Anti-depressant Drugs

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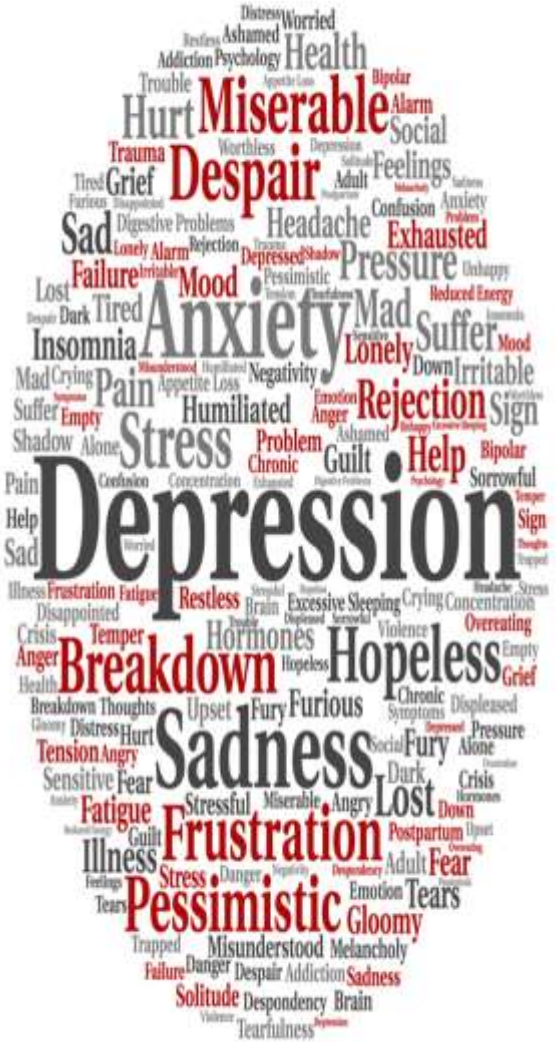
Depression

- Depression is a serious disorder that affects 300 million adults worldwide

Symptoms of depression:

- Intense feeling of sadness
- Hopelessness & despair
- Inability to experience pleasure in usual activities
- Changes in sleep patterns and appetite
- Loss of energy
- Suicidal thoughts



Antidepressants

1. Selective serotonin re-uptake inhibitors **(SSRIs)**
2. Serotonin/norepinephrine re-uptake inhibitors **(SNRIs)**
3. Atypical antidepressants
4. Tricyclic antidepressants **(TCAs)**
5. Monoamine oxidase inhibitors **(MAOs)**

MECHANISM OF ANTIDEPRESSANT DRUGS

- Most clinically useful antidepressant drugs potentiate, either **directly or indirectly**, the actions of **norepinephrine and/or serotonin in the brain**

- **Amine theory**, which proposes that depression is due to **a deficiency of monoamines**, such as **norepinephrine & serotonin**, at certain key sites in the brain

1. SELECTIVE SEROTONIN REUPTAKE INHIBITORS

- Selective serotonin reuptake inhibitors **(SSRIs)** are a group of antidepressant drugs that **specifically inhibit serotonin reuptake**

- **Tricyclic antidepressants** that nonselectively **inhibit the uptake of norepinephrine and serotonin**

- **SSRIs** have **little blocking activity at muscarinic, α-adrenergic, and histaminic H1 receptors**

- Therefore, common side effects associated with **tricyclic antidepressants**, such as orthostatic hypotension, sedation, dry mouth, and blurred vision, **are not commonly seen with the SSRIs**

- Because they have **fewer adverse effects** and are relatively **safe even in overdose,** SSRIs have largely **replaced tricyclic antidepressants and monoamine oxidase inhibitors** as the drugs of choice in treating depression

SSRIs

Include:

1. **fluoxetine,**
2. **citalopram,**
3. **escitalopram,**
4. **fluvoxamine,**
5. **paroxetine, and**
6. **sertraline**

Actions

- **SSRIs block reuptake of serotonin**, leading to increased concentrations of neurotransmitter in synaptic cleft and, ultimately, to greater postsynaptic neuronal activity

- Antidepressants, including SSRIs, typically take at least **2 weeks to produce significant improvement in mood**, and **maximum benefit may require up to 12 weeks or more**

- Approximately **40%** of depressed patients treated with adequate doses for **4 to 8 weeks do not respond** to the antidepressant agent
- Patients that do not respond to one antidepressant **may respond to another**
- Approximately **80% or more** will respond to at least one antidepressant drug
- These drugs **do not usually produce** central nervous system (CNS) stimulation or mood elevation **in normal individuals**

Therapeutic uses

1. Depression
2. Obsessive-compulsory disorders (OCDs)
3. Panic disorders
4. Generalized anxiety disorders
5. Posttraumatic stress disorders

- All of the SSRIs are well absorbed after **oral** administration
- **Peak levels** are seen in approximately **2-8 hours**
- The majority of SSRIs have **plasma half-lives** that range between **16-36 hours**
- **Metabolism** by **P450 enzymes &** glucuronide or sulfate conjugation

Adverse effects

- **Sleep disturbances:** sedation, insomnia
- **Sexual dysfunction:** Loss of libido, delayed ejaculation & anorgasmia
- **Use in children and teenagers:** suicidal thinking
- Overdoses: seizures

2 .Serotonin/norepinephrine re-uptake inhibitors (SNRIs)

- **Venlafaxine and duloxetine**
- Inhibit re-uptake of both serotonin & norepinephrine
- Effective in depressed patients in which SSRIs are ineffective
- Effective in treating **chronic painful symptoms** accompanied by depression (backache, muscle aches) & **neuropathic pain (e.g. diabetic peripheral neuropathy)**
- SNRIs have no activity at adrenergic, muscarinic or histamine receptors

3. ATYPICAL ANTIDEPRESSANTS

- The atypical antidepressants are a mixed group of agents that have actions at several different sites

Include

1. **bupropion,**
2. **mirtazapine,**
3. **nefazodone, and**
4. **trazodone**

4. TRICYCLIC ANTIDEPRESSANTS

- Tricyclic antidepressants (TCAs) block norepinephrine and serotonin reuptake into the neuron

The TCAs include the

1. tertiary amines:

imipramine (the prototype drug),

amitriptyline,

clomipramine,

doxepin

2. Secondary amines:

- **desipramine**
- **nortriptyline**

➢ **All have similar therapeutic efficacy &** choice of drug may depend on:

- ➢ patient tolerance to side effects prior response
- ➢ pre-existing medical conditions
- ➢ duration of action

Mechanism of Action

1. **Inhibition of neurotransmitter reuptake:**

- **TCAs potent inhibitors of neuronal reuptake** of norepinephrine & serotonin into presynaptic nerve terminals

- They cause **increased concentrations of monoamines** in synaptic cleft, resulting in antidepressant effects

2. **Blocking of receptors:**

- TCAs also block **α-adrenergic, histaminic, and muscarinic receptors**

Actions:

- TCAs **elevate mood, improve mental alertness, increase physical activity** in patients with major depression
- Panic disorders

Therapeutic uses:

- TCAs are effective in treating **moderate to severe major depression**
- **Imipramine** has been used **to control bed-wetting in children (enuresis, incontinence)** (older than 6 years) by causing contraction of internal sphincter of bladder
- TCAs, particularly **amitriptyline**, have been used to treat **migraine headache** and **chronic pain syndromes** (for example, **"neuropathic"pain**) in a number of conditions for which the cause of pain is unclear

- Tricyclic antidepressants are well absorbed after **oral administration**
- Because of their **lipophilic nature**, they are widely distributed & **readily penetrate into CNS**
- **Have a narrow therapeutic index**

Adverse effects

- **Blockade of muscarinic receptors** leads to blurred vision, xerostomia (dry mouth), urinary retention, constipation)
- **TCAs block α-adrenergic receptors**, causing orthostatic hypotension, dizziness, and reflex tachycardia (most serious in elderly)
- Overdose **life-threatening arrhythmias**
- **Sedation** due to block of **histamine H1 receptors**
- Weight gain
- **Sexual dysfunction:** (erectile dysfunction in men and anorgasmia in women)

5. MONOAMINE OXIDASE INHIBITORS

- **Monoamine oxidase (MAO)** is mitochondrial enzyme found in **nerve, gut & liver**
- In neuron, **MAO catalyses oxidative deamination & inactivation of excess neurotransmitters** (norepinephrine, dopamine, and serotonin) that leak out of synaptic vesicles

- **MAO inhibitors inactivate MAO enzyme**, permitting neurotransmitters to escape degradation and to accumulate within presynaptic neuron & leak into synaptic space

- This cause **activation of norepinephrine and serotonin receptors**, and is responsible for indirect antidepressant action of these drugs

➢Three MAO inhibitors are currently available for treatment of depression:

1. **phenelzine,**
2. **tranylcypromine** and
3. **selegiline** (was first-approved for Parkinson's disease), but is now also approved for depression, is the first antidepressant available in a **transdermal delivery system**

Mechanism of action

- Most MAO inhibitors, such as phenelzine, form stable complexes with the enzyme, causing **irreversible inactivation**

- This results in **increased stores of norepinephrine, serotonin & dopamine** within the neuron and subsequent diffusion of excess neurotransmitter into synaptic space

- These drugs inhibit not only MAO in brain but also **MAO in liver and gut that catalyze oxidative deamination of drugs** and **potentially toxic substances,** such as **tyramine**, which is found in certain foods

- **MAO inhibitors** therefore show **high incidence** of **drug-drug and drug-food interactions**

Therapeutic uses

MAO inhibitors are indicated for depressed patients who are **unresponsive or allergic to TCAs or who experience strong anxiety**

Adverse effects

- Severe and often unpredictable side effects due to **drug-food and drug-drug interactions** limit the widespread use of MAO inhibitors

- **Tyramine**, which is contained in certain foods, such as aged cheeses and meats, chicken liver, pickled or smoked fish ,red wines, is normally inactivated by MAO in gut

- Individuals receiving MAO inhibitor are unable to degrade tyramine

- **Tyramine** causes **release of large amounts of stored catecholamines** from nerve terminals, resulting in headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures & stroke

- Patients must therefore be educated to avoid tyramine-containing foods.

- Drowsiness, orthostatic hypotension, blurred vision, dry mouth, dysuria & constipation
- **MAO inhibitors and SSRIs** should not be co-administered due to risk of life-threatening **"serotonin syndrome"** characterized by hyperthermia, muscle rigidity, myoclonus (clonic muscle twitching), changes in mental status (confusion, agitation)
- Both types of drugs require washout periods of at least 2 weeks before the other type is administered

Thank you