THE CHOICE OF ANTIPSYCHOTICS: CONTEMPORARY KNOWLEDGE

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ABSTRACT

Antipsychotics are a group of psychoactive drugs that eliminate delusions and hallucinations, improve the ability to test reality and lead to the reintegration of psychological functions and enable a return to reality. In addition to antipsychotic, they also have sedative, anxiolytic, antidepressant, antimanic stabilizing, anti-suicidal and antiemetic effects, therefore the drugs are used in the treatment of various other non-psychotic disorders. The objective of this paper is to point out the contemporary findings in the best choice of antipsychotics. We live in the period of psychopharmacology's rapid progress and our possibilities in the treatment of psychotic disorders are increasing. In recent decades, treatment with antipsychotics has been significantly improved due to the development of new antipsychotics with better therapeutic effect and safer profile of side effects. The basic mechanism of action of antipsychotics is dopamine receptors, with an effect on the noradrenaline, serotonin, histamine, adrenergic, and cholinergic systems, and indirectly on the gamma-aminobutyric acid and glutamine system. All this makes the mechanism of action of antipsychotics extremely complex. There are several different subdivisions of antipsychotics, and in clinical practice the most common division is the so-called typical and atypical. Typical antipsychotics that achieve their mechanism of action by blocking the D2 receptor show effectiveness in the treatment of positive symptoms of schizophrenia, but have a much lower effect in the treatment of negative, affective and cognitive symptoms. They often have significant side effects. Atypical antipsychotics work on both positive and negative symptoms of psychosis. In severe forms of psychosis, they are often insufficient in the treatment of positive symptoms, so we are forced to use a combination of antipsychotics. Although antipsychotic monotherapy is the ideal therapy, in practice we are often forced to combine two or more antipsychotics, as well as combine antipsychotics with other groups of psychopharmaceuticals. It is not easy to answer whether combinations of antipsychotics are useful or not. The key to success is an individual approach, careful selection of the type and dose of antipsychotics, and the inclusion of psycho and socio-therapeutic methods that are indicated in each case individually.

Keywords: antipsychotics, choice, contemporary knowledge.

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INTRODUCTION

Psychopharmacotherapy is immensely moving forward, and today has specific, selective and planned synthesized drugs and precisely knows their molecular level of function, targeted symptoms and mental disorders. The continuous adoption of new knowledge about psychopharmaceuticals has improved treatment, returned mental patients to their personal milieu, and promoted biological psychiatry as a key branch of psychiatry. The revolutionary contribution of the psychopharmacotherapy era in the treatment of mental patients is the transformation of the atmosphere of mental hospitals into an atmosphere almost identical or even better than the atmosphere on wards for physical diseases. As a results of the general progress of psychiatry, and above all the possibilities of modern psychopharmacotherapy, psychiatrists (in a team with other mental health experts) are now able to make a minor or major recovery in almost all patients, and more often a complete recovery.

Today, the treatment to mental disorders alongside the ever-increasing progress of psychiatry and better understanding of mental disorders is based on two fundamental principles:

1. Multidimensional (several therapeutic procedures are used simultaneously)
2. Integral (the treatment affects both the patient and the environment).

Antipsychotics are a group of psychoactive drugs for the treatment of various forms of psychosis, which eliminate crazy ideas and hallucinations, improve the ability to test reality and lead to the reintegration of psychological functions and enable a return to reality. In addition to antipsychotic, they also have sedative, anxiolytic, antidepressant, antimanic stabilizing, anti-suicidal, and antiemetic effects, so they are used in the treatment of various other non-psychotic disorders. There are several groups of different antipsychotics and they are divided in various ways, and recently the most common division is the so-called typical and atypical (1-3).

