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Review of New Generation Neuroleptics in the Treatment of Psychosis

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Abstract: Antipsychotics Antipsychotics are drugs that restore dopamine imbalance in the mesocortical, mesolimbic, nigrostriatal and tuberoinfundibular pathways of the brain, causing psychotic states. For this reason, drugs in this group are also called antipsychotics. Antipsychotics act on the dopaminergic system in such a way that they eliminate psychotic symptoms - first of all, perceptual delusions (auditory, visual, tactile hallucinations), delirium and psychomotor agitation.

Before the discovery of neuroleptics, in the treatment of psychosis, mainly herbal preparations (Bellena, Henbane, and opiates), bromides, intravenous calcium and narcotic sleep were used. In the late 40s of the XX century, lithium salts and antihistamines began to be used in the treatment of psychosis. In addition, insulin coma and electroconvulsive therapy, as well as psychosurgery (lobotomy) were used.

The very first antipsychotic was chlorpromazine (chlorpromazine), which was synthesized as an antihistamine in 1950; its effectiveness was discovered in 1952 during preliminary tests. Aminazine entered the market and has been widely used since 1953 to enhance anesthesia and as a sedative, including in schizophrenia. Isolated in 1952, reserpine (Rauwolfia alkaloid) was also used as an antipsychotic drug, but then gave way to more effective drugs due to its relatively low antipsychotic activity. In the 1950s, other rauwolfia alkaloids were used to treat psychosis: deserpidine (harmonyl), rescinamine (moderil) and raudixin, which also gave way to synthetic antipsychotics. In 1958, first-generation synthesized antipsychotics such as haloperidol appeared,

The term "neuroleptics" is often used as the name of the first generation of antipsychotic drugs - the so-called typical (classical) antipsychotics. The term “neuroleptics” was proposed in 1967, when the classification of the first psychotropic drugs was being developed, and referred mainly to drugs that not only have a pronounced antipsychotic effect, but also can often cause neurological (extrapyramidal) disorders characteristic of them - neuroleptic parkinsonism, akathisia , dystonic reactions, etc. In particular, these side effects often develop while taking antipsychotics such as haloperidol, chlorpromazine and triftazin, and are often accompanied by mental side effects: depression, severe fear and anxiety, emotional indifference.

Initially, it was even believed that the development of an antipsychotic effect is impossible without the appearance of extrapyramidal disorders and that the therapeutic effect can be correlated and measured by the severity of these neurological side effects [9]. However, subsequently, new drugs appeared: clozapine, risperidone, olanzapine, quetiapine, amisulpride, ziprasidone, aripiprazole, etc., which are much less likely to cause side effects characteristic of typical neuroleptics, primarily neurological ones. The emergence of these drugs, called atypical antipsychotics (atypical antipsychotics), called into question the very term "neuroleptic" in its former sense [2]. Instead of this term, the term "antipsychotics" is often used in relation to these drugs.

The names "large tranquilizers" (major tranquilizers) and "ataractics" (ataractics) neuroleptics were due to the pronounced sedative, hypnotic and tranquilizing-anti-anxiety effect they cause and the specific state of indifference to external stimuli ("ataraxia"). These names have fallen out of use, since not all antipsychotics have a sedative and hypnotic effect, and some of them, on the contrary, even have an activating, disinhibitory and energizing effect, especially noticeable in small doses.

In the second half of the 1960s, the first representatives of parenteral prolonged forms of antipsychotics (fluphenazine - decanoate, fluphenazine - enanthate, perphenazine - enanthate, flupentixol-decanoate, fluspirilene) were developed and put into practice. In 1968, clozapine appeared, the founder of the group of atypical antipsychotics, which practically did not cause extrapyramidal side effects, and in the late 1980s and early 1990s, other atypical antipsychotics appeared. However, after 8 out of 16 patients who developed agranulocytosis while taking clozapine died in Finland in the 1970s, the drug was removed from the US market, although it continued to be used in other countries. Re-marketed in the US in 1990 as it was found to be effective in treatment-resistant schizophrenic psychoses,

Treatment with neuroleptics is prescribed for psychotic conditions that occur against the background of diseases, for example: schizophrenia, schizoaffective disorder, bipolar affective disorder, mania of various etiologies, depression, brain damage (for example, TBI, stroke), neurological diseases (for example, epilepsy, Parkinson's disease) , dementia. Treatment with antipsychotics is usually long-term. Depending on the disease, the course of taking antipsychotics can last from 3 years, in the presence of a chronic disease, they are taken for life.

GENERATIONS OF NEUROLEPTICS

The leading classification of antipsychotics is based on their chemical structure and therapeutic mechanism of action. It includes three generations of antipsychotic drugs:

First generation antipsychotics (typical antipsychotics);

Second generation antipsychotics (atypical antipsychotics);

Third generation antipsychotics (new generation antipsychotics).

Typical antipsychotics are derivatives of chemical compounds - thioxanthene, phenothiazine, buterophenone; atypical antipsychotics - derivatives of 1,4-dibenzodiazepine, substituted benzamide and other chemical structures; neuroleptics of a new generation - partial agonists of dopamine receptors. First generation antipsychotics quickly and effectively relieve psychotic states, but have pronounced non-core actions, unlike second and third generation antipsychotics. Antipsychotics of the new generation have an innovative mechanism of action from previous generations.

Generations of neuroleptics

FIRST GENERATION NEUROLEPTICS (TYPICAL)

Typical antipsychotics are usually divided into three types according to the mechanism of action on the receptors that cause the antipsychotic effect - weak, moderate and strong. Weak antipsychotics have a low affinity for dopamine receptors and a high affinity for histamine, muscarinic, and α-adrenergic receptors. Strong, on the contrary, actively bind to dopamine receptors and have low affinity for muscarinic and α-adrenergic receptors.

Antipsychotics of the first generation have a pronounced antipsychotic effect. However, they may not be suitable for all patients due to lack of response to treatment (about 3 out of 10 patients with schizophrenia do not stop positive symptoms) or due to the occurrence of side effects - impaired consciousness, dystonia, limb tremors, tardive dyskinesia.

NEUROLEPTICS SECOND GENERATION (ATYPICAL)

As a rule, when prescribing antipsychotic treatment, preference is given to second-generation drugs. Atypical antipsychotics block dopamine receptors selectively, thereby reducing the risk of developing extrapyramidal disorders. In addition, unlike typical antipsychotics, they have additional therapeutically significant positive effects:

Smooth out negative symptoms;

Reduce the risk of developing mild cognitive impairment;

Less likely to cause extrapyramidal disorders;

Do not contribute to the occurrence of tardive dyskinesia.

Some atypical antipsychotics reduce suicidal tendencies during remission through, for example, a sedative effect; others - allow you to cope with anxiety and insomnia and, on the contrary, when the patient is lethargic, second-generation antipsychotics are selected that do not cause a strong sedative effect

When prescribing atypical neuroleptics, the assessment of therapeutic efficacy and side effect profile is carried out at a distance of 4–8 weeks. In particular, during this period, it is necessary to monitor weight and body mass index, fasting blood glucose, and blood pressure. The patient should be notified by the attending physician about the first signs of the development of diabetes, adhere to the principles of rational nutrition and engage in physical activity.

NEUROLEPTICS OF THE THIRD (NEW) GENERATION

Antipsychotics of the third generation have a mechanism of action different from typical and atypical antipsychotics. The mechanism of the drugs of the first generations is to block receptors, which, of course, helps to effectively stop acute and long-term psychotic states and conduct maintenance treatment. However, residual symptoms, individual side-effect profile and some difficulties in selecting the appropriate drug for a particular patient do not allow them to become a benchmark for the treatment of psychosis.

The principle of action of new generation antipsychotics is partial agonism to D2- and D3-dopamine receptors, which are a weaker synthetic analogue of dopamine. Taking such drugs allows patients to reduce negative symptoms, cognitive impairment, neurological, metabolic, endocrine and other disorders, and more effectively restore the ability to live independently. In other words, the latest generation of neuroleptics have an extended spectrum of therapeutic efficacy, an improved safety and tolerability profile.

The principle of partial agonism of new generation antipsychotics is an innovative mechanism that has taken the treatment of schizophrenia to a new level by achieving the following effects:

the effectiveness of relieving positive symptoms is comparable to first and second generation antipsychotics;

efficiency is achieved by acting on the receptors of "weakened" dopamine, and not by blocking the receptors;

therapeutic efficacy in relation to negative symptoms is determined by mild decompensation of neurotransmission in the dopaminergic system (an inaccessible effect for first and second generation antipsychotics);

the risk of extrapyramidal symptoms (EPS) is minimized or, as a rule, absent;

have significantly improved tolerability.

Third-generation antipsychotics are represented by several drugs. The first of them began to be used since 2002 (Aripiprazole), the subsequent ones - since 2015 (for example, Brexpiprazole, Cariprazine). Naturally, the list of newer neuroleptics will expand, but you need to know that the Food and Drug Administration (FDA) designates their mechanism of action as "unknown."

THE MECHANISM OF ACTION OF NEUROLEPTICS

The therapeutic mechanism of action of neuroleptics is associated with the relief of increased dopamine activity in the mesolimbic pathway, one of the dopaminergic nerve pathways. The mesolimbic pathway connects the substantia nigra and the ventral tegmentum with the structures of the limbic system. This pathway is responsible for the processes in the body associated with

neuroendocrine regulation, emotions, memory, the ability to learn and experience pleasure. In addition, this system is partially responsible for controlling the onset of motor reactions and their affective variations.

The mechanism of action of neuroleptics

BLOCKADING OF DOPAMINE RECEPTORS

Elevated levels of dopamine in the mesolimbic pathway cause psychotic states and productive symptoms (eg, hallucinations, delusions, active manifestation of anxiety). Typical neuroleptics, by reducing dopamine activity by blocking more than 65% of D2 receptors, reduce positive psychotic symptoms.

The mechanism of action of first-generation antipsychotics can cause non-core effects - motor restlessness, involuntary muscle contractions, contributes to the development of a depressive or anxious state, emotional depression, anhedonia. Such effects, as they appear, are stopped by dosage adjustment or symptomatic therapy.

Long-term blockade of D2 receptors in mesolimbic structures leads to an increase in the sensitivity of receptors or an increase in their number, and attempts by neurons to restore intersynaptic connections. In this connection, there is hypersensitivity to dopamine and a potential risk of developing psychosis even with a slight increase in the level of the neurotransmitter. Psychosis "hypersensitivity" (positive symptoms) can be triggered by alcohol, tobacco smoking and other dopamine-increasing substances, including drugs.

PARTIAL BLOCK OF DOPAMINE RECEPTORS

Some atypical neuroleptics, which partially block 2D dopamine receptors, mimic the neurotransmitter in its "attenuated form". Thus, the mechanism of action of second-generation antipsychotics is associated with a “soft” correction of dopamine levels, which contributes to a moderate reduction in positive symptoms and reduces the risk of non-profile effects.

Treatment with second-generation antipsychotics reduces the risk of anhedonia, hyperprolactinemia, hypersensitivity psychosis, tardive dyskinesia, and extrapyramidal disorders. However, the drugs are still not without side effects, in particular, when they are taken, norepinephrine activity in the substantia nigra remains, which can cause the development of akathisia (internal restlessness, desire for physical activity) with prolonged use.

Blockade of serotonin 5-HT2A-, 5-HT1A-, 5-HT2C RECEPTORS

The mechanism of action of another group of atypical antipsychotics is associated with the ability to bind to serotonin 5-HT2A receptors, indirectly affecting the level of dopamine. 5-HT2A receptors bind the serotonin and dopamine systems, and their blocking leads to a decrease in the activity of the dopamine neuron directly and indirectly, by reducing the release of GABA.

With an increase in the level of serotonin, 5-HT1A receptors, which are responsible for the self-regulation of the serotonin neuron, inhibit their activity. Through this, the effect of serotonin on 5-HT2A receptors is stopped and the activity of the dopamine neuron is reduced. A similar, but "soft" effect can be achieved by an agonist that mimics the effect of serotonin on 5-HT1A receptors.

Some second-generation antipsychotics block serotonin 5-HT2C receptors, increasing dopamine levels and decreasing serotonin. The resulting processes in the intermediate GABA neurons can reduce the production of dopamine. Drugs that act on α2-adrenergic receptors (analogues of 5-HT1A receptors) work on the same principle. Their blockade by an antipsychotic leads to the release of norepinephrine, inhibiting its reuptake and, accordingly, increasing its activity.

These processes explain the therapeutic effect of second-generation antipsychotics, which is aimed not only at relieving psychotic symptoms, but also at improving cognitive functions, reducing negative symptoms, and depressive states. In other words, second-generation drugs are able to correct the level of dopamine, norepinephrine and serotonin in the brain (mainly in the prefrontal cortex).

MULTIRECEPTOR BLOCK

Antipsychotics of the third generation have the property of a multireceptor blockade, affecting the dopamine, serotonin, cholinergic, adrenergic and other systems associated with the onset of psychotic states. They have an extended profile of therapeutic effect, stopping positive symptoms and reducing negative ones; non-core effects in clinical practice are extremely rare.

SIDE EFFECTS OF NEUROLEPTICS

When treated with antipsychotics, neuroleptic syndrome may occur. Extrapyramidal disorders of the syndrome are expressed in hypo- or hyperkinetic disorders. The first are characterized by a decrease in motor activity, stiffness of the muscular skeleton, tremor of the limbs, problems with maintaining balance; the second - tremor, involuntary movements, muscle twitching, spasms of chewing muscles, stiffness of movements, slow speech, motor activity. Typically, the neuroleptic syndrome includes both hypo- and hyperkinetic disorders.

Side effects of neuroleptics

In neuroleptic syndrome, muscle spasms are paroxysmal in nature. Usually they affect the facial and neck muscles - the muscles of the lips, tongue, jaws, eyes, pharynx, throat contract. In some cases, vegetative disorders appear, up to the occurrence of fainting.

ANXIETY, MOTOR ACTIVITY

In addition to extrapyramidal disorders, against the background of taking antipsychotics, akathisia phenomena may occur:

- anxiety, anxiety;
- excited state;
- emotional indifference;
- sleep disturbances, insomnia;
- feeling of restlessness;
- "anxiety in the legs";
- the need to move.

LATE DYSKINESIA

If treatment with neuroleptics is carried out for a long enough time (from 2 years), there is a risk of developing tardive dyskinesia. It is expressed in involuntary movements of the lips, tongue, facial expressions, limbs that cannot be controlled.

DISORDERS OF THE AUTONOMIC SYSTEM

Disorders of the autonomic nervous system can manifest themselves in postural hypotension (a drop in blood pressure during an upright position), dysuric disorders (painful, difficult urination), gastrointestinal disorders (diarrhea, constipation), excessive sweating, weight gain, visual impairment, and impaired work of the cardiovascular system.

Women may develop dysmenorrhea (with an increase in prolactin in the blood), disrupt the cycle, and manifestations of pseudohermaphroditism may occur; in men - gynecomastia, decreased libido, delayed ejaculation, galactorrhea (milk secretion from the mammary glands), hirsutism (excessive hair growth). In rare cases, there is an increased sensitivity of the skin to sunlight and ultraviolet rays, dermatitis, pigmentation and allergic reactions.

SEVERE COMPLICATIONS OF NEUROLEPTIC THERAPY

In cases where the patient is not observed by the attending physician (does not make control visits, does not notify the doctor about changes in the state of health that cause anxiety and concern, does not follow the recommendations for control and diagnostic measures), there is a risk of developing severe complications of neuroleptic therapy, for example:

allergic reactions;

toxic reactions;

hepatitis;

pathology of the organ of vision;

violations of blood biochemistry.

In addition, in the treatment of antipsychotics, there is a risk of developing mental disorders (for example, asthenic-type depression), severe sleep disorders, delirium (patients with organic pathology of the central nervous system, the elderly, children fall into the risk category), epileptiform seizures.

Reception of antipsychotics of any generation should be carried out in accordance with the recommendations of the attending physician. Refusal to take or increase the dosage unilaterally is unacceptable. Control visits are mandatory, including unplanned ones, if there are signs of deterioration in well-being. Diagnostic recommendations, including a biochemical blood test, make it possible to evaluate the effectiveness of therapy and prevent the development of complications.

LIST OF NEUROLEPTIC DRUGS

Depending on the case (the intensity of the manifestation of one or another psychotic symptomatology; the characteristics of the course of the disease), the state of health, contraindications and other important factors from the point of view of therapy, neuroleptic drugs are selected. Their dosages are adjusted in the course of treatment, often there is a change in the drug, symptomatic therapy is prescribed.

FIRST GENERATION NEUROLEPTICS

Among the typical antipsychotics used for the rapid relief of acute conditions, the best known are:

haloperidol;

fluphenazine;

flupentixol;

clopromazine;

chlorprothixene;

levomepromazine;

melperone;

perphenazine;

zuclopenthixol;

sulpiride.

NEUROLEPTICS OF THE SECOND GENERATION

Atypical antipsychotics, because of their improved action profile, are used as the mainstay of therapy in diseases with psychotic symptoms. In clinical practice, the following antipsychotics are most widely used:

amisulpride;

aripiprazole;

clozapine;

olanzapine;

quetiapine;

risperidone;

sertinadol;

ziprasidone.

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