

## ANTI-DEPRESSANTS

### DEPRESSION:

- Depression is characterized by disturbances in sleep and appetite as well as deficits in cognition and energy
- Major depressive disorder (MDD) is characterized by depressed mood most of the time for at least 2 weeks and/or loss of interest or pleasure in most activities
- Thoughts of guilt, intense feelings of sadness, hopelessness, despair, worthlessness, and suicide are common
- **Biogenic amine theory** proposes that depression is due to a deficiency of monoamines, such as norepinephrine and serotonin, at certain key sites in the brain
- Coronary artery disease, diabetes, and stroke are more common in depressed patients
- Depression may considerably worsen the prognosis for patients with a variety of comorbid medical conditions

### TYPES OF DEPRESSION

- Major depression
- Chronic depression (Dysthymia)
- Atypical depression
- Bipolar disorder/Manic depression
- Seasonal depression (SAD)

### CAUSES OF DEPRESSION

- Genetics
- Death/Abuse
- Medications

### ANTI-DEPRESSANT drugs:

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Atypical antidepressants
- Tricyclic antidepressants (TCAs)
- Monoamine oxidase inhibitors (MAOIs)

| SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)      | TRICYCLIC ANTIDEPRESSANTS (TCAs)     |
|--|--------------------------------------|
| <i>Citalopram</i> CELEXA                             | <i>Amitriptyline</i> GENERIC ONLY    |
| <i>Escitalopram</i> LEXAPRO                          | <i>Amoxapine</i> GENERIC ONLY        |
| <i>Fluoxetine</i> PROZAC                             | <i>Clomipramine</i> ANAFRANIL        |
| <i>Fluvoxamine</i> LUVOX                             | <i>Desipramine</i> NORPRAMIN         |
| <i>Paroxetine</i> PAXIL                              | <i>Doxepin</i> SILENOR               |
| <i>Sertraline</i> ZOLOFT                             | <i>Imipramine</i> TOFRANIL           |
| SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs) | <i>Maprotiline</i> GENERIC ONLY      |
| <i>Desvenlafaxine</i> PRISTIQ                        | <i>Nortriptyline</i> PAMELOR         |
| <i>Duloxetine</i> CYMBALTA                           | <i>Protriptyline</i> VIVACTIL        |
| <i>Levomilnacipran</i> FETZIMA                       | <i>Trimipramine</i> SURMONTIL        |
| <i>Venlafaxine</i> EFFEXOR                           | MONOAMINE OXIDASE INHIBITORS (MAOIs) |
| ATYPICAL ANTIDEPRESSANTS                             | <i>Isocarboxazid</i> MARPLAN         |
| <i>Bupropion</i> WELLBUTRIN, ZYBAN                   | <i>Phenelzine</i> NARDIL             |
| <i>Mirtazapine</i> REMERON                           | <i>Selegiline</i> EMSAM              |
| <i>Nefazodone</i> GENERIC ONLY                       | <i>Tranylcypromine</i> PARNATE       |
| <i>Trazodone</i> GENERIC ONLY                        |                                      |
| <i>Vilazodone</i> VIIBRYD                            |                                      |
| <i>Vortioxetine</i> TRINTELLIX                       |                                      |

#### SELECTIVE SEROTONIN REUPTAKE INHIBITORS:

- group of chemically diverse antidepressant drugs that specifically inhibit serotonin reuptake
- little ability to block the dopamine transporter
- little blocking activity at muscarinic,  $\alpha$  adrenergic, and histaminic  $H_1$  receptors

#### Actions:

- take at least 2 weeks to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more
- Patients that do not respond to one antidepressant may respond to another, and approximately 80 percent or more will respond to at least one antidepressant drug

#### Therapeutic uses:

- primary indication is depression

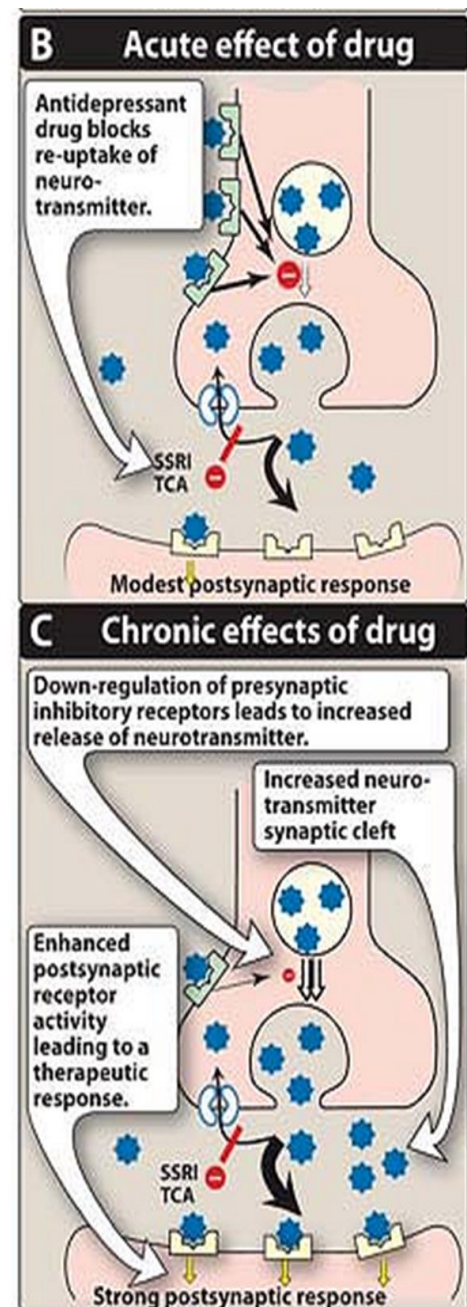
- obsessive-compulsive disorder (fluvoxamine)
- panic disorder
- generalized anxiety disorder
- posttraumatic stress disorder
- social anxiety disorder
- premenstrual dysphoric disorder,
- bulimia nervosa

#### Pharmacokinetics:

- well absorbed after oral administration
- Food has little effect on absorption (except with sertraline)
- plasma half-lives range between 16 and 36 hours

#### Adverse effects:

- fewer and less severe adverse effects than the TCAs and MAOIs.
- headache, sweating, anxiety and agitation, gastrointestinal effects, weakness and fatigue, sexual dysfunction, changes in weight, sleep disturbances
- all antidepressants lower the seizure threshold
- **serotonin syndrome** include the symptoms of hyperthermia, muscle rigidity, sweating, myoclonus (clonic muscle twitching), and changes in mental status and vital signs
- **Discontinuation syndrome:** headache, malaise and flu-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern
- Use in children and teenagers



#### SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS:

- **Venlafaxine** and **duloxetine**, **Milnacipran** selectively inhibit the re-uptake of both serotonin and norepinephrine
- effective in treating depression in patients in whom SSRIs are ineffective

- relieve physical symptoms of neuropathic pain, such as diabetic peripheral neuropathy

#### **Pharmacokinetics:**

- Well absorbed orally
- half-life of **venlafaxine** is approximately 11 hours and 27 percent bound to plasma protein
- half-life of **duloxetine** is approximately 12 hours and highly bound to plasma protein
- Duloxetine should not be administered to patients with hepatic insufficiency
- Food delays the absorption of the drug

#### **Side effects:**

- **Venlafaxine:** nausea, headache, sexual dysfunction, dizziness, insomnia, sedation, and constipation
- At high doses, there may be an increase in blood pressure and heart rate
- Duloxetine: nausea, dry mouth, and constipation, Sexual dysfunction

#### **TRICYCLIC ANTI-DEPRESSANTS:**

- block norepinephrine and serotonin reuptake into the neuron
- All have similar therapeutic efficacy, and the choice of drug may depend on patient tolerance to side effects, prior response, pre-existing medical conditions, and duration of action

#### **Mechanism of action:**

##### **1-Inhibition of neurotransmitter reuptake; norepinephrine and serotonin**

- At therapeutic concentrations, they do not block dopamine transporters
- **Maprotiline** and **desipramine** are selective inhibitors of norepinephrine reuptake

##### **2- Blocking of receptors:**

- block serotonergic, alpha adrenergic, histaminic, and muscarinic receptors

#### **Actions:**

- elevate mood, improve mental alertness, increase physical activity
- onset of the mood elevation is slow, requiring 2 weeks or longer

#### **Therapeutic uses:**

- effective in treating moderate to severe major depression

- **Imipramine** has been used to control bed-wetting in children (older than 6 years) by causing contraction of the internal sphincter of the bladder
- **amitriptyline**, have been used to treat migraine headache and chronic pain syndromes

#### **Pharmacokinetics:**

- well absorbed upon oral administration
- widely distributed and readily penetrate into the CNS
- Half lives range 4 to 17 hours

#### **Adverse effects:**

- Blockade of muscarinic receptors causes blurred vision, xerostomia (dry mouth), urinary retention, constipation, and aggravation of narrow-angle glaucoma
- Block of alpha adrenergic receptors cause orthostatic hypotension, dizziness, and reflex tachycardia
- TCAs have a narrow therapeutic index
- TCAs may worsen certain medical conditions, such as unstable angina, benign prostatic hyperplasia, epilepsy, and patients with preexisting arrhythmias
- Sexual dysfunction in men, and anorgasmia in women

#### **ATYPICAL ANTIDEPRESSANTS:**

- mixed group of agents that have actions at several different sites
- They are not any more efficacious than the tricyclic antidepressants or SSRIs, but their side effect profiles are different

#### **Bupropion:**

- Bupropion has a unicyclic aminoketone structure
- acts as a weak dopamine and norepinephrine reuptake inhibitor (NDRI)
- Bupropion somewhat resembles amphetamine in chemical structure and, like the stimulant, has central nervous system (CNS) activating properties
- It is also effective as a smoking cessation aid
- Shorter half life i.e. 7-12 hours
- Its unique structure results in a different side-effect profile than most antidepressants
- Side effects include dry mouth, sweating, nervousness, tremor
- incidence of sexual dysfunction is low

- increases risk for seizures at high doses

#### **Mirtazapine:**

- noradrenergic and specific serotonergic antidepressant (NaSSA)
- Mirtazapine was introduced in 1994
- It has a tetracyclic chemical structure and belongs to the piperazino-azepine group of compounds
- enhances serotonin and norepinephrine neurotransmission via blockade of presynaptic  $\alpha_2$  adrenergic receptors
- Also block 5-HT<sub>2</sub> receptors
- It is a sedative because of its potent antihistaminic activity, which may be used to advantage in depressed patients having difficulty sleeping
- like bupropion, it is one of the few antidepressants not associated with sexual dysfunction side effects

#### **Nefazodone and trazodone:**

- These drugs block postsynaptic 5-HT<sub>2A</sub> receptors
- Inhibition of this receptor in both animal and human studies is associated with substantial anxiolysis, antipsychotic, and antidepressant effects
- also weak inhibitors of both SERT and NET
- Trazodone's structure includes a **triazolo moiety** that is thought responsible for antidepressant effects
- Its primary metabolite, m-chlorophenylpiperazine (m-cpp), is a potent 5-HT<sub>2</sub> antagonist
- The most common use of **Trazodone** in current practice is as an unlabeled hypnotic, since it is highly sedating and not associated with tolerance or dependence
- **Nefazodone** is chemically related to trazodone
- Its primary metabolites, hydroxynefazodone and m-cpp are both inhibitors of the 5-HT<sub>2</sub> receptor
- Lethal cases of **hepatic failure** have been reported with Nefazodone used (FDA black box warning in 2001 implicating it in hepatotoxicity)
- With chronic use, these agents desensitize 5-HT<sub>1A</sub> presynaptic autoreceptors causing increased serotonin release
- **Both agents are sedating** because of their potent H<sub>1</sub>-blocking activity

## Monoamine Oxidase Inhibitors (MAOIs)

- MAOIs were introduced in the 1950s
- now rarely used in clinical practice because of **toxicity** and potentially **lethal food and drug interactions**
- Their primary use now is in the treatment of depression unresponsive to other antidepressants
- The hydrazines derivatives (**phenelzine** and **isocarboxazid**) and **tranylcypromine** bind irreversibly and nonselectively with MAO-A and –B
- other MAOIs (**selegiline**) have more selective (MAO-B) or reversible properties
- Selegiline was prior-approved for Parkinson's disease
- selegiline have amphetamine-like metabolites, so it has substantial CNS-stimulating effects
- These drugs inhibit not only MAO in the brain but also MAO in the liver and gut
- It results in inhibition of oxidative deamination of drugs and potentially toxic substances, such as tyramine, which is found in certain foods
- The MAO inhibitors therefore show a high incidence of drug-drug and drug-food interactions
- Selegiline administered as the transdermal patch produce less inhibition of hepatic MAO at low doses, because it avoids first-pass metabolism

### Therapeutic uses:

- MAO inhibitors are indicated for depressed patients who are unresponsive or allergic to TCAs or who experience strong anxiety
- Patients with low psychomotor activity may benefit from the stimulant properties of the MAO inhibitors
- These drugs are also useful in the treatment of phobic states
- A special subcategory of depression, called atypical depression, may respond to MAO inhibitors
- Common symptoms of atypical depression include increased appetite or weight gain, sleepiness or excessive sleep, and feeling extremely sensitive to rejection.

### Pharmacokinetics:

- These drugs are well absorbed after oral administration
- antidepressant effects require at least 2 to 4 weeks of treatment
- MAO inhibitors are metabolized and excreted rapidly in the urine

- when switching antidepressant agents, a minimum of 2 weeks of delay must be allowed after termination of MAO inhibitor therapy and the initiation of another antidepressant from any other class

#### **Adverse effects:**

- The most common adverse effects of the MAOIs leading to discontinuation of these drugs are **orthostatic hypotension** and **weight gain**
- Individuals receiving an MAO inhibitor are unable to degrade tyramine obtained from the diet (tyramine-containing foods)
- Tyramine causes the release of large amounts of stored catecholamines from nerve terminals, resulting in occipital headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures, and possibly, stroke
- **Phentolamine** or **prazosin** are helpful in the management of tyramine-induced hypertension
- Other side effects include drowsiness, blurred vision, dry mouth, dysuria, and constipation
- MAO inhibitors and SSRIs should not be coadministered due to the risk of the life-threatening **serotonin syndrome**
- Both types of drugs require washout periods of at least 2 weeks before the other type is administered, with the exception of fluoxetine (it should be discontinued at least 6 weeks before a MAO inhibitor is initiated)
- Combination of **MAOIs** and **Bupropion** can produce seizures

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*Pharmacology IV*