In the selection of antipsychotics, it is important to keep in mind that different antipsychotics can cause clinically specific effects in different patients, and these effects are not always well studied in randomized clinical trials. This means that average clinical effects in clinical trials may not be the best indicator of the range of possible clinical responses in individual cases. The recommended optimal doses from clinical trials often do not coincide with the optimal doses used in clinical practice (too high for some drugs, too low for others). Research almost always compares monotherapy and placebo, and in practice many patients use two antipsychotics or antipsychotics and other psychotropic drugs (4). In practice, this means that evidence-based medicine is not always completely feasible and useful for the patient.

CREATIVE PSYCHOPHARMACOTHERAPY

During and after the Decade of the Brain (1990-1999), there was a great expansion of psychopharmacotherapy with the appearance of many different, often

controversial concepts of psychopharmacotherapy paradigms and therapeutic algorithms. The registration of a large number of new psychopharmaceuticals with antipsychotic effects significantly contributed to the emergence of a psychopharmacotherapy renaissance and the overcoming of therapeutic nihilism in the treatment of schizophrenia.

The treatment of schizophrenia must be comprehensive and multidimensional

The clinical complexity of mental disorders requires assessment, understanding and formulation through four fundamental perspectives if we wish to obtain a reliable diagnostic model as well as effective and comprehensive therapy. There are four fundamental perspectives: 1. disease perspective, 2. dimensional perspective of personal vulnerability and resilience; 3. behavioral perspective and 4. narrative perspective. The mentioned perspectives do not exclude one another, but complement each other in the creation of a holistic diagnostic and therapeutic model. At different stages of treatment, one perspective is usually primary, and others are secondary, but also important. Thus, for example, in the acute stage of treatment of schizophrenia or bipolar disorder, the primary perspective of the disease is to determine the appropriate psychopharmacotherapy with the aim of achieving fast and complete remission as soon as possible. In the psychopharmacotherapy phases of maintenance and prevention of a new episode of the disease, the behavioral perspective (behavior change), dimensional (change of mental model) or life story perspective (creation of a new life scenario) are primary, where psychopharmacotherapy is extremely important, but not sufficient. Complete treatment includes all four perspectives in understanding, defining and treating any clinical problem or disease, including schizophrenia.

Creative psychopharmacotherapy of schizophrenia is based on an individualized approach

A whole series of various factors can affect the individually different therapeutic response and treatment outcomes, which should be taken into account when selecting the optimal psychopharmacotherapy for each individual patient. When selecting psychopharmaceuticals, it is important to consider: 1. specifics of the clinical picture and the course of the disease; 2. patient's previous experience with medication; 3. significant comorbid conditions; 4. possible side effects; 5. possible pharmacokinetic variations in patients; 6. possible interactions with other drugs; 7. the experience of close relatives with drugs; 8. individual patient preference; 9. availability of the drug for the patient.

Creative psychopharmacotherapy includes drugs optimally adapted for each stage of treatment

We usually distinguish three phases of schizophrenia treatment: 1st phase of treatment of an acute episode of the disease with the aim of calming down and eliminating symptoms as quickly as possible, 2nd phase of stabilization with the aim of maintaining the achieved results and further improvement of the patient's health, and 3rd phase of maintaining

remission and preventing relapse of the disease, that is, the prevention of the occurrence of a new episode of the disease. At each stage of treatment, it is necessary to choose suitable psychoactive drugs that enable the control and elimination of as many symptoms as possible, that is, therapeutic problems. The drugs that led to the successful treatment of the acute phase of the disease may not always be the optimal choice for maintenance therapy.

Creative psychopharmacotherapy increases benefit and reduces the risk during treatment

A creative approach in psychopharmacotherapy is always aimed at increasing the patient's well-being and reducing the risk of undesirable drug side effects and treatment complications. Despite a large number of new antipsychotics, monotherapy is not successful in a significant number of patients with schizophrenia, and undesirable side effects often compromise treatment. Optimal combinations of psychoactive drugs can achieve desirable therapeutic synergism, but also prevent or eliminate certain side effects, which can significantly contribute to complete remission in a large number of patients with schizophrenia.

