ANTIPSYCHOTICS

Schizophrenia is a disturbance in the metabolic balance of the brain and in neurotransmitter activity at certain brain areas. Although, no "anti-schizophrenic" medicine has been invented so far, the use of available antipsychotic drugs enables remission or alleviation of psychotic symptoms, as well as protection against disease relapses.

Remember!

As early therapy onset as possible is key significant, as well as its appropriate continuation. The compliance with medication regimens five-time reduces the risk of schizophrenia relapse, what presents higher therapeutic efficacy than in case of therapy of many chronic somatic conditions.

Unfortunately, some patients do not understand the necessity of medication in remission period. Their spontaneous withdrawal from therapy impairs their well-being, triggers relapse of psychosis and opens a straight route to subsequent hospitalisation.
Antipsychotics were for many years called neuroleptics - this name is still used and is a synonym of antipsychotic medications. They were introduced in the 50s of the previous age.

Until their introduction, schizophrenia was treated by administration of sedatives or sleeping pills - that only calmed down patients but did not result in regression of symptoms of the illness nor ensured prevention of its relapse.

Since antipsychotic drugs have been known and used for more than 50 years, the mechanisms of their action, the safety of their dosage and adverse effects have been learned very well. Anti-psychotic drugs eliminate schizophrenia symptoms and, in chronic administration, may stabilise the mental state of the patient and largely protect against schizophrenia relapse. Their action reduces mainly the positive symptoms of schizophrenia, while affecting other ones to a lesser extent.

It is worth knowing that ...
The compliance with doctor's recommendations is the most effective method to decline the risk of relapse.

The mechanism of action of anti-psychotic medicines

The mechanisms of action of these drugs are related to their effects on various chemical substances, produced and active in the human brain (so called neurotransmitters), for example, serotonin or acetylcholine. The most important, however, is the effect of these drugs on another neurotransmitter – dopamine.

Remember!

All antipsychotics reduce the stimulation of dopamine receptors, thus enhancing resistance to stress and reducing the symptoms of schizophrenia, mainly positive.

At the same time, many adverse effects of these drugs are also related to their effects on dopamine receptors – this applies particularly to the, so called, classic antipsychotics (classic neuroleptics).

It is worth knowing that ...

The first effects of antipsychotic drugs are expected to emerge after 4 to 6 weeks of therapy.

If symptoms show no visible improvement after this time, the attending physician usually decides to switch over to new medications. With some drugs, the desirable outcome is seen even later – after 2 or 3 months of treatment.

Therefore, therapy should never be discontinued without doctor's
decision. If the response to current therapy is disappointing, the physician should be consulted. If the patient experiences significant side effects, which cannot be controlled with corrective drugs, medications may be changed at any time.

Medical agents, use at schizophrenia onset (the first episode) and in its relapses

Previously only typical, classic antipsychotics were used, while currently, primarily atypical medications are preferred, due to their greater safety and more comfortable treatment for the patient.

Today, all the known rules of treatment of schizophrenia (so-called therapy standards) recommend treatment of early stages of schizophrenia, using only atypical drugs.

This does not apply to clozapine which is introduced only after two unsuccessful treatments with other drugs – it is a recommendation of physicians in most countries of the world, including Poland.

Several rules should be followed in selection of an agent to treat schizophrenia relapse. These are the rules:

- If the patient functioned well on the previous drug, and stopped taking it because he or she felt already cured, it is usually recommended to return to the previous drug in the previous dose.
- If the patient stopped taking the drug because of side effects, especially because of severe extrapyramidal symptoms, one may return to the previous drug at a lower, but still effective dose, or restore its previous dose along with a corrective medication, or one may try to change the classic drug to an atypical drug.
- If the patient did not follow the instructions, associated with taking oral medication, it can be exchanged to the same drug in long-acting formulation (depot).
- If deterioration occurred despite good tolerance and right
dosage, the physician will change the drug to another, with a higher chance of recovery. In many cases this will be an atypical antipsychotic agent.

Apart from these rules, the physician's experience is important, along with the patient's proposals resulting from his or her previous treatment.

Types of antipsychotic medications

Depending on dosage frequency, these medicines can be divided into the following two groups:

- oral, short-acting – daily doses,
- long-action injections – doses administered in longer time intervals

Another division is associated with the mechanism of action. The medicines are divided into two groups:

- typical (classic),
- atypical (second generation).

<table>
<thead>
<tr>
<th>Typical (classic) antipsychotics</th>
<th>Atypical antipsychotics (newer generation); anti-psychotic medicines of the second generation</th>
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</thead>
<tbody>
<tr>
<td>they mostly reduce positive symptoms</td>
<td>they reduce negative symptoms and symptoms of disorganisation more effectively that typical drugs, they also exert anti-depressant effects and reduce cognitive deficits</td>
</tr>
<tr>
<td>their efficacy is mainly related to their impact on dopamine receptors</td>
<td>their broad profile of action (and therefore impact on the regression of various types of symptoms) is associated with the fact that they also affect other neurotransmitters, such as serotonin</td>
</tr>
<tr>
<td>they induce typical side effects – so called, extrapyramidal symptoms</td>
<td>they cause mild or none extrapyramidal symptoms</td>
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<tr>
<td>they rarely cause weight gain</td>
<td>they more often cause body weight gain</td>
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<tr>
<td>some of them (haloperidol, flupentixol, zuclopentixol) are available only in depot formulation</td>
<td>risperidone and olanzapine are their long-acting representatives</td>
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**Comparison of typical and atypical antipsychotic medicines**

Until the introduction of the first atypical drugs (the 1970s – 1990s), classic drugs were used in each case of schizophrenia.
Currently, due to the introduction of many atypical drugs, which surpass the classic drugs as regards beneficial effects on symptoms of disorganization, cognitive, depression and negative symptoms; and because of the lower risk of side effects, especially of the, so-called, extrapyramidal symptoms, the frequency of their use has decreased significantly.

Classic antipsychotics are usually chosen in the following situations in the course of psychosis treatment:

- when a patient previously responded well to these drugs, so they were not only effective and safe, but also accepted by the patient;
- when a patient is non-compliant in the course of treatment, interrupts treatment – then it may be appropriate to use sustained release drugs, the so-called depot drugs. Up to now it was only possible with the use of classic drugs – currently there is also a long-acting injectable atypical antipsychotic available;
- when a family member of the patient suffered from psychosis and responded well to classic antipsychotics and poorly responded to atypical drugs or responded with side effects.

Atypical antipsychotic medicines

They were introduced in the 70s of the 20th century and are increasingly used in the treatment of psychoses, especially in the treatment of patients after hospital discharge. At present, in Poland, the following atypical antipsychotic medicines are used: clozapine, sulpiride, risperidone, olanzapine, quetiapine, amisulpride, sertindole, aripiprazole and ziprasidone. These drugs largely differ from one another (especially in terms of side effects), more than classic antipsychotics between one another.

Remember!
These are drugs that usually cause only minimal extrapyramidal
symptoms. On the other hand, they exert significant effects on negative, depressive, cognitive and disorganization symptoms associated with schizophrenia.

Since 1st December 2007, atypical medicines have been available for schizophrenic patients at a flat rate.

### Adverse effects of anti-psychotic medicines

It is worth knowing that ...
A significant number of people taking these drugs develop the, so-called, extrapyramidal syndromes (EPS).

They usually appear after dose increase or in chronic administration. See the table below for the most common four types of the extrapyramidal syndrome.

<table>
<thead>
<tr>
<th>Extrapyramidal syndrome</th>
<th>Its symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson's syndrome</td>
<td>tremor (usually hands, head), muscle rigidity, bradykinesia</td>
</tr>
<tr>
<td>dystonias</td>
<td>sudden muscle spasms, such as bending the neck, sudden upward movement of the eyes, and even spasms impeding swallowing</td>
</tr>
<tr>
<td>akathisia</td>
<td>inability to sit or stand still, so-called, restless legs syndrome</td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td>strange, rhythmic involuntary movements, most often of the face, continuous lip movements (so-called rabbit syndrome) rhythmic tongue movements</td>
</tr>
</tbody>
</table>

When using weaker classic drugs one may also expect, especially at the beginning, sudden drops in blood pressure, and thus dizziness, or even fainting episodes. They occur particularly when standing up, so at the beginning of treatment patients should have pressure measured in both the supine and sitting position, and be instructed that when getting out of bed they should do it slowly and spend longer time (about a minute) sitting with legs taken out of bed.
Another side effect, which can be disruptive, especially at the beginning of the therapy, is excessive daytime sleepiness. Other side effects of the drugs in this group are relatively rare and the physician should evaluate whether they actually occur in a particular case.

Prophylactics of extrapyramidal symptoms

Remember!
It is certainly better to prevent their occurrence, than to treat them. The best way to prevent extrapyramidal symptoms is the use of drugs which rarely cause them, i.e. newer-generation (atypical) antipsychotics.

However, in many patients, typical drugs are the drugs of choice - then it is reasonable to consider the following issues (only a doctor decides):

- replacement of strong typical drug by its weaker formulation,
- application of correcting agents,
- consider dose reduction,
- it may, however be necessary to replace the typical drug by an atypical formulation..

At the same time, the patient should keep in mind that it is very important for the physician to get information about the severity of extrapyramidal symptoms – thanks to this the physician can adjust the therapy so that treatment is effective and safe.

Metabolic syndrome
It is worth knowing that ...

Metabolic syndrome is a term, coined by general practitioners to describe metabolic disorders, particularly regarding the level of sugar and lipid levels, including cholesterol.

In the era of the second generation antipsychotics, it has turned out that many patients with schizophrenia treated with these drugs may have impaired glucose and lipid metabolism up to fully symptomatic metabolic syndrome which comprises:

- "visceral" obesity – waist circumference > 102 cm in men and 88 cm in women,
- significantly increased body weight with the body mass index (BMI) equal or higher from 25 (BMI is calculated by dividing body weight by the square of body height in metres, e.g., when body weight is 99 kg and body height - 1.85 m, then 99 : 1.85^2 = 99 : 3.42 = 28.9, i.e., BMS equals in this case almost 29),
- significantly increased level of the "bad" cholesterol (LDL-C),
- increased level of triglycerides,
- significantly increased blood sugar level (hyperglycaemia).

Certainly, in most patients, even those treated with antipsychotic medications with the greatest risk of metabolic changes, only individual symptoms of metabolic syndrome may occur, but some of them may demonstrate fully symptomatic metabolic syndrome.

It is worth knowing that ...

In order to prevent the risk of metabolic disorders or metabolic syndrome, resulting from adverse effects of the use of antipsychotic drugs, it is necessary to significantly change diet and increase physical exercise (effort).

It is, however, difficult for the majority of people, both healthy and schizophrenic. Therefore, one must follow certain rules for early detection of metabolic disorders and choice of antipsychotic drugs.
associated with a greater or lesser risk of metabolic syndrome. These are the rules:

BMI

- should be monitored in all patients on antipsychotic medication,
- weighing a patient at each visit during the first 6 months after initiation of antipsychotic therapy,
- increase of BMI by 1.0 is an indication to change the medication to a drug with lesser risk of weight gain.

Waist circumference:

- evaluation as in BMI;

Diabetes

- fasting blood glucose assessment before starting any antipsychotic therapy,
- patients with a high risk of developing diabetes should be monitored (fasting glucose or HbA1c) in the first four months and then, at least, once a year.

One should also remember that the highest risk of body weight increase, lipid disorders and hypoerglycaemia, sometimes also diabetes, is associated with olanzapine, amisulpride and quetiapine; risperidone and sertindole are neutral for these metabolic symptoms, while aripiprazole and ziprasidone induce metabolic disorders most rarely.
Hyperprolactinaemia and its symptoms

Prolactin is a hormone secreted by the pituitary gland serving in women to sustain pregnancy, initiate and maintain lactation. Women have higher levels of prolactin than men, especially during pregnancy and after birth, when breastfeeding. Prolactin level is controlled by dopaminergic receptors located nearby.

It is worth knowing that ...

In the case of administration of a drug acting as dopamine antagonist, and that is how antipsychotics act, there is an increase in prolactin levels, which were earlier "under control" of the normally functioning dopaminergic system.

This increase in prolactin levels is called "antipsychotic-induced hyperprolactinaemia" (AIHP). Hyperprolactinaemia causes menstrual disorders in women, up to amenorrhoea. Both in women and in men, hyperprolactinaemia may cause swelling or tenderness of breasts, or even galactorrhoea, and sexual disorders.

Chronic hyperprolactinemia, particularly in women can result in symptoms of osteoporosis. AIHP is mostly a result of the application of classic neuroleptics, in particular in the form of depot. Out of the latests anti-psychotic drugs, AIHP may occur after oral risperidone (in daily dose > 6-8 mg) or amisulpride.

In the event of the occurrence of symptoms which may indicate AIHP it is sometimes necessary to determine the level of prolactin.
in the blood serum, and in the case of its significant and sustained increase - decrease of the dose of an antipsychotic drug administered so far, replacement of the drug with an atypical drug with a lower risk AIHP or inclusion of a drug with dopaminergic activity.

At the same time, it should be remembered that hyperprolactinaemia may have a completely different cause, for example, it may simply be a physiological sign of pregnancy or, which is of course rare, a symptom of a tumour of the pituitary gland.

**Sexual disorders in schizophrenia**

It is worth knowing that ...

Problems with sexual dysfunction, actual as regards patients and decision-making in case of their doctors, seem to be particularly important for patients with schizophrenia, namely for two reasons.

Firstly, most of antipsychotics substantially affect the biological basis of sexual functioning due to their antidopaminergic effect. Secondly, people with schizophrenia, due to their problems with communicating their complaints and worse appearance, may not be able to inform about their sexual functioning.

Do you know that ...

50% of men and 30% of women with schizophrenia reveal sexual
dysfunction.

60% of women and only 30% of men with schizophrenia have experienced intimate relationships.

Sexual problems of schizophrenics apply in particular to men and include: More and more research reflects the impact of antipsychotics on sexual functions. Recent studies also suggest that the adverse effects on the sexual sphere may be associated with deterioration in quality of life and poorer adherence to recommendations, which in turn usually leads to an increase in the frequency of relapses.

Research also suggests that the burden of the adverse effect of antipsychotics on sexual functions may be equal to the burden of some psychotic symptoms. Sexual dysfunctions, both in women and in men on anti-psychotic therapy, are usually associated with hyperprolactinemia.

How long should antipsychotics be taken?

An important issue here is taking antipsychotics in remission, so when the patient usually feels good, and the patient and his or her family believe that more medication is not needed. A sufficiently long period of taking these drugs protects the patient against relapse of schizophrenia. Medication should never be discontinued without first consulting the prescribing physician.
It is worth knowing that ...

Medication break is absolutely contraindicated in remission of schizophrenia. Regular and long-term therapy with antipsychotics is the most effective method to protect the patient from relapse.

The duration of remission in schizophrenia depends on the number of previous episodes, response to treatment, patient's support, resistance to stress, and many other factors. If remission continues long enough and is not accompanied by any stressful circumstances or a co-morbidity, the prescribing physician may be consulted about possible modifications or temporary discontinuation of antipsychotic medications. However, the risk of relapse should be weighted against possible benefits.

Dear Patient!

Do you feel quite ok during medication? Are you tired of daily swallowing of tablets which remind you about the experienced psychosis? Do you suffer of adverse effects? If something like this happens, consult your doctor – together you will easier come to ways to solve these problems. Do not break the therapy yourself!

Administration routes for anti-
psychotic drugs

Classic drugs may be used in oral tablets, in fluid via i.m. injections and in depot injections.

All the oral formulations require daily dosage or even several times a day.

Neuroleptic of depot type and long-acting anti-psychotic drugs need more rare dosage - usually per 2-4 weeks.

Oral drugs for daily use

It is worth knowing that ...

All the anti-psychotic drugs are available in tablets or capsules - some of them as solutions as well.

In order to maintain effective (therapeutic) concentration of medicine in blood, it has to be used every day in equal time intervals, some of them requires several doses a day, what may impede regular medication. It is then good to create a system of "reminders" or ask your relatives to help maintain the required therapeutic regimen.

It is worth knowing that ...

In case of schizophrenia, many patients changes dosage levels
without consultation with their doctor. It happens that caregivers find medicines in drawers, in bed or in flowerpots - usually when the patient goes to hospital with subsequent relapse.

Thus a number of caregivers, who aim at helping their patients in regular medicine intake, feel reluctance or even demonstrates symptoms of aggression. In medical literature, such situations are referred to as the functionality of "home medicinal police". In such situations, it is important to talk with a doctor about forms of psychotropic drugs which do not require daily use (more details on this issue can be found below and in the fragment "Long-acting drugs" in the article "Modern therapeutic forms").

Long-acting drugs (DEPOT)

It is worth knowing that ...

So far, we have presented a group of several typical neuroleptics in formulations, enabling their slow release after intramuscular injection.

These include oil solutions of medicinal agents, administered via injection into the gluteus. In result, the patient receives a dose of the medicine in almost constant concentration, just as in daily oral doses. Injections are made every 2–4 weeks, as drug concentrations remain stable during such time intervals.

In this way, the patient does not need to remember every day about taking a given number of tablets, while the need for
repeated injection allows the physician, the patient and his or her family to supervise the process of therapy. The number of side effects of depot neuroleptics is not higher than after oral administration. The medicinal agents available in depot forms, include haloperidol, flupentixol and zuclopenthixol.

Drugs in depot form are now more and more often replaced by new long-acting therapies - long-acting atypical drugs.

**It is worth knowing that ...**

Long-acting atypical drugs combine in their activity the features of atypical antipsychotic drugs: high efficacy against positive, negative and cognitive symptoms of schizophrenia, with convenient dosage (1-2 doses per month). With their advantages, the long-acting antipsychotics have become in many countries the basis in long-term treatment of schizophrenia. These drugs area also available in Poland, considerably facilitating the treatment of schizophrenic patients.