PHARMACOLOGY OF ANTIDEPRESSANT DRUGS (LITERATURE REVIEW)

Djanaev G.Yu
Tashkent Medical AcademyTashkent, Uzbekistan
Mustanov T.B
Kakhkharova Sh.B
Alfraganus University, Tashkent, Uzbekistan

Abstract: *This review covers mechanisms of action, efficacy, side effects, and toxicity of various classes of antidepressants:tricyclic antidepressants, monoamine oxidase inhibitors, second-generation antidepressants including the selective inhibitors of serotonin reuptake, and novel drugs such as mirtazapine, nefazodone, and venlafaxine. After the clinical aspects of depression are introduced in this article, the pharmacology of the newer generation drugs is reviewed in relationship to the older compounds. The information in this review will help clinicians treat acute depression with pharmacological agents. Despite extensive research to find a diagnostic test, the diagnosis of depression remains clinical. The criteria for the diagnosis of major depression5 are the core signs and symptoms, including depressed mood, diminished pleasure or interest in activities, pronounced change in appetite or weight, alterations in sleep (insomnia or hypersomnia), psychomotor agitation or retardation, fatigue or loss of energy, inability to concentrate, indecisiveness, and thoughts of death, dying, or suicide. When fewer antidepressant compounds were available, the drugs were classified either as tricyclic antidepressants or as monoamine oxidase inhibitors (MAOIs), a classification that mixes a structural criterion with a functional one. At present, a broad range of structures make up the antidepressant pharmacopoeia, but there are only a few known functional (possibly therapeutic) effects of these compounds. Therefore, a functional classification of antidepressants is more useful than a structural.*

Key words: *antidepressant , Amitriptyline, Fluoxetine, Maprotiline, Nialamide ,Transamine, Selective agents (MAO-A inhibitors), Moclobemide*

INTRODUCTION

Antidepressant drugs are the mainstay for the treatment of depression. Usually, antidepressants are given in combination with some form of limited supportive psychotherapy. For mild depression, psychotherapy alone may be of use. However, evidence is accumulating that the combination of antidepressant treatment and some form of psychotherapy may be superior to either treatment alone, especially for more severe and recurrent depression

Antidepressants are substances used to treat depression.

They are divided into the following groups.

