable in the infant's plasma.
- ♣ The drugs should be used with caution in persons with hepatic and renal diseases.
- ♣ The TCAs should not be administered during a course of electroconvulsive therapy, primarily because of the risk of serious adverse cardiac effects.

TCA..

DRUG INTERACTIONS

→ Monoamine Oxidase Inhibitors

- ♣ The TCAs should not be taken within 14 days of administration of an MAOI.

→ Antihypertensives

- ♣ The TCAs block the therapeutic effects of antihypertensive medication.
- ♣ The antihypertensive effects of the β -adrenergic receptor antagonists (e.g. propranolol [Inderal] and clonidine [Catapres]) may be blocked by the TCAs.
- ♣ The co administration of a TCA and α -methyldopa (Aldomet) may cause behavioral agitation.

→ Antiarrhythmic Drugs

- ♣ The antiarrhythmic properties of TCAs can be additive to those of quinidine, an effect that is further exacerbated by the inhibition of TCA metabolism by quinidine.

→ Dopamine Receptor Antagonists

- ♣ Concurrent administration of TCAs and DRAs increases the plasma concentrations of both drugs.
- ♣ Desipramine plasma concentrations may increase twofold during concurrent administration with perphenazine (Trilafon).
- ♣ The DRAs also add to the anticholinergic and sedative effects of the TCAs.
- ♣ Concomitant use of serotonin-dopamine antagonists (SDAs) also increase those effects.

→ Central Nervous System Depressants

- ♣ Opioids, alcohol, anxiolytics, hypnotics, and over-the-counter cold medications have additive effects by causing CNS depression when co-administered with TCAs.
- ♣ Persons should be advised to avoid driving or using dangerous equipment if sedated by TCAs.

→ Sympathomimetics

- ♣ Tricyclic drug use with sympathomimetic drugs may cause serious cardiovascular effects.

→ Oral Contraceptives

- ♣ Birth control pills may decrease TCA plasma concentrations through the induction of hepatic enzymes.

→ Other Drug Interactions

- ♣ Nicotine may reduce TCA concentrations.
- ♣ Plasma concentrations may also be lowered by ascorbic acid, ammonium chloride, barbiturates, cigarette smoking, carbamazepine, chloralhydrate, lithium(Eskalith), and primidone (Mysoline)
- ♣ TCA plasma concentrations may be increased by concurrent use of acetazolamide(Diamox), sodiumbicarbonate, acetylsalicylic acid, cimetidine, thiazide diuretics, fluoxetine, paroxetine, and fluvoxamine (Luvox).
- ♣ Plasma concentrations of the TCAs may rise three- to four fold when administered concurrently with fluoxetine, fluvoxamine, and paroxetine.

LABORATORY INTERFERENCES

- ♣ The tricyclic compounds are present at low concentrations and are not likely to interfere with other laboratory assays.
- ♣ It is possible that they may interfere with the determination of conventional neuroleptic blood concentrations because of their structural similarity and the low concentrations of some neuroleptics.

DOSAGE AND CLINICAL GUIDELINES

- ♣ Persons who intend to take TCAs should undergo routine physical and laboratory examinations, including a **CBC, a white blood cell count with differential, and serum electrolytes with liver function tests.**
- ♣ An EKG should be obtained for all persons, especially women older than 40 years of age and men older than 30 years of age.
- ♣ The TCAs are contraindicated in persons with a QTc greater than 450 milliseconds.
- ♣ initial dose should be small and should be raised gradually

- ♣ Because of the availability of highly effective alternatives to TCAs, a newer agent should be used if there is any medical condition that may interact adversely with the TCAs.
- ♣ Elderly persons and children are more sensitive to TCA adverse effects than are young adults.
- ♣ In children, the EKG should **be regularly monitored** during use of a TCA.
- ♣ The dosages and therapeutic blood levels for the TCAs vary among the drugs
- ♣ With the exception of protriptyline , all of the TCAs should be started at 25 mg a day and increased as tolerated.

- ♣ Divided doses at first reduce the severity of the adverse effects, although most of the dosage should be given at night to help induce sleep if a sedating drug such as amitriptyline is used.
- ♣ Eventually, the entire daily dose can be given at bedtime.
- ♣ A common clinical mistake is to stop increasing the dosage when the person is tolerating the drug but taking less than the maximum therapeutic dose and does not show clinical improvement.
- ♣ The clinician should routinely assess the person's pulse and orthostatic changes in BP while the dosage is being increased.

Nortriptyline

- ♣ use should be started at 25 mg a day.
- ♣ Most patients need only 75 mg a day to achieve a blood level of 100 mg/nL.
- ♣ However, the dosage may be raised to 150 mg a day if needed.

Amoxapine

- ♣ use should be started at 150 mg a day and raised to 400 mg a day.

Protriptyline

- ♣ use should be started at 15 mg a day and raised to 60 mg a day.

Maprotiline

- ♣ has been associated with an increased incidence of seizures if the dosage is raised too quickly or is maintained at too high a level
- ♣ use should be started at 25 mg a day and increased over 4 weeks to 225 mg a day.
- ♣ It should be kept at that level for only 6 weeks and then be reduced to 175 to 200 mg a day

- ♣ Persons with chronic pain may be particularly sensitive to adverse effects when TCA use is started.
 - Therefore, treatment should begin with low dosages that are raised in small increments.
- ♣ persons with chronic pain may experience relief on long-term low-dosage therapy, such as amitriptyline or nortriptyline at 10 to 75 mg a day.
- ♣ The TCAs should be avoided in children except as a last resort.

TCA..

- ♣ Dosing guidelines in children for **imipramine** include initiation at 1.5 mg/kg a day.
 - The dosage can be titrated to no more than 5 mg/kg a day.
 - In enuresis, the dosage is usually 50 to 100 mg a day taken at bedtime.

Clomipramine

- ♣ use can be initiated at 50 mg a day and increased to no more than 3 mg/kg or 200 mg a day.

Amitriptyline

- ♣ can be started with 25 mg and increase up maximum dose (300mg) if no side effect developed.

TCA..

- ♣ When TCA treatment is discontinued,
 - the dosage should first be decreased to three-fourths the maximal dosage for a month.
 - At that time, if no symptoms are present, drug use can be tapered by 25 mg (5 mg for protriptyline) every 4 to 7 days.
- ♣ Slow tapering avoids a cholinergic rebound syndrome consisting of nausea, upset stomach, sweating, headache, neck pain, and vomiting.
 - This syndrome can be treated by reinstituting a small dosage of the drug and tapering more slowly than before.
- ♣ Several case reports note the appearance of rebound mania or hypomania after the abrupt discontinuation of TCA use.

TCA..

Plasma Concentrations and Therapeutic Drug Monitoring

- ♣ Clinical determinations of plasma concentrations should be conducted after 5 to 7 days on the same dosage of medication and 8 to 12 hours after the last dose.
- ♣ Because of variations in absorption and metabolism, there may be a 30 to 50 fold difference in the plasma concentrations in persons given the same dosage of a TCA.
- ♣ Nortriptyline is unique in its association with a therapeutic window—that is,
 - plasma concentrations below 50 ng/mL or above 150 ng/mL may reduce its efficacy

TCA..

- ♣ Plasma concentrations may be useful in confirming compliance, assessing reasons for drug failures, and documenting effective plasma concentrations for future treatment.
- ♣ Clinicians should always treat the person and not the plasma concentration.
- ♣ Some persons have adequate clinical responses with seemingly sub therapeutic plasma concentrations, and other persons only respond at supra therapeutic plasma concentrations without experiencing adverse effects.
 - The latter situation, however, should alert the clinician to monitor the person's condition with, for example, serial EKG recordings.