Rational choice of antipsychotics

Although still empirical, nowadays we know a lot more about the nature of schizophrenia and the mechanisms of action of antipsychotics. The choice of treatment depends on a whole series of different factors; the clinical picture and severity of symptoms, the availability of antipsychotics, the profile of side effects, possible interactions with other drugs, the presence of other physical and neurological diseases, etc. In the acute phase, an antipsychotic or their combinations should be chosen to cover as many symptoms as possible, and to be tolerable as possible. While combinations of antipsychotics cannot usually be avoided in the acute phase, in maintenance therapy one should always strive for monotherapy including newer antipsychotics with good tolerance taken in a single daily dose (e.g. paliperidone or olanzapine).

Antipsychotics in a sufficient dose and for sustainable period of time

The purpose of treatment is not only to suppress or eliminate the symptoms of schizophrenia, but also to stop the schizophrenic process, to eliminate the causes that can lead to a relapse of the disease, and prevent suicidal and self-destructive behavior, reintegrate the patient into the community as well as possible, enable psychosocial development and the best possible quality of life. Therefore, the optimal choice of antipsychotics is as important as the sufficient dose and duration of therapy. Hypo dosing of antipsychotics causes insufficient therapeutic responses and absence of complete remission, while premature discontinuation and excessive dose reduction are the most common causes of symptom relapse and disease recurrence.

Optimization of treatment by dose adjustment

The optimal dose should be found for each individual patient, which achieves the best therapeutic effect with the least, or, if possible, without significant side effects. If high doses are necessary to achieve therapeutic effects, then they

should be gradually reduced as soon as the therapeutic effect stabilizes (5-8).

CHOICE OF ANTIPSYCHOTICS

Factors influencing the choice of antipsychotics are: severity and type of clinical picture, patient characteristics, presence of comorbidities, experience of the clinician, previous response to treatment, tolerability profile of antipsychotics. The ideal therapy for psychotic disorders would be antipsychotic monotherapy. But, in everyday practice, two or more antipsychotics are often used. Data from the literature show that in Norway this is present in 35.6% (9) and in Spain 55.5% of cases (10).

There is no complete agreement among scientists regarding treatment in the prodromal phase, but most advocate that different psycho and socio-therapeutic methods should be the initial response. Some experts believe that treatment should be started with lower doses of atypical antipsychotics.

In the treatment of the first psychotic episode, it is recommended to introduce an antipsychotic of the second or third generation as the first line of therapy as soon as possible. It is started with a low dose that is carefully titrated until the minimum effective dose of the drug is reached.

In the case of a repeated episode or exacerbation of the disease, it is recommended to increase the dose of the antipsychotic to which the patient previously had a favorable therapeutic response, and if necessary, up to the necessary upper limit of the recommended therapeutic dose.

In maintenance therapy after the first episode, antipsychotics should be prescribed for at least one year, for the second episode for up to five years, and for a repeated psychotic episode for life (11).

Combinations of antipsychotics should be used in psychotic patient with severe symptoms, long duration of illness, therapeutic resistance and long hospitalizations. Combinations are used to improve the effect and/or reduce unwanted reactions (12,13).

The choice of antipsychotics in relation to the unwanted effect is not at all easy and is completely personalized, i.e. custom for each patient. There are studies that indicate that ziprasidone, aripiprazole, risperidone and paliperidone work best in relation to unwanted sedation. In relation to unwanted weight gain, aripiprazole and ziprasidone are the most preferred, and in relation to extrapyramidal symptoms, clozapine, quetipin, ziprasidone, aripiprazole and olanzapine. Due to unwanted sexual disturbances, risperidone and paliperidone should be avoided. Unwanted anticholinergic effects are most often shown by risperidone, ziprasidone, aripiprazole and quetipine (14).

Long-acting antipsychotics

The clinical course of the disease can be divided into presymptomatic, prodromal, psychotic and chronic phases. The aspiration of today's psychiatry is to identify the patient at the earliest stage in order to prevent further progression of the disease with adequate therapy. The goal of schizophrenia treatment is clinical, social and personal remission of the patient and prevention of disease relapse (5). Antipsychotics are administered orally and intramuscularly. Treatment usually commences with one of the second-generation antipsychotics in oral form, since, despite the listed side effects, they greatly contributed to the treatment of

schizophrenia and allow 80% of patients to go into remission after the first psychotic episode. However, 80% of patients treated with oral therapy experience a relapse within five years, and it has been shown that the long-term effectiveness of such treatment is limited due to patient non-cooperation (15). As many as 40-60% of patients treated with oral antipsychotics stop taking their medications as prescribed within two years. There are many reasons for patients not taking their medication. Individuals unintentionally forget to take the medicine, some have a problem with understanding the instructions, while some consciously refuse to take the medicine due to prejudice towards their illness, stigma, fear of dependence and responsibility, occurrence of side effects, lack of information, but also due to mental disorganization and their own ambivalence. Since a positive correlation has been observed between patients' long-term consumption of therapy and a reduced risk of relapse, the fight against refusing therapy of the biggest challenges of psychiatry today (16). For this reason, there was a need to develop a strategy for the long-term treatment of schizophrenia and find a drug that would combine the positive characteristics of oral therapy and provide the possibility of maintaining two continuous drug concentrations in the blood and improve cooperation and thus reduce relapses, which led to the development of long-acting antipsychotics (17). They are administered intramuscularly, every two to four weeks. We have at our availibility: Haldol depot (haloperidol decanoate), Moditen depot (fluphenazine decanoate), Rispolept Consta (risperidone microspheres), and Zypadhera (olanzapine palmoate hydrate). Despite many potential advantages, the use of long-acting antipsychotics is reserved for patients who stop taking therapy, patients with multiple relapses, and for those who request therapy themselves (18), thus they are rarely used in clinical practice. Research shows that in many countries the proportion of patients treated with long-acting antipsychotics does not exceed 25% (19).

One of the main advantages of this type of antipsychotic therapy is the possibility of early recognition of discontinuation of therapy or non-compliance with treatment instructions, which is not the case with oral therapy. This way, the doctor can contact the patient if he misses an appointment for receiving therapy and try to influence the patient’s cooperation. The method of dosing the drug once every two to four weeks is considered an advantage by patients because, in addition to being easy to use, they do not have to think about taking the therapy every day and potentially hesitate about it (20).

Antipsychotics and complementary medicine

A new type of psychiatry, called integrative psychiatry, selectively includes elements of complementary and alternative medicine in practical work (21, 22). Depending on the type of schizophrenia or another psychotic disorder, the phase of the disease or the clinical picture in the phase of remission, the wishes and needs of each patient, and the cultural characteristics of the environment in which he lives should be taken into account. It is desirable to recommend some form of complementary therapy at some stage of the disease. It is certain that there are a large number of patients for whom modern medical methods and the listed complementary

methods can help, such as some type of diet and nutritional therapy, herbal therapy, manipulative therapy or, for example, energy therapy. It certainly cannot be harmful if a properly medicated schizophrenic patient goes to bioenergetic massage, takes certain herbal medicines or a multivitamin product. The most common natural medicines used in the treatment of schizophrenia are: omega 3 - fatty acids (DHA and EPA), ginkgo - ginkgo biloba, lecithin, glycine, gluten, multivitamin products. There is growing evidence that this type of complementary therapy helps in healing. They are not a substitute for traditional treatment methods. With appropriate use, the severity of the appropriate approach to the treatment of schizophrenia is not diminished. They should be recommended with caution and aligned with the therapy recommended by modern medicine for people who do not like or have difficulty accepting "chemical" drugs as additional therapy to standard psychoactive drugs (23-25, 1).

CHOICE OF ANTIPSYCHOTICS – OUR EXPERIENCES

There is no ideal antipsychotic. A well-chosen antipsychotic administered in a therapeutic dose must control psychotic symptoms and cause as few side effects as possible. The choice should be made individual, taking into account the symptoms of the disease of the individual patient and the profile of the side effects of the drug.

In the treatment of the first episode, which is characterized by a relatively mild clinical picture, we almost always use outpatient treatment. In drug therapy, we most often use an atypical antipsychotic, monotherapy with possible combination with an anxiolytic... (Risperidone, Olanzapine, Quetipain, Aripiprazole... Diazepam, Bromazepam)

In the treatment of repeated psychotic episodes or Sch psychosis characterized by a relatively mild clinical picture, we most often use an atypical antipsychotic or a combination of atypical or atypical and typical antipsychotic. (Risperidone, Olanzapine, Quetiapine, Aripiprazole...+ Haloperidol, Clozapine, Promazine...)

In the treatment of psychotic disorders characterized by a severe or very severe clinical picture in the initial phase, we usually use a typical antipsychotic in combination with another typical or atypical antipsychotic along with an anxiolytic, a mood stabilizer... (Haloperidol, Fluphenazine, Promethazine, Clozapine, Risperidone, Olanzapine, Diazepam...)

CONCLUSION

When prescribing antipsychotics, a rational choice and a personalized approach are very important in order to obtain the best therapeutic effect and as few as possible side effects. Older antipsychotics often have side effects in the form of neuroleptic phenomena (akathisia, dystonic reactions, akinesia, tardive dyskinesia...), and newer antipsychotics cause various manifestations of metabolic syndromes (obesity, hypertension, hyperglycemia, hypertriglyceridemia, hypercholesterolemia).

When dosing antipsychotics, it is important to know that they have a wide therapeutic range, and when determining the dose, the experience of a psychiatrist is also important in order to determine an adequate effective dose without or with as few side effects as possible. Once started,

treatment with antipsychotics often lasts a long time, sometimes lifelong. The purpose of extended treatment is to suppress psychotic symptoms and prevent relapses of psychotic illness. A special advantage in extended treatment is the so-called retard and depot forms of the drug that are usually prescribed weekly or monthly. If possible, it is best to treat a psychotic patient with only one antipsychotic, and if necessary, two or more antipsychotics can be combined. Antipsychotics can be combined with anxiolytics, hypnotics and mood stabilizers. The combination with antidepressants is rarely justified and most often incorrect. Antiparkinsonian drugs should only be given in case of side effects, and never as a preventive measure. For patients who do not like or have difficulties in accepting standard antipsychotic therapy, drugs and methods recommended by science-based complementary medicine can be recommended as additional therapy.

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IZBOR ANTIPSIHOTIKA: SUVREMENE SPOZNAJE

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SAŽETAK

Antipsihotici su skupina psihoaktivnih lijekova koji otklanjaju sumanute ideje i halucinacije, poboljšavaju sposobnost testiranja realiteta i dovode do reintegracije psihičkih funkcija i omogućavaju povratak u realnost. Osim antipsihotičnog imaju i sedativni, anksiolitički, antidepresivni, antimanični stabilizirajući, antisuicidalni i antiemetični učinak pa se primjenjuju u lječenju raznih drugih nepsihotičnih poremećaja. Cilj ovog rada je ukazati na suvremene spoznaje u izboru antipsihotika.

Živimo u razdoblju brzog napretka psihofarmakologije i naše mogućnosti u liječenju psihotičnih poremećaja su sve veće. Posljednjih desetljeća liječenje antipsihoticima je značajno unaprijeđeno zbog razvoja novih antipsihotika s boljim terapijskim učinkom i sigurnijim profilom nus pojava. Bazični mehanizam djelovanja antipsihotika su dopaminski receptori uz djelovanje i na noradrenalinski, serotoninