ANTIDEPRESSANTS

DEPRESSION

It is a mental illnesses characterized by pathological changes in mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration . It can be severe and some times Fatal.

Symptoms

Depressed mood most of the day

Markedly diminished interest or pleasure

Significant weight loss /gain

Insomnia or hypersomnia

Agitation  Fatigue or loss of energy

Change in appetite

Lack of concentration

Poor self esteem

Thought of suicide or death.

Types of Depression

Major depression

Chronic depression (Dysthymia)

Atypical depmression

Bipolar disorder/Manic depression

Seasonal depression (SAD)

Mechanism Of Depression

Depression is associated with changes in the level of neurotransmitters in the brain that help nerve cells to communicate.E.x Serotonin,Dopamine,Nor epinephrine The level can be influenced by physical illness,genetics,substance abuse,diet,hormonal chnages, brain injuries or social circumstances.

ANTIDEPRESSANTS .

Drug which enhance alertness and may result in an increased output of behaviour. Potentiate directly or indirectly the action of • Dopamine • Serotonin • Nor adrenaline The purpose of antidepressants is to increase the neurotransmitters in the synapse.

They are used for the relief of symptoms of moderate and severe depression. Antidepressants are taken for atleast 4-6 months. They can be used alone or in combination with other medications

Types of Antidepressants

Tricyclic anti-depressants (TCAs).

Monoamine oxidase inhibitors (MAOIs).

Selective serotonin reuptake inhibitors (SSRIs)

Atypical anti-depressants (Others)

TRICYCLIC ANTIDEPRESSANTS

They have been employed in drug therapy since the late 1950s. Largest group of drug agents used for the treatment of depression. Referred as “ tri cyclic ” compounds –three rings.

Properties of TCA

Characteristic three ring nucleus.

All are metabolized in liver . High protein binding. High lipid solubility. N N R1 R2 A B C 1 2 37 5 6 8 9 10 11

Classification of TCA

Imipramine ,Amytriptiline 'Desipramine 'Nortriptyline ,Protryptyline ,Doxepin

MECHANISM OF ACTION

Inhibit the re-uptake of neurotransmitters. They inhibit serotonin,nor epinephrine or dopamine reuptake at pre synaptic nerve terminals thus lead to increased concentration of these transmitters in the synaptic cleft.  Takes up to 4 weeks for all TCA antidepressants to have an effect.

Imipramine •

Closely related to antipsychotic drug Phenothiazines. Used to treat wide class of depression. It is a prototype drug of class TCA. It is also used to treat nocturnal enuresis. Usual dose 50-150 mg daily.

Therapeutic Uses Severe major depression Phobic and panic anxiety disorders Neuropathic pain Obsessive compulsive disorder (OCD) Nocturnal enuresis; Imipramine has been used to control bed-wetting in children (older than six years) by causing contraction of the internal sphincter of the bladder.

Adverse Effects  Dry mouth Constipation Blurred vision  Mydriasis  Metallic taste  Urine retention Drowsiness Sedation weight gain

Chemical

19. Monomethyl amines are more potent than dimethylamines as shown for imipramine and desipramine. Replacement of hetrocyclic N with C,activity is retained. Branching of side chain does not activity of the drug as seen in the case of imipramine and trimipramine.

20. Cis form is more potent than trans form.

. Mono amine oxidase inhibitors

Treatment of depression began with the use of MAOIs in 1950’s. These drugs are not widely used today, although a small number of patients appear to do better in MAOIs than TCAs or the newer drugs.

Properties

Are readily absorbed from GI tract  Widely distributed throughout the body. May have active metabolites, inactivated by acetylation. Effects persist even after these drugs are no longer detectable in plasma (1-3 weeks)

Classification of MAOIs Phenelzine Isocarboxacid Tranylcypromine

Mechanism of action of MAOIs

MAO is a mitochondrial enzyme found in nerve and other tissues. Monoamine oxidase breaks down norepinephrine, serotonin, and dopamine. When monoamine oxidase is inhibited, norepinephrine, serotonin, and dopamine are not broken down, increasing the concentration of all three neurotransmitters in the brain.

MAOIs may reversibly or irreversibly inactivate the enzymes by making stable complexes with the enzymes,permitting neurotransmitter molecules to escape degradation and accumulate within synaptic cleft. This may cause activation of nor epinephrine and serotonin receptors responsible for anti depressant action.

PHENELZINE NH2 H N White powder freely soluble in water.  Insoluble in ethanol. It has low sedative properties.

Therapeutic Uses

Indicated for depressed patients who are unresponsive or allergic to TCAs.  Patient with low psychomotor activity. Treatment of phobic states

Adverse Effects 

Drowsiness/Fatigue

Constipation

Nausea

Diarrhea

Dizziness

Low blood pressure Lightheadedness, Decreased urine output Sleep disturbances

Chemical structures of MAOIs CH3 N O O H N N H CH3 CH3 H N N H O N NH2 H N Isocarboxazide Phenelzine Iproniazid

SAR of MAOIs Electron withdrawing groups increase potency. Some MAOIs are related to Amphetamine. Cyclization of side chain of Amphetamine results in Tranylcypromine. TRANYLCYPROMINE

Selective Serotonin Reuptake Inhibitors

A group of chemically unique drugs More modern group of drugs in use.  1st drug fluoxetine available in 1988.  Safest antidepressant for use.

Properties Good absorption after oral administration

Important biotransformation in the liver

Long half-lives of elimination(s) 

fluoxetine (T1/2=50h) Drug mostly excreted from kidney. Few drugs are excreted from feaces.

Mechanism of action

Inhibition of serotonin reuptake into the presynaptic cell, increasing the level of serotonin leading to greater post synaptic neuronal activity. They do not have significant effect on Nor epinephrine & Dopamine.

They typically take 2 to 12 weeks to produce improvement in mood.

Classification of SSRIs

Fluoxetine

Sertraline 

Paroxetine

Fluvoxamine

Escitalopram.

Fluoxetine. White crystalline powder Soluble in methanol sparingly  soluble in water. Treatment of endogenous  depression. Usual dose 20-80 mg daily

Therapeutic Uses

Depression  Obsessive compulsive disorder (the only indication for fluvoxamine )  Panic disorder  Generalized anxiety  Premenstrual dysphoric disorder  Bulimia nervosa (only fluoxetine is approved for this last indication)

Adverse Effects

Anxiety Insomnia Agitation Sexual dysfunction. Weight gain.

Atypical Anti Depressants

 They are a mixed group of agents that have actions at several different sites  Atypical antidepressants ease depression by affecting chemical messengers (neurotransmitters) used to communicate between brain cells.  Like other types of antidepressants, atypical antidepressants affect neurotransmitters including dopamine, serotonin and nor epinephrine.  Changing the balance of these chemicals seems to help brain cells send and receive messages, which in turn boosts mood.

Classification

Bupropion 

Trazodone 

Mianserin

Mechanism of action 

It is similar to that of SSRIs. It inhibits the re uptake of serotonin leading to increase concentration in brain.

Bupropion White solid in appearance Soluble in water and ethanol. Drug belong to class Atypical antidepressants. Similar in action to SSRIs. Very potent to use.

Therapeutic Uses

Atypical antidepressants are frequently used in patients with major depression who have inadequate responses or intolerable side effects during first-line treatment with selective serotonin reuptake inhibitors (SSRIs)  Atypical antidepressants are often first-line treatment if the drug has a desirable characteristic (eg, sexual side effects and weight gain occur less often with bupropion than SSRIs).

Adverse Effects

Anxiety Restlesness Blurred vision Constipation Agitation Dry mouth Nausea

Discontinution of Antidepressants Antidepressants should be gradually tapered and should not be abruptly discontinued. Abruptly stopping an antidepressant in some patients can cause discontinuation syndrome.

Conclusion

Depression is a serious condition that often can be effectively treated with available therapies. Side effects and drug interactions are barriers to successful treatment. Some side effects of antidepressants resolve with continued use while other side effects can be managed by dose reduction or adding other therapies. Appropriate management of side effects and avoidance of drugs that may interact with antidepressants may improve the success of antidepressant therapy.