I. Agents that block the neuronal uptake of monoamines

1. Non-selective agents that block the neuronal uptake of serotonin and noradrenaline

Imizin Amitriptyline

2. Means of selective influence

A. Blockers of neuronal uptake of serotonin

Fluoxetine

B. Blockers of the neuronal uptake of noradrenaline

Maprotiline

II. Monoamine oxidase (MAO) inhibitors

1. Non-selective agents (MAO-A and MAO-B inhibitors)

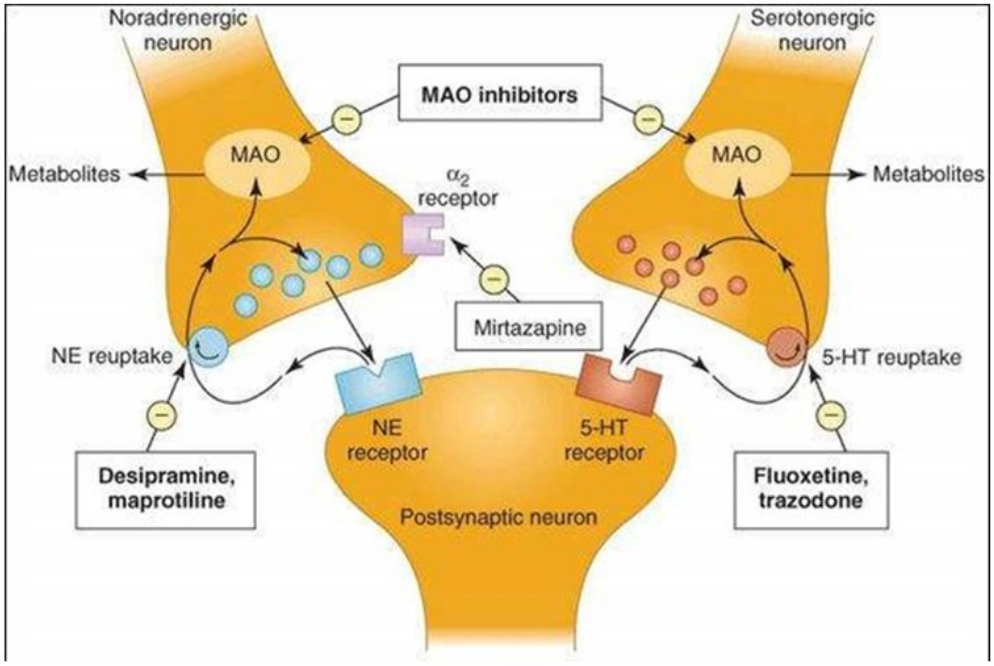
Nialamide Transamine

2. Selective agents (MAO-A inhibitors)

Moclobemide

1 Antidepressants with a sedative effect are sometimes called thymoleptics (from the Greek. thymos - soul, soul, leptos - gentle, delicate), and stimulating antidepressants - thymeretics (from the Greek. ereto - to tickle).

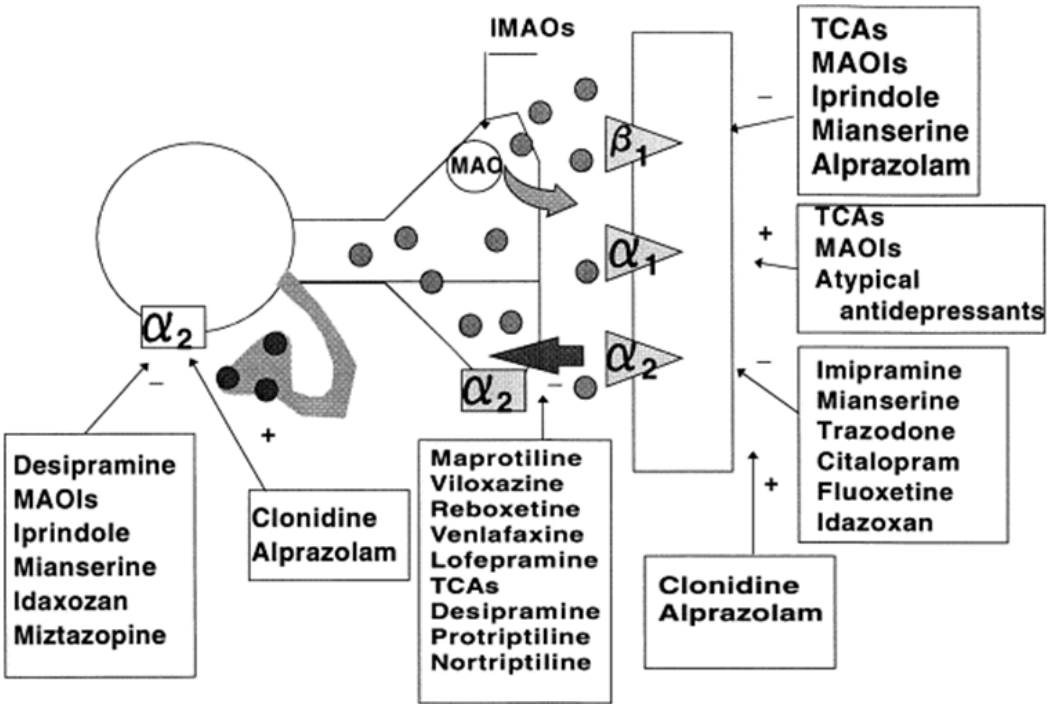
In medical practice, drugs of the first group, which are tricyclic antidepressants, are widely used (see structure). They are nonselective antidepressants that block the neuronal reuptake of serotonin and noradrenaline. Imizin (imipramine, melipramine, tofranil) is one of their representatives. It has high anti-depressant properties, which are manifested along with a weak sedative effect. At the same time, under certain conditions, psychostimulant properties also appear (sometimes excitement, euphoria, insomnia can be observed



There are a number of assumptions about the mechanism of action of our image. One of the most widely accepted hypotheses is that its antidepressant effect is related to its ability to reduce the neuronal reuptake of noradrenaline and serotonin1. This leads to the accumulation of a large concentration of mediators in the receptor area, increasing their effect. In particular, increasing the inhibitory effect of serotonin on the limbic system (amygdala) may be one of our important antidepressant mechanisms.

The drug also blocks presynaptic α2-adrenoreceptors (increases noradrenaline release), serotonin (5HT1A-1D) and histamine receptors.

1 In addition, there are assumptions that the antidepressant effect of our and other antidepressants of this type may be associated with a decrease in the density of serotonin 5-NT2-receptors, α2 - and β-adrenoreceptors in the MNS.



In addition to central effects, some peripheral m-cholinoblockers (such as atropine), α1-adrenoblockers, such as papaverine, and strong antihistamines are effective.

Imizin is well absorbed from the gastrointestinal tract. It is mainly metabolized in the liver. One of its metabolites - desmethylimipramine (dezipramin) - has high anti-depressant activity and is used in medical practice. It is mainly excreted by the kidneys (40% - on the 1st day), partly by the intestines as metabolites, conjugates and unchanged.

When using myzine in depression, the therapeutic effect occurs after 2-3 weeks. Side effects are often related to the atropine-like properties of ours (dry mouth, accommodation disorder, tachycardia, constipation, difficulty urinating). There are also disorders in the cardiovascular system. In therapeutic doses, it can reduce our arterial blood pressure. Against the background of its influence, orthostatic hypotension sometimes develops. High doses can cause tachycardia and arrhythmias. There may be undesirable deviations in mental activity. This is manifested by an excessive sedative effect or, on the contrary, excitement, hallucinations, insomnia. Headache, tremor, allergic skin reactions, jaundice, rarely leukopenia and agranulocytosis can be observed when using Imizin. The drug also causes weight gain.

Imizin cannot be used in urinary disorders associated with glaucoma, hypertrophy of the prostate gland. It cannot be used together with non-selective MAO inhibitors, as toxic effects occur. If

if it is necessary to use these two antidepressants consecutively, the interval after stopping the use of MAO inhibitor should not be less than 1.5-2 weeks.

Clomipramine (anafranil) is a similar drug. This has a stronger effect on serotonin reuptake.

triptysol is similar in structure to imigin. The pharmacodynamics and pharmacokinetics of amitriptyline and imizin are similar. In addition to antidepressant activity, amitriptyline also has psychosedative properties. There is no trigger effect (see Fig. 11.1). In addition, it is superior to its root in its m-holino-blocking and antihistamine effects. Amit-riptilin is one of the most active antidepressants. Its therapeutic effect is determined after 10-14 days.

A z a f e n (pipofezinum) also belongs to tricyclic antidepressants. It has moderate antidepressant activity and sedative effect. It differs favorably from the above antidepressants by the absence of m-cholinoblocking properties. Azafen is used to treat mild to moderate depression. The drug is well absorbed. Side effects are observed only in some cases, so azafen is often recommended for elderly patients. Recommended for drinking.

These drugs have a non-selective effect on the neuronal reuptake of serotonin and noradrenaline. At the same time, drugs with selective action have also been created. For example, only compounds that inhibit the neuronal reuptake of serotonin have been synthesized. Fluoxetin (Prozac, Framex) is one such drug. According to its chemical structure, it is a derivative of phenoxypropylamine. It has high antidepressant activity similar to tricyclic antidepressants. The effect develops gradually (within 1-4 weeks). It differs from tricyclic anti-depressants in that it does not have any sedative effect, usually has a slight psychostimulant property, does not have m-cholinoblocking property or is expressed to a small extent, does not affect adrenoreceptors. When fluoxetine is used, hemodynamics is stable. Body weight increases or decreases. In addition, fluoxetine is characterized by low toxicity.

It is well absorbed after enteral administration. Metabolized in the liver. One of its metabolites, norfluoxetine, has high antidepressant activity. t1/2 = 1-3 days for fluo-oxetine (7-15 15 days for norfluoxetine). Metabolites and unchanged drug are excreted by the kidneys.

Side effects include loss of appetite, nausea, nervousness, headache, insomnia, skin rashes. It is forbidden to use fluoxetine together with non-selective MAO inhibitors, because the so-called "serotonin syndrome" associated with the accumulation of excessive concentrations of serotonin may develop. It can present with life-threatening muscle stiffness, hyperthermia, and cardiovascular collapse. It should be remembered that there should be an interval of at least 2 weeks between the use of fluoxetine and non-selective MAO inhibitors.

nteractions of fluoxetine with food substances have not been determined (unlike non-selective MAO inhibitors).

Fluoxetine is widely used in medical practice for the treatment of depressive states.

For medical practice, a number of new drugs that selectively affect the neuronal reuptake of serotonin - sertraline, paroxetine, etc. invited. Paroxetine (Paxil) has the highest selective effect. In vitro experiments showed that paroxetine inhibits reuptake of serotonin 320 times stronger than noradrenaline (sertraline - 190 times, fluoxetine -

20 times). Paroxetine has high antidepressant and anxiolytic (anti-panic) activity. It has m-cholinoblocking effect to a lesser extent.

It is completely absorbed when administered enterally. The drug is used once a day. The effect develops in 1-4 weeks. The duration of treatment varies from months to months and depends on the type of depression. Paroxetine is well absorbed. Side effects are rarely observed. There may be nausea, headache, sometimes dry mouth, drowsiness, dizziness, etc.

In addition, a drug selectively blocking the neuronal reuptake of noradrenaline - m a p ro ti li n (ludiomil) was synthesized. Pharmacological properties and instructions for use are similar.

It is slowly absorbed from the digestive tract. It undergoes biotransformation in the liver.

Maprotiline and its metabolites are mainly excreted by the kidneys.

De z i p r a m i n also has a high effect on the neuronal uptake of noradrenaline. As mentioned above, it is a metabolite of ours. The nature of the effect is similar to the root. It has mild sedative and anticholinergic effects.

Currently, non-selective MAO inhibitors (which act on MAO-A and MAO-V) are rarely used due to their high toxicity. When choosing antidepressants, preference is usually given to drugs that affect the neuronal retention of monoamines.

Nonselective MAO inhibitors inhibit the process of oxidative deamination of noradrenaline and serotonin, which leads to their accumulation in brain tissue in significant amounts. Most drugs of this group irreversibly inhibit MAO. In this regard, in order for MAO to be restored, it must be synthesized again, for which a significant time is required (up to 2 weeks). Its maximum inhibition occurs a few hours after absorption of MAO inhibitors. However, the antidepressant effect develops after 7-14 days.

In addition to the antidepressant effect, MAO inhibitors are characterized by clear psychostimulant properties (they cause euphoria, excitement, insomnia; see

Against the background of the action of MAO inhibitors, the pressor effect of sympathomimetics (phenamine, ephedrine, tyramine), including food products (for example, cheese contains a significant amount of tyramine1), increases sharply. These substances help release excess noradrenaline from adrenergic endings, which accumulates in them as a result of inhibition of MAO. In this case, a hypertensive crisis2 occurs.

Reduction of MAO under the influence of inhibitors occurs not only in MNS, but also in peripheral tissues. In addition, these drugs suppress the activity of not only MAO, but also a number of other enzyme systems. For example, MAO inhibitors prolong the effect of inhalation anesthetics, opioid analgesics, antiepileptics and a number of other drugs due to the inhibition of microsomal liver enzymes.

MAO inhibitors have hypotensive activity. In angina pectoris, they reduce pain (apparently due to blocking the central pathways of reflexes from the heart). MAO inhibitors are well absorbed from the digestive tract. They are mainly excreted by the kidneys. MAO inhibitors have relatively high toxicity. It mainly affects the liver (it can cause severe hepatitis). In addition, they stimulate the MNS, which causes insomnia and, in some cases, tremors and convulsions. Orthostatic hypotension may occur with the use of these substances.

MAO inhibitors do not develop drug dependence.

A large number of hydrazine derivatives have been synthesized as MAO inhibitors. However, only some hydrazine preparations such as nialamide (niamide, nuredal) are used in medical practice. This is the least of its kind

1 Under normal conditions, tyramine is extensively inactivated by MAO in the intestinal wall and liver.

2 Such interaction of non-selective MAO inhibitors with sympathomimetics contained in food is often called "cheese effect".

is one of the effective antidepressants. However, its toxic effects on the liver and other side effects are rarely expressed.

T r a n s a m i n (tranylcypromine, parnate) chemical compounds belong to another class ("nohydrazine"). It is a phenylcyclopropylamine, which is similar in structure to phenylalkylamines (for example, phenamine). Transamine is a strong, irreversible inhibitor of MAO. It is one of the most effective antidepressants in this group. Its therapeutic effect occurs somewhat faster than most hydrazines (nialamide - after 12-14 days, transamine - after 2-7 days). The pharmacodynamics of Transamine is similar to other MAO inhibitors. It should be added that there are some sympathomimetic effects.

Hepatotoxicity of "Nohydrazine" compounds is less compared to drugs of the hydrazine group.

In recent years, in particular, drugs that selectively inhibit MAO-A have attracted attention. They are moclobemide (aurorix), pyrazidol, etc. includes. They have a shorter duration of action than irreversible MAO inhibitors. In addition, when using them, the likelihood of developing a hypertensive crisis, which is observed as a result of interaction with food sympathomimetics (for example, tyramine), typical for non-selective MAO inhibitors, is reduced. Moclobemide is a benzamide derivative.

Pyrazidol is a tetracyclic compound. According to its chemical structure, it can be included in indole derivatives. Antidepressant effect of pyrazidol, depending on the condition of the patient, is combined with sedative (on the background of panic, anxiety) or excitatory (on the background of relaxation) effects. The mechanism of its antidepressant effect is explained by its inhibitory effect on MAO-A and the ability to inhibit the neuronal uptake of noradrenaline. Pyrazidol has no m-cholinoblocking activity. The drug is well absorbed. Few side effects. Pyrazidol is prescribed for drinking.

CONCLUSION

The newer second-generation antidepressants have distinct pharmacologic advantages in comparison with the tricyclic antidepressants and the older second-generation compounds. These advantages are clearly seen from their synaptic effects, in which most newer second-generation antidepressants are practically devoid of blocking effects at neurotransmitter receptors. Although the newer second-generation antidepressants are much closer to being the ideal antidepressant than are the older compounds, none completely fulfills the criteria for being the ideal drug.

REFERENCES:

1. Richelson E. Pharmacology of antidepressants //Mayo Clinic Proceedings. – Elsevier, 2001. – Т. 76. – №. 5. – С. 511-527.

2. Frazer A. Pharmacology of antidepressants //Journal of Clinical Psychopharmacology. – 1997. – Т. 17. – №. 2. – С. 2S-18S.

3. Johnson L. E. et al. Focus: Plant-based Medicine and Pharmacology: The Potential for Kratom as an Antidepressant and Antipsychotic //The Yale journal of biology and medicine. – 2020. – Т. 93. – №. 2. – С. 283.

4. Calvi A. et al. Antidepressant drugs effects on blood pressure //Frontiers in cardiovascular medicine. – 2021. – Т. 8. – С. 704281.

5. Dai W. et al. Natural products for the treatment of stress-induced depression: Pharmacology, mechanism and traditional use //Journal of Ethnopharmacology. – 2022. – Т. 285. – С. 114692.

6. Machado-Vieira R. et al. The timing of antidepressant effects: a comparison of diverse pharmacological and somatic treatments //Pharmaceuticals. – 2010. – Т. 3. – №. 1. – С. 19-41.

7. Katzung BG, Masters SB Trevor, AJ, eds. (2004). Basic & Clinical Pharmacology.

8. Харкевич Д. А. Фармакология с общей рецептурой. – 2017.