TCA..

Overdose Attempts with TCA

- ♣ Overdose attempts with TCAs are serious and can often be fatal.
- ♣ Prescriptions for these drugs should be non-refillable and for no longer than 1 week at a time for patients at risk for suicide.
- ♣ Amoxapine may be more likely than the other TCAs to result in death when taken in overdose.
- ♣ The newer antidepressants are safer in overdose.

TCA..

- ♣ Symptoms of overdose include agitation, delirium, convulsions, hyperactive deep tendon reflexes, bowel and bladder paralysis, dysregulation of BP and temperature, and mydriasis.
- ♣ The patient then progresses to coma and perhaps respiratory depression.
- ♣ Cardiac arrhythmias may not respond to treatment.
- ♣ Because of the long half-lives of TCAs, the patients are at risk of cardiac arrhythmias for 3 to 4 days after the overdose,
so they should be monitored in an intensive care

Selective Serotonin Reuptake Inhibitors

- ♣ Fluoxetine (Prozac), the first selective serotonin reuptake inhibitor (SSRI) marketed in the United States.
- ♣ Fluoxetine was followed by other SSRIs. These include
 - Sertraline (Zoloft)
 - Paroxetine (Paxil)
 - Fluvoxamine (Luvox)
 - Citalopram (Celexa)
 - Escitalopram (Lexapro)
 - Vilazodone (Viibryd)
- ♣ All SSRIs appear to be equally effective in the treatment of mood and anxiety disorders

Selective Serotonin Reuptake Inhibitors

N.B -

- ♣ Fluvoxamine

- is not FDA approved as an antidepressant, a fact that is due to a marketing decision.
- It is considered an antidepressant in other countries.

- ♣ Although all SSRIs are equally effective, there are meaningful differences in pharmacodynamics, pharmacokinetics, and side effects, differences that might affect clinical responses among individual patients.

- ♣ There can be distressing withdrawal symptoms when SSRIs are stopped abruptly.

- This is especially true with paroxetine, but also occurs when other SSRIs with short half-lives are stopped

Selective Serotonin Reuptake Inhibitors

Cont'..d

Pharmacokinetics of SSRI

- ♣ A significant difference among the SSRIs is their broad range of serum half-lives.
- ♣ Fluoxetine has the longest half-life: 4 to 6 days; its active metabolite has a half-life of 7 to 9 days.
- ♣ The half-life of sertraline is 26 hours, and its less active metabolite has a half-life of 3 to 5 days.
- ♣ The half-lives of the other three, which do not have metabolites with significant pharmacological activity, are
 - 35 hours for citalopram
 - 27 to 32 hours for escitalopram
 - 21 hours for paroxetine, and 15 hours for fluvoxamine

- ♣ the SSRIs are well absorbed after oral administration and have their peak effects in the range of 3 to 8 hours.
- ♣ Absorption of sertraline may be slightly enhanced by food.
- ♣ There are also differences in plasma protein-binding percentages among the SSRIs:
 - with sertraline, fluoxetine , and paroxetine being the most highly bound and escitalopram being the least bound.

Selective Serotonin Reuptake Inhibitors

Cont'..d

- ♣ Because the SSRIs have such a wide therapeutic index, it is rare that other drugs produce problematic increases in SSRI concentrations.
- ♣ The most important drug-drug interactions involving the SSRIs occur as a result of the SSRIs inhibiting the metabolism of the co administered medication.
- ♣ Each of the SSRIs possesses a potential for slowing or blocking the metabolism of many drugs.
- ♣ Fluvoxamine is the strong liver enzyme inhibitor. It has a marked effect on several of the CYP enzymes(1A2,3A4)

Selective Serotonin Reuptake Inhibitors

Cont'..d

- ♣ Fluoxetine and paroxetine also possess significant effects on the CYP2D6 isozyme,
 - which may interfere with the efficacy of opiate analogs, such as codeine and hydrocodone, by blocking the conversion of these agents to their active form.
 - Thus, co administration of fluoxetine and paroxetine with an opiate interferes with its analgesic effects.
- ♣ Sertraline, citalopram, and escitalopram are least likely to complicate treatment because of interactions.

Selective Serotonin Reuptake Inhibitors

Cont'..d

Pharmacodynamics of SSRI

- ♣ The SSRIs are believed to exert their therapeutic effects through serotonin reuptake inhibition.
 - They derive their name because they have little effect on reuptake of norepinephrine or dopamine.
- ♣ Often, adequate clinical activity and saturation of the 5-HT transporters are achieved at starting dosages.
- ♣ As a rule, higher dosages do not increase antidepressant efficacy but may increase the risk of adverse effects.

Selective Serotonin Reuptake Inhibitors

Cont'..d

- ♣ Citalopram and escitalopram are the most selective inhibitors of serotonin reuptake :
 - with very little inhibition of norepinephrine or dopamine reuptake
 - very low affinities for histamine H1, γ -aminobutyric acid (GABA), or benzodiazepine receptors.
- ♣ Fluoxetine weakly inhibits norepinephrine reuptake and binds to 5-HT 2C receptors,
- ♣ sertraline weakly inhibits norepinephrine and dopamine reuptake, and
- ♣ Paroxetine has significant anticholinergic activity at higher dosages and binds to nitric oxide synthase.

Selective Serotonin Reuptake Inhibitors

Cont'..d

- ♣ A pharmacodynamic interaction appears to underlie the antidepressant effects of combined fluoxetine-olanzapine
 - When taken together, these drugs increase brain concentrations of norepinephrine.
- ♣ Concomitant use of SSRIs and drugs in the triptan class (sumatriptan, naratriptan, rizatriptan , and zolmitriptan) may result in a serious pharmacodynamic interaction—the development of a serotonin syndrome.
- ♣ However, many people use triptans while taking low doses of an SSRI for headache prophylaxis without adverse reaction.
 - A similar reaction may occur when SSRIs are combined with tramadol (Ultram).

Selective Serotonin Reuptake Inhibitors

Cont'd

Therapeutic Indications of SSRI

→ Depression

- ♣ all SSRIs other than fluvoxamine have been approved by the FDA for treatment of depression.
- ♣ The continued role of SSRIs as first-line treatment thus reflects their simplicity of use, safety, and broad spectrum of action
- ♣ before shifting to non-SSRI antidepressants, it is most reasonable to try other agents in the SSRI class for persons who did not respond to the first SSRI.

→ Suicide

- ♣ all depressed patients should be closely monitored during the period of maximal risk, the first few days and weeks they are taking SSRIs.

→ Depression During Pregnancy and Postpartum

- ♣ Rates of relapse of major depression during pregnancy among women who discontinue, attempt to discontinue, or modify their antidepressant regimens are extremely high.
- ♣ Rates range from 68 to 100 percent of patients.
- ♣ Thus, many women need to continue taking their medication during pregnancy and postpartum.
- ♣ There is no increased risk for major congenital malformations after exposure to SSRIs during

SSRI...

- ♣ the risk of relapse in to depression when a newly pregnant mother is taken off SSRIs is several-fold higher than the risk to the fetus of exposure to SSRIs
- ♣ No clinically significant neonatal complications are associated with SSRI use
- ♣ Paroxetine
 - should be avoided during pregnancy
 - In 2005, the FDA issued an alert that paroxetine increases the risk of birth defects, particularly heart defects, when women take it during the first 3 months of pregnancy

SSRI...

- ♣ Paroxetine should usually not be taken during pregnancy, but for some women who have already been taking paroxetine, the benefits of continuing paroxetine may be greater than the potential risk to the baby.
- ♣ Women taking paroxetine who are pregnant, think they may be pregnant, or plan to become pregnant should talk to their physicians about the potential risks of taking paroxetine during pregnancy.
- ♣ Very small amounts of SSRIs are found in breast milk and no harmful effects have been found in breast fed babies.

SSRI...

- ♣ Concentrations of sertraline and escitalopram are especially low in breast
- ♣ in some cases, reported concentrations may be higher than average.

N.B

- ♣ No decision regarding the use of an SSRI is risk free.
- ♣ It is thus important to document that communication of potential risks to the patient has taken place.

SSRI...

→ Depression in Elderly and Medically Ill Persons

- ♣ The SSRIs are safe and well tolerated when used to treat elderly and medically ill persons.
- ♣ As a class, they have little or no cardiotoxic, anticholinergic, antihistaminergic, or α -adrenergic adverse effects.
- ♣ Paroxetine does have some anticholinergic activity, which may lead to constipation and worsening of cognition.

Elderly

- ♣ The SSRIs can produce subtle cognitive deficits, prolonged bleeding time, and hyponatremia, all of which may impact the health of this population.
- ♣ The SSRIs are effective in post stroke depression and dramatically reduce the symptom of crying

SSRI...

Depression in Children

- ♣ **Fluoxetine** has most consistently demonstrated effectiveness in reducing symptoms of depressive disorder in both children and adolescents.
- ♣ **Sertraline** has been shown to be effective in treating social anxiety disorder in this population, especially when combined with cognitive-behavioral therapy

— Obsessive-Compulsive Disorder

- ♣ Fluvoxamine, paroxetine, sertraline, and fluoxetine are indicated for treatment of OCD in persons over the age of 18 years.
- ♣ Fluvoxamine and sertraline have also been approved for treatment of pediatric OCD (ages 6 to

SSRI...

- ♣ The SSRI dosages for OCD may need to be higher than those required to treat depression
- ♣ Patients who fail to obtain adequate relief of their OCD symptoms with an SSRI often benefit from the addition of a small dose of **risperidone**
- ♣ A number of disorders are now considered to be within the OCD spectrum that can benefit from treatment with SSRIs. These are :
 - trichotillomania
 - eyebrow picking
 - nose picking, nail biting
 - compulsive picking of skin blemishes, and cutting
- ♣ Other spectrum disorders hypochondriasis , and body dysmorphic disorder compulsive gambling, compulsive shopping

SSRI...

→ Panic Disorder

- ♣ **Paroxetine** and **sertraline** are indicated for treatment of panic disorder, with or without agoraphobia
 - These agents work less rapidly than do the benzodiazepines alprazolam and clonazepam but are far superior to the benzodiazepines for treatment of panic disorder with comorbid depression
- ♣ **Citalopram**, **fluvoxamine**, and **fluoxetine** also may reduce spontaneous or induced panic attacks.
- ♣ Because fluoxetine can initially heighten anxiety symptoms, persons with panic disorder must begin taking small dosages (5 mg a day) and increase the dosage slowly.
 - Low doses of benzodiazepines may be given to manage this side effect.

SSRI...

→ Social Anxiety Disorder

- ♣ SSRIs are effective agents in the treatment of social phobia
 - They reduce both symptoms and disability.
- ♣ The response rate is comparable to that seen with the MAOI phenelzine, the previous standard treatment.
- ♣ The SSRIs are safer to use than MAOIs or benzodiazepines.

→ Posttraumatic Stress Disorder

- ♣ Pharmacotherapy for PTSD must target specific symptoms in three clusters:

5/29/2020 1) reexperiencing 2) avoidance 3)

SSRI...

- ♣ For long-term treatment, SSRIs appear to have a broader spectrum of therapeutic effects on specific PTSD symptom clusters than do TCAs and MAOIs.
- ♣ **Benzodiazepine augmentation is useful in the acute symptomatic state.**
- ♣ SSRIs are associated with marked improvement of both intrusive and avoidant symptoms.

→ Generalized Anxiety Disorder

- ♣ SSRIs may be useful for the treatment of specific phobias, generalized anxiety disorder, and separation anxiety disorder.
- ♣ In addition, cognitive-behavioral or other psychotherapies can be added for greater efficacy

SSRI...

→ Bulimia Nervosa and Other Eating Disorders

- ♣ **Fluoxetine** is indicated for treatment of bulimia, Dosages of 60 mg a day are significantly more effective than 20 mg a day.

→ Anorexia Nervosa

- ♣ Fluoxetine has been used in inpatient treatment of anorexia nervosa to attempt to control co morbid mood disturbances and obsessive-compulsive symptoms.
- ♣ Effective treatments for anorexia include cognitive-behavioral, interpersonal, psychodynamic, and family therapies in addition to a trial with SSRIs.

SSRI...

→ Obesity

- ♣ Fluoxetine , in combination with a behavioral program, has been shown to be only modestly beneficial for weight loss.
- ♣ A significant percentage of all persons who take SSRIs, including fluoxetine , lose weight initially but later may gain weight.
- ♣ all SSRIs may cause initial weight gain

→ Premenstrual Dysphoric Disorder

- ♣ PMDD is characterized by debilitating mood and behavioral changes in the week preceding menstruation that interfere with normal functioning.
- ♣ Sertraline, paroxetine, fluoxetine, and fluvoxamine have been reported to reduce the symptoms of

SSRI...

- ♣ The effects of SSRIs on menstrual cycle length are mostly unknown and may warrant careful monitoring in women of reproductive age.

→ Premature Ejaculation

- ♣ The antiorgasmic effects of SSRIs make them useful as a treatment for men with premature ejaculation
- ♣ The SSRIs permit intercourse for a significantly longer period and are reported to improve sexual satisfaction in couples in which the man has premature ejaculation.
- ♣ Fluoxetine and sertraline have been shown to be effective for this purpose.

SSRI...

→ Paraphilias

- ♣ The SSRIs may reduce obsessive-compulsive behavior in people with paraphilias.
- ♣ The SSRIs diminish the average time per day spent in unconventional sexual fantasies, urges, and activities.
- ♣ Evidence suggests a greater response for sexual obsessions than for paraphilic behavior.

→ Autism

- ♣ Obsessive-compulsive behavior, poor social relatedness, and aggression are prominent autistic features that may respond to serotonergic agents such as SSRIs and clomipramine.

SSRI...

- ♣ Sertraline and fluvoxamine have been shown in controlled and open-label trials to mitigate aggressiveness, self-injurious behavior, repetitive behaviors, some degree of language delay, and (rarely) lack of social relatedness in adults with autistic spectrum disorders.
- ♣ Fluoxetine has been reported to be effective for features of autism in children, adolescents, and adults

SSRI...

Precautions and Adverse Reactions of SSRI

→ Sexual Dysfunction

- ♣ All SSRIs cause sexual dysfunction
 - it is the most common adverse effect of SSRIs associated with long-term treatment
- ♣ It has an estimated incidence of between 50 and 80 percent.
- ♣ The most common complaints are **anorgasmia** , **inhibited orgasm**, and **decreased libido**.
- ♣ Some studies suggest that sexual dysfunction is dose related, but this has not been clearly established

SSRI...

- ♣ Unlike most of the other adverse effects of SSRIs, sexual inhibition rarely resolves in the first few weeks of use but usually continues as long as the drug is taken.
 - In some cases, there may be improvement over time
- ♣ Treatment of SSRI-induced sexual dysfunction with
 - sildenafil (Viagra), which are used to treat erectile dysfunction.
 - Ultimately, patients may need to be switched to antidepressants that do not interfere with sexual functioning, drugs such as mirtazapine or bupropion

SSRI...

→ Gastrointestinal Adverse Effects

- ♣ GI side effects are very common and are mediated largely through effects on the serotonin 5-HT₃ receptor
- ♣ The most frequent GI complaints are **nausea** , **diarrhea** , **anorexia** , **vomiting**, **flatulence**, and **dyspepsia**.
- ♣ Sertraline and fluvoxamine produce the most intense GI symptoms
- ♣ Paroxetine, because of its anticholinergic activity, frequently causes constipation
- ♣ Nausea and loose stools are usually dose related and transient, usually resolving within a few

SSRI...

- ♣ Sometimes flatulence and diarrhea persist, especially during sertraline treatment
- ♣ Initial anorexia may also occur and is most common with fluoxetine.
- ♣ SSRI-induced appetite and weight loss begin as soon as the drug is taken and peak at 20 weeks, after which weight often returns to baseline
- ♣ Up to one third of persons taking SSRIs will gain weight, sometimes more than 20 lbs.
 - This effect is mediated through a metabolic mechanism, increase in appetite, or both
- ♣ Paroxetine is associated with more frequent, rapid, and pronounced weight gain than the other SSRIs, especially among young women

SSRI...

→ Cardiovascular Effects

- ♣ All SSRIs can lengthen the QT interval in otherwise healthy people and cause drug-induced long QT syndrome, especially when taken in overdose
- ♣ The risk of QTc prolongation increases when an antidepressant and an antipsychotic are used in combination
- ♣ Citalopram stands out as the SSRI with the most pronounced effect QT intervals
- ♣ Quinidine should be used with caution with any medications that can prolong the QT interval and inhibit CYP3A4, particularly in patients with cardiac disease

SSRI...

→ Headaches

- ♣ **Fluoxetine** is the most likely to cause headache.
- ♣ On the other hand, all SSRIs are effective prophylaxis against both migraine and tension-type headaches in many persons.

→ Anxiety

- ♣ Fluoxetine may cause anxiety, particularly in the first few weeks of treatment.
 - However, these initial effects usually give way to an overall reduction in anxiety after a few weeks
- ♣ Increased anxiety is caused considerably less frequently by **paroxetine** and **escitalopram**, which may be better choices if sedation is desired, as in mixed anxiety and depressive disorders

SSRI...

→ Insomnia and Sedation

- ♣ the major effect SSRIs exert in the area of insomnia and sedation is improved sleep resulting from treatment of depression and anxiety.
- ♣ As many as **25 percent** of persons taking SSRIs note trouble sleeping , excessive somnolence, or overwhelming fatigue.
- ♣ **Fluoxetine** is the most likely to cause insomnia , for which reason it is often taken in the morning.
- ♣ Sertraline and fluvoxamine are about equally likely to cause insomnia as somnolence
- ♣ citalopram and especially paroxetine often cause somnolence.

SSRI...

- ♣ **Escitalopram** is more likely to interfere with sleep than its isomer, citalopram.
- ♣ Some persons benefit from taking their SSRI dose before going to bed, but others prefer to take it the morning
- ♣ SSRI-induced insomnia can be treated with
 - **benzodiazepines**,
 - **trazodone** (clinicians must explain the risk of priapism), or
 - **other sedating medicines**.
- ♣ Significant SSRI-induced somnolence often requires **switching to use of another SSRI or bupropion**.

SSRI...

→ Other Sleep Effects

- ♣ Many persons taking SSRIs report recalling extremely vivid dreams or nightmares.
 - They describe sleep as “**busy.**”
- ♣ Other sleep effects of the SSRIs include **bruxism** , **restless legs** , **nocturnal myoclonus** , and **sweating**

→ Emotional Blunting

- ♣ Emotional blunting is a largely overlooked but frequent side effect associated with chronic SSRI use.
- ♣ Patients report an inability to cry in response to emotional situations, a feeling of apathy or indifference, or a restriction in the intensity of emotional experiences.

SSRI...

- ♣ Emotional blunting often leads to treatment discontinuation, even when the drugs provide relief from depression or anxiety.

→ Yawning

- ♣ Close clinical observation of patients taking SSRIs reveals an increase in yawning.
- ♣ This side effect is not a reflection of fatigue or poor nocturnal sleep but is the result of SSRI effects on the hypothalamus

→ Seizures

- ♣ Seizures have been reported in 0.1 to 0.2 percent of all patients treated with SSRIs
- ♣ Seizures are more frequent at the highest doses of SSRIs (e.g., fluoxetine 100 mg a day or higher)

SSRI...

→ Extrapyrarnidal Symptoms

- ♣ The SSRIs may rarely cause akathisia , dystonia , tremor, cogwheel rigidity, torticollis , opisthotonos , gait disorders, and bradykinesia .
- ♣ are cases of tardive dyskinesia have been reported
- ♣ People with well-controlled Parkinson's disease may experience acute worsening of their motor symptoms when they take SSRIs

→ Anticholinergic Effects

- ♣ Paroxetine has mild anticholinergic activity that causes dry mouth, constipation, and sedation in a dose-dependent fashion.
- ♣ Most persons taking paroxetine do not experience cholinergic adverse effects

SSRI...

→ Hematologic Adverse Effects

- ♣ The SSRIs can cause functional impairment of platelet aggregation but not a reduction in platelet number.
 - Easy bruising and excessive or prolonged bleeding manifest this pharmacological effect
- ♣ Special monitoring is suggested when patients use SSRIs in conjunction with anticoagulants or aspirin.
- ♣ Concurrent use of SSRIs and nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with a significantly increased risk of gastric bleeding.
 - In cases where this combination is necessary, use of proton pump inhibitors should be considered

SSRI...

→ Electrolyte and Glucose Disturbances

- ♣ The SSRIs may acutely decrease glucose concentrations; therefore, diabetic patients should be carefully monitored
- ♣ Long-term use may be associated with increased glucose levels
- ♣ Rare cases of SSRI-associated hyponatremia.

→ Endocrine and Allergic Reactions

- ♣ the SSRIs can **increase prolactin** levels and cause mammoplasia and galactorrhea in both men and women
- ♣ Breast changes are reversible up on discontinuation of the drug, but this may take several months to occur.

SSRI...

- ♣ Various types of rashes appear in about 4 percent of all patients;
 - in a small subset of these patients, the allergic reaction may generalize and involve the pulmonary system, resulting rarely in fibrotic damage and dyspnea.
 - SSRI treatment may have to be discontinued in patients with drug-related rashes.

→ Serotonin Syndrome

- ♣ Concurrent administration of an SSRI with an MAOI, l-tryptophan or lithium can raise plasma serotonin concentrations to toxic levels, producing a constellation of symptoms called **serotonin syndrome**.

SSRI...

♣ Symptoms and signs of serotonin syndrome

1. diarrhea
2. restlessness
3. extreme agitation, hyper reflexia , and autonomic instability with possible rapid fluctuations in vital signs;
4. myoclonus , seizures , hyperthermia , uncontrollable shivering, and rigidity;
5. delirium, coma, status epilepticus , cardiovascular collapse, death.

SSRI...

♣ **Treatment of the serotonin syndrome**

- removing the offending agents and
- promptly instituting comprehensive supportive care with nitroglycerine, cyproheptadine, methysergide (Sansert), cooling blankets,
 - chlorpromazine (Thorazine), dantrolene (Dantrium), benzodiazepines,
- anticonvulsants, mechanical ventilation, and paralyzing agents.

→ **Sweating**

- ♣ Some patients experience sweating while being treated with SSRIs

SSRI...

- ♣ Nocturnal sweating may drench bed sheets and require a change of night clothes.
- ♣ **Terazosin** (Hytrin) ,1 or 2 mg per day, is often dramatically effective in counteracting sweating.

Overdose

- ♣ The adverse reactions associated with overdose of vilazodone at doses of 200 to 280 mg included serotonin syndrome, lethargy, restlessness, hallucinations, and disorientation.

SSRI...

Selective Serotonin Reuptake Inhibitor Withdrawal

- ♣ The abrupt discontinuance of SSRI use, especially one with a shorter half-life such as paroxetine or fluvoxamine, has been associated with a **withdrawal syndrome** that may include
 - dizziness, weakness, nausea
 - headache, rebound depression, anxiety, insomnia
 - poor concentration
 - upper respiratory symptoms
 - paresthesias
 - migraine-like symptoms.

♣ usually does not appear until after **at least 6 weeks**

SSRI...

- ♣ Persons who experienced transient adverse effects in the first weeks of taking an SSRI are more likely to experience discontinuation symptoms.
- ♣ Fluoxetine is the SSRI least likely to be associated with this syndrome because the half-life of its metabolite is more than 1 week, and it effectively tapers itself .
- ♣ Fluoxetine has therefore been used in some cases to treat the discontinuation syndrome caused by termination of other SSRIs.

SSRI...

DRUG INTERACTIONS

- ♣ The SSRIs do not interfere with most other drugs
- ♣ A serotonin syndrome can develop with concurrent administration of MAOIs, L-tryptophan, lithium, or other antidepressants that inhibit reuptake of serotonin
- ♣ Fluoxetine, sertraline, and paroxetine can raise plasma concentrations of TCAs, which can cause clinical toxicity
- ♣ Combined use of SSRIs and NSAIDs increases the risk of gastric bleeding
- ♣ The SSRIs, particularly fluvoxamine, should not be used with clozapine because it raises clozapine concentrations, increasing the risk of seizure.

SSRI...

- ♣ The SSRIs may increase the duration and severity of zolpidem (Ambien)-induced side effects, including hallucinations

Fluoxetine

- ♣ Fluoxetine can be administered with tricyclic drugs, but the clinician should use **low dosages of the tricyclic drug**
 - Because it is metabolized by the hepatic enzyme CYP2D6, fluoxetine may interfere with the metabolism of other drugs
- ♣ Fluoxetine may slow down the metabolism of **carbamazepine**, **antineoplastic agents**, **diazepam**, and **phenytoin**
- ♣ fluoxetine that may affect the plasma levels of benzodiazepines, antipsychotics, and lithium

SSRI...

Sertraline

- ♣ Sertraline may displace warfarin from plasma proteins and may increase the prothrombin time.
- ♣ Has similar drug interaction profile with fluoxetine, although sertraline does not interact as strongly with the CYP2D6 enzyme

Paroxetine

- ♣ has a higher risk for drug interactions than does either fluoxetine or sertraline because it is a more potent inhibitor of the CYP2D6 enzyme.
- ♣ Cimetidine can increase the concentration of sertraline and paroxetine
- ♣ phenobarbital and phenytoin can decrease the concentration of paroxetine

SSRI...

- ♣ Because of the potential for interference with the CYP2D6 enzyme, the coadministration of paroxetine with other **antidepressants**, **phenothiazines**, and **antiarrhythmic drugs** should be undertaken with caution.
- ♣ Paroxetine may increase the anticoagulant effect of **warfarin**.
- ♣ Co administration of **paroxetine** and **tramadol** may precipitate serotonin syndrome in elderly persons

Fluvoxamine

- ♣ Among the SSRIs, fluvoxamine appears to present the most risk for drug-drug interactions.
- ♣ Fluvoxamine is metabolized by the enzyme CYP3A4, which may be inhibited by ketoconazole

SSRI...

- ♣ **Fluvoxamine** may increase the half-life of **alprazolam**, **triazolam**, and **diazepam**, and it should not be co administered with these agents.
- ♣ Fluvoxamine may increase theophylline levels threefold and warfarin levels twofold
 - thus, the serum levels of the latter drugs should be closely monitored and the doses adjusted accordingly
- ♣ Fluvoxamine raises concentrations and may increase the activity of clozapine, carbamazepine, methadone, propranolol and diltiazem
- ♣ Fluvoxamine has no significant interactions with lorazepam or digoxin

SSRI...

Citalopram

- ♣ Citalopram is not a potent inhibitor of any CYP enzymes.
- ♣ Concurrent administration of **cimetidine** increases concentrations of citalopram by **about 40 percent**.
- ♣ Citalopram increases the plasma concentrations of **metoprolol** twofold, but this usually has no effect on blood pressure or heart rate

Escitalopram

- ♣ Escitalopram is a moderate inhibitor of CYP2D6 and has been shown to significantly raise **desipramine** and **metoprolol** concentrations.

SSRI...

Vilazodone

- ♣ Vilazodone dose should be reduced to 20 mg when co administered with CYP3A4 strong inhibitors.
- ♣ Concomitant use with inducers of CYP3A4 can result in inadequate drug concentrations and may diminish effectiveness.

LABORATORY INTERFERENCES

- ♣ The SSRIs do not interfere with any laboratory tests

DOSAGE AND CLINICAL GUIDELINES

Fluoxetine

- ♣ Fluoxetine is available in
 - 10 and 20 mg capsules,
 - 10-mg tablet,
 - 90-mg enteric-coated capsule for once-weekly administration
 - an oral concentrate (20 mg/5 mL)
- ♣ For depression, the initial dosage is usually **10 or 20 mg** orally each day,
 - usually given **in the morning**, because insomnia is a potential adverse effect of the drug
- ♣ Fluoxetine should be taken **with food** to minimize the possible nausea

SSRI...

- ♣ The long half-lives of the drug and its metabolite contribute to a 4-week period to reach steady-state concentrations
- ♣ The maximum dosage recommended by the manufacturer is **80 mg** a day
- ♣ Alternatively, because of the long half-life of fluoxetine, its use can be initiated with an **every-other-day** administration schedule.

SSRI...

Sertraline

- ♣ Sertraline is available in scored 25, 50, and 100 mg tablets
- ♣ For the initial treatment of depression, sertraline use should be initiated with a dosage of **50 mg** once daily
- ♣ To limit the GI effects, some clinicians begin at 25 mg a day and increase to 50 mg a day after 3 weeks.
- ♣ Patients who do not respond after 1 to 3 weeks may benefit from dosage increases of **50 mg** every week up to a maximum of **200 mg** given once daily
- ♣ Sertraline can be administered in the morning or the evening.

SSRI...

- ♣ Sertraline oral concentrate (1 mL = 20 mg) has 12 percent alcohol content and must be diluted before use.
- ♣ When used to treat panic disorder, sertraline should be initiated at **25 mg** to reduce the risk of provoking a panic attack.

Paroxetine

- ♣ paroxetine is available
 - in scored 20-mg tablets
 - in unscored 10, 30, 40 mg tablets
 - orange-flavored 10-mg/5-mL oral suspension
- ♣ Paroxetine use for the treatment of depression is usually initiated at a dosage of **10 or 20 mg** a day.

SSRI...

- ♣ an increase in the dosage should be considered when an adequate response is not seen in **1 to 3** weeks.
 - At that point, the clinician can initiate upward dose titration in 10-mg increments **at weekly** intervals to a maximum of **50 mg** a day
- ♣ persons who experience GI upset may benefit by taking the drug with food.
- ♣ Paroxetine can be taken initially as a single daily dose in the evening; higher dosages may be divided into two doses per day.

SSRI...

- ❖ Paroxetine is the SSRI most likely to produce a discontinuation syndrome because plasma concentrations decrease rapidly in the absence of continuous dosing.
- ❖ To limit the development of symptoms of abrupt discontinuation, paroxetine use should be tapered gradually, with dosage reductions every 2 to 3 weeks.

Fluvoxamine

- ❖ Fluvoxamine is the only SSRI not approved by the FDA as an antidepressant
- ❖ It is indicated for social anxiety disorder and OCD
- ❖ The effective daily dosage range is 50 to 300

SSRI...

- ♣ A usual starting dosage is **50 mg** once a day at bedtime for the first week, after which the dosage can be adjusted according to the adverse effects and clinical response
- ♣ Dosages above **100 mg** a day may be divided in to twice-daily dosing
- ♣ A temporary dosage reduction or slower upward titration may be necessary if nausea develops over the first 2 weeks of therapy.
- ♣ Although fluvoxamine can also be administered as a single evening dose to minimize its adverse effects, its short half-life may lead to interdose withdrawal.

SSRI...

- ♣ All fluvoxamine formulations should be swallowed with food without chewing the tablet.
- ♣ Abrupt discontinuation of fluvoxamine may cause discontinuation syndrome owing to its short half-life.

Citalopram

- ♣ **Citalopram** is available in 20 and 40mg scored tablets and as a liquid (10 mg/5 mL).
- ♣ The usual starting dosage is **20 mg** a day for the first week, after which it usually is increased to **40 mg** a day

SSRI...

- ♣ for elderly persons or persons with hepatic impairment, 20 mg a day is recommended, with an increase to 40 mg a day only if there is no response at 20 mg a day
- ♣ Tablets should be taken once daily in either the morning or the evening with or without food

Escitalopram

- ♣ Escitalopram is available as 10 and 20 mg scored tablets, as well as an oral solution at a concentration of 5 mg/5 mL.
- ♣ The recommended dosage of escitalopram is 10 mg per day

SSRI...

Vilazodone

- ♣ Vilazodone is available as 10, 20, and 40mg tablets
- ♣ Treatment should be titrated, starting with an initial dose of **10 mg** once daily for 7 days, followed by **20 mg** once daily for an additional 7 days, and then an increase to **40 mg** once daily
- ♣ Vilazodone should be taken with food.
 - If vilazodone is taken without food, inadequate drug concentrations may result and the drug's effectiveness may be diminished

SSRI...

- ♣ **Vilazodone** is not approved for use in children.
- ♣ The safety and efficacy of vilazodone in pediatric patients have not been studied.
- ♣ **No dose adjustment** is recommended on the basis of age.
- ♣ **No dose adjustment** is recommended in patients with mild or moderate hepatic impairment.
- ♣ Vilazodone has not been studied in patients with severe **hepatic impairment**.
- ♣ No dose adjustment is recommended in patients with mild, moderate, or severe **renal impairment**.

SSRI...

Pregnancy and Breast-Feeding

- ♣ With the exception of paroxetine, the SSRIs are safe to take during pregnancy when deemed necessary for treatment of the mother
- ♣ There are no controlled human data regarding vilazodone use during pregnancy nor are there human data regarding drug concentrations in breast milk
- ♣ Transient QTc prolongation has been noted in newborns whose mother was being treated with an SSRI during pregnancy

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

- ♣ There are currently **four** serotonin- norepinephrine reuptake inhibitors (SNRIs)

1. venlafaxine
2. desvenlafaxine succinate
3. duloxetine
4. levomilnacipran

- ♣ A fifth SNRI, **milnacipran (Savella)**, available in other countries as an antidepressant, has U.S.

- FDA approval in the United States as a treatment for fibromyalgia

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

- ♣ The term **SNRI** reflects the belief that the therapeutic effects of these medications are mediated by concomitant blockade of neuronal **serotonin (5-HT)** and **norepinephrine** uptake transporters
- ♣ The SNRIs are also sometimes referred to as **dual reuptake inhibitors**, a broader functional class of antidepressant medications that includes tricyclic antidepressants (TCAs)
- ♣ What distinguishes **the SNRIs from TCAs** is their relative lack of affinity for other receptors, especially

VENLAFAXINE AND DESVENLAFAXINE

- ♣ Venlafaxine is well absorbed from the gastrointestinal (GI) tract.
- ♣ Venlafaxine has a half-life of about 3.5 hours.
- ♣ It is metabolized by hepatic cytochrome P450 (CYP) 2D6.
- ♣ Venlafaxine is a potent inhibitor of serotonin and norepinephrine reuptake and a weak inhibitor of dopamine reuptake.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

Therapeutic Indications

♣ **Venlafaxine** is approved for treatment of four disorders :

- Major depressive disorder
- Generalized anxiety disorder
- Social anxiety disorder
- Panic disorder

♣ Other Indications of venlafaxine

- obsessive-compulsive disorder, panic disorder, agoraphobia , social phobia , attention-deficit/hyperactivity disorder, and patients with a dual diagnosis of depression and cocaine dependence

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

- ♣ **Venlafaxine** has also been used in chronic pain syndromes with good effect

Precautions and Adverse Reactions

- ♣ **Venlafaxine** has a safety and tolerability profile similar to that of the more widely prescribed SSRI class
- ♣ **Nausea** is the most frequently reported treatment-emergent adverse effect associated with venlafaxine and DVS therapy.
 - initiating therapy at lower dosages may also attenuate nausea
 - When extremely problematic, treatment-induced nausea can be controlled by prescribing a **selective 5-HT3 antagonist or mirtazapine**

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

- ♣ Venlafaxine and DVS therapy is associated with sexual side effects:
 - predominantly **decreased libido** and a **delay to orgasm** or **ejaculation**
 - The incidence of these side effects may exceed **30 to 40 percent** when there is direct, detailed assessment of sexual function
- ♣ Other common side effects include headache, insomnia , somnolence, dry mouth, dizziness, constipation, asthenia ,sweating, and nervousness
- ♣ Higher-dose venlafaxine therapy is associated with

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

- ❖ Venlafaxine and DVS are commonly associated with a **discontinuation syndrome**.
 - This syndrome is characterized by the appearance of a constellation of adverse effects during a rapid taper or abrupt cessation, including **dizziness, dry mouth, insomnia, nausea, nervousness, sweating, anorexia, diarrhea, somnolence, and sensory disturbances**.
- ❖ It is recommended that, whenever possible, a slow taper schedule should be used when longer-term treatment must be stopped.
- ❖ Fatal overdoses have been documented subsequently, typically involving venlafaxine ingestion in combination with other drugs, alcohol, or both

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

- ❖ information concerning use of venlafaxine and DVS by pregnant and nursing women is **not available at this time**.
- ❖ Venlafaxine and DVS are excreted in breast milk
- ❖ Clinicians should carefully weigh the risks and benefits of venlafaxine use by pregnant and nursing women.

Drug Interactions

- ❖ Venlafaxine is metabolized in the liver primarily by the **CYP2D6 isoenzyme**
- ❖ Venlafaxine is itself a relatively weak inhibitor of **CYP2D6**, although it can increase levels of substrates, such as **desipramine** or **risperidone**.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

- ❖ Cimetidine (Tagamet) appears to inhibit the first-pass hepatic metabolism of venlafaxine
- ❖ Combined use of sustained-release bupropion (Wellbutrin SR) has been shown to increase plasma concentrations of venlafaxine.
- ❖ Venlafaxine may raise plasma concentrations of concurrently administered haloperidol (Haldol).
- ❖ Venlafaxine is contraindicated in patients taking **MAOIs** because of the risk of a pharmacodynamic interaction i.e **serotonin syndrome**
- ❖ MAOI **should not be started for at least 7 days** after stopping venlafaxine.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

Laboratory Interferences

- ♣ Data are not currently available on laboratory interferences with venlafaxine

Dosage and Administration

- ♣ Venlafaxine is available in 25, 37.5, 50 , 75, a nd 100 mg tablets and 37.5 , 75, a nd 150-mg extended-release capsules
- ♣ The tablets and the extended-release capsules are **equally potent**, and persons stabilized with one can switch to an equivalent dosage of the other

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

- ♣ Because the immediate-release tablets are rarely used due to their tendency to cause **nausea** and **the need for multiple daily doses**, the dosage recommendations that follow refer to use of the extended-release capsules
- ♣ The initial therapeutic dosage is 75 mg a day given once a day.
 - However, most persons are started at a dosage of 37.5 mg for 4 to 7 days to minimize adverse effects, particularly nausea
- ♣ the dosage can be raised in increments of 75 mg a day every 4 or more days.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

- ♣ the dosage of venlafaxine should be halved in persons with significantly diminished hepatic or renal function.
- ♣ If discontinued, venlafaxine use should be gradually tapered over **2 to 4 weeks** to avoid withdrawal symptoms
- ♣ There are minor differences in the doses used for major depression, generalized anxiety disorder, and social anxiety disorder
 - lower mean dosages are typically used, with most patients taking 75 to 150 mg per day
- ♣ DVS is available as 50 and 100 mg extended-release tablets.
- ♣ The therapeutic dose for most patients is 50 mg a day

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

DULOXETINE

Pharmacological Actions

- ♣ **Duloxetine** is formulated as a delayed-release capsule to reduce the risk of severe nausea associated with the drug
- ♣ It is well absorbed, but there is a 2-hour delay before absorption begins.
- ♣ Peak plasma concentrations occur 6 hours after ingestion
- ♣ Food delays the time to achieve maximum concentrations from **6 to 10 hours** and reduces the extent of absorption by about **10 percent**.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

- ♣ Duloxetine has an elimination half life of about 12 hours (range, 8 to 17 hours).
- ♣ Steady-state plasma concentrations occur after 3 days.
- ♣ Elimination is mainly through the isozymes **CYP2D6** and **CYP1A2**.
- ♣ About 70 percent of the drug appears in the urine as metabolites and about 20 percent is excreted in the feces.
- ♣ Duloxetine is 90 percent protein bound.

Therapeutic Indications

- ♣ Depression
- ♣ Neuropathic Pain Associated with Diabetes and Stress Urinary Incontinence
 - **Duloxetine** is the first drug to be approved by the FDA as a treatment for neuropathic pain associated with diabetes
 - Duloxetine is currently awaiting approval as a treatment for stress urinary incontinence, the inability to

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

- The action of duloxetine in the treatment of stress urinary incontinence is associated with its effects in the **sacral spinal cord**, which in turn increase the activity of the striated urethral sphincter.
- Duloxetine will be marketed under the name **Yentreve** for this indication

Precautions and Adverse Reactions

- ♣ The most common adverse reactions are nausea , dry mouth, dizziness, constipation, fatigue, decreased appetite, anorexia ,somnolence, and increased sweating
- ♣ Close monitoring is suggested when using duloxetine in

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

- ♣ Duloxetine has been shown to increase blood sugar and hemoglobin A1C levels during long-term treatment.
- ♣ Patients with substantial alcohol use should not be treated with duloxetine because of possible hepatic effects.
- ♣ It also should not be prescribed for patients with hepatic insufficiency and end-stage renal disease or for patients with uncontrolled narrow-angle glaucoma
- ♣ Abrupt discontinuation of duloxetine should be avoided because it may produce a discontinuation syndrome similar to that of venlafaxine

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

- ♣ Clinicians should avoid the use of duloxetine by pregnant and nursing women unless the potential benefits justify the potential risks.

Drug Interactions

- ♣ Duloxetine is a moderate inhibitor of CYP450 enzymes.

Laboratory Interferences

- ♣ Data are not currently available on laboratory interferences with duloxetine

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

Dosage and Administration

- ♣ Duloxetine is available in 20, 30, and 60 mg tablets
- ♣ The recommended therapeutic, and maximum, dosage is **60mg** per day
- ♣ The **20** and **30 mg** doses are useful for either initial therapy or for twice-daily use as strategies to reduce side effects

MILNACIPRAN AND LEVOMILNACIPRAN

- ♣ Milnacipran is only FDA approved for the treatment of **fibromyalgia**
- ♣ Compared with venlafaxine, milnacipran is approximately five times more potent for inhibition of **norepinephrine uptake** than for 5-HT reuptake inhibition

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

♣ Milnacipran

- has a half-life of approximately 8 hours
- Metabolized in the liver,
- has no active metabolites
- is primarily excreted by the kidneys

♣ Milnacipran is available as 12.5, 25, 50, and 100-mg tablets.

- ♣ The standard recommended milnacipran dose is as follows:
- day 1, 12.5 mg once daily;
 - days 2 and 3, 12.5 mg twice daily;
 - days 4 to 7, 25 mg twice daily; and
 - day 7 and beyond, 50 mg twice daily

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

- ♣ **Levomilnacipran** was approved in 2013 by the FDA as a treatment for major depressive disorder in adult
 - It is taken once daily as a sustained-release formulation
 - The only dose-related adverse events were urinary hesitation and erectile dysfunction

Mirtazapine (Remeron)

♣ Mirtazapine

- it increases both norepinephrine and serotonin through a mechanism other than reuptake blockade or monoamine oxidase inhibition
- ♣ Mirtazapine is also more likely to reduce rather than cause nausea and diarrhea.
- ♣ Characteristic side effects include increased appetite and sedation.

Mirtazapine

- ❖ Mirtazapine is administered orally and is rapidly and completely absorbed.
- ❖ It has a half-life of about 30 hours.
- ❖ Plasma clearance may be slowed up
 - to 30 percent in persons with impaired hepatic function,
 - up to 50 percent in those with impaired renal function,
 - up to 40 percent slower in elderly males, and
 - up to 10 percent slower in elderly females.
- ❖ The mechanism of action of mirtazapine is
 - antagonism of central presynaptic α_2 -adrenergic

Therapeutic Indications of Mirtazapine

- ♣ Mirtazapine is effective for the treatment of depression.
- ♣ It is highly sedating, making it a reasonable choice for use in depressed patients with severe or long-standing insomnia.
- ♣ Antidepressant effect and stimulation of appetite clearly could be seen as being beneficial for cancer patient
- ♣ Mirtazapine has no significant pharmacokinetic interactions with other antidepressants.

Precautions and Adverse Reactions of Mirtazapine

- ❖ Somnolence, the most common adverse effect of mirtazapine, occurs in over 50 percent of persons -so avoid driving or operating dangerous machinery
- ❖ Mirtazapine potentiates the sedative effects of Alcohol and benzodiazepines.
-So Avoid Alcohol
- ❖ Mania or hypomania occurred in clinical trials at a rate similar to that of other antidepressant drugs.
- ❖ Mirtazapine may also increase serum cholesterol concentration to 20 percent
- ❖ In 2-3% Elevations of alanine transaminase (ALT) levels to more than three times the upper limit of normal

Precautions and Adverse Reactions of Mirtazapine con...

- ♣ In 0.3 percent of persons, the absolute neutrophil count dropped to $500/\text{mm}^3$ or less within 2 months of onset of use
- ♣ A few persons experience orthostatic hypotension while taking mirtazapine.
- ♣ Mirtazapine should not be used within 14 days of use of a monoamine oxidase inhibitor.

Dosage and Administration of Mirtazapine

- ♣ Mirtazapine is available in 15-, 30-, and 45-mg scored tablets.
- ♣ Mirtazapine is also available in 15-, 30- and 45-mg orally disintegrating tablets.
- ♣ If persons fail to respond to the initial dose of 15 mg of mirtazapine before sleep,
 - the dosage may be increased in 15-mg increments every 5 days to a maximum of 45 mg before sleep.
- ♣ Lower dosages may be necessary in elderly persons or persons with renal or hepatic insufficiency.

- # Buspirone
- ❖ Buspirone is well absorbed from the gastrointestinal (GI) tract
 - ❖ Peak plasma levels are achieved 40 to 90 minutes after oral administration.
 - ❖ Because of a short half-life (2 to 11 hours), buspirone is dosed three times daily.
 - ❖ Buspirone acts as an agonist, partial agonist, or antagonist on serotonin 5-HT_{1A} receptors.
 - ❖ Its most pronounced action, as a presynaptic agonist at these receptors, inhibits release of serotonin, with consequent antianxiety effects.
 - ❖ Action as an agonist at postsynaptic receptors appears to account for antidepressant activity.

Therapeutic Indications

♣ **Generalized Anxiety Disorder**

- demonstrated efficacy only in the treatment of generalized anxiety disorder.
- ♣ buspirone is generally more effective for symptoms of anger and hostility, equally effective for psychic symptoms of anxiety, and less effective for somatic symptoms of anxiety.
- ♣ The full benefit of buspirone is evident only at dosages above 30 mg a day.
- ♣ Compared with the benzodiazepines, buspirone has a delayed onset of action

- 
- ❖ The most common adverse effects of buspirone are headache, nausea, dizziness, and, rarely, insomnia.

❖ **Drug Interactions**


- The coadministration of buspirone and haloperidol (Haldol) results in increased blood concentrations of haloperidol.
- Buspirone should not be used with monoamine oxidase inhibitors (MAOIs) to avoid hypertensive episodes
- Drugs or foods that inhibit CYP450 3A4, for example, erythromycin (E-mycin),, nefazodone (Serzone), and grapefruit juice, increase buspirone plasma concentrations.

Dosage and Clinical Guidelines of Buspirone

- ♣ treatment is usually initiated with either 5 mg orally three times daily or 7.5 mg orally twice daily.
- ♣ The dosage can be raised 5 mg every 2 to 4 days to the usual dosage range of 15 to 60 mg a day.

Bupropion

- ❖ Unlike other currently used antidepressants, **bupropion does not act on the serotonin system.**
- ❖ It is a norepinephrine and dopamine reuptake inhibitor.
- ❖ Bupropion is the only medication approved by the FDA for the prevention of **seasonal depressive episodes** of patients with seasonal affective disorder (SAD).
- ❖ bupropion use as add-on therapy to other antidepressants, most commonly SSRIs.

- 
- ## Pharmacologic Actions of Bupropion
- ✦ Three formulations of bupropion are available
 - 1) immediate release (taken three times daily);
 - 2) sustained release (taken twice daily); and
 - 3) extended release (taken once daily).
 - ♣ Immediate-release bupropion is well absorbed from the gastrointestinal (GI) tract.
 - ♣ The mechanism of action for the antidepressant effects of bupropion is poorly understood
 - although it presumably involves inhibition of dopamine and norepinephrine reuptake.

Therapeutic Indications of Bupropion

♣ Depression

- the therapeutic efficacy of bupropion in depression is well established in both outpatient and inpatient settings.

♣ Seasonal Affective Disorder

- Bupropion has been found to prevent seasonal major depressive episodes in patients with a history of SAD.

♣ Smoking Cessation

- bupropion is indicated for use in combination with behavioral modification programs for smoking cessation.
- Bupropion is most effective when combined with nicotine substitutes (NicoDerm, Nicotrol).

♣ Bipolar Disorders

♣ **Attention-Deficit/Hyperactivity Disorder**

- Bupropion is used as a second-line agent, after the sympathomimetics, for treatment of ADHD.
- ♣ Bupropion is an appropriate choice for
 - persons with comorbid ADHD and depression or
 - persons with comorbid ADHD, conduct disorder, or substance abuse.

♣ **Hypoactive Sexual Desire Disorder**

- Bupropion is often added to drugs, such as SSRIs, to counteract sexual side effects and
- may be helpful as a treatment for nondepressed individuals with hypoactive sexual desire disorder.
- Bupropion may improve sexual arousal, orgasm completion, and sexual satisfaction.

Precautions and Adverse Reactions

- ♣ Headache, insomnia, dry mouth, tremor, and nausea are the most common side effects of bupropion use.
- ♣ Restlessness, agitation, and irritability may also occur.
- ♣ Patients with severe anxiety or panic disorder should not be started on bupropion.
- ♣ bupropion can cause psychotic symptoms, including hallucinations, delusions, and catatonia, as well as delirium.

- ## Dosage and Clinical Guidelines
- ♣ Immediate-release bupropion is available in 75-, 100-, and 150-mg tablets.
 - ♣ Sustained-release bupropion is available in 100-, 150-, 200-, and 300-mg tablets.
 - ♣ Initiation of immediate-release bupropion in the average adult person should be 75 mg orally twice a day.
 - On the fourth day of treatment, the dosage can be raised to 100 mg three times a day.
 - ♣ the recommended dosage is 300 mg.
 - ♣ The maximal dosage, 450 mg a day, should be given as 150 mg three times a day.

Nefazodone

- ♣ Nefazodone (Serzone) is indicated for the treatment of major depression.
- ♣ it did not cause the sexual side effects and sleep disruption
- ♣ It produce problematic sedation, nausea, dizziness, and visual disturbances. rare cases of sometimes fatal hepatotoxicity
- ♣ The usual effective dose is 300 to 600 mg a day.
- ♣ Nefazodone is also effective for treatment of
 - panic disorder and panic with comorbid depression symptoms, of generalized anxiety disorder, premenstrual dysphoric disorder, and chronic pain.

Nefazodone...

- ♣ The recommended starting dosage of nefazodone is 100 mg twice a day, but 50 mg twice a day may be better tolerated, especially by elderly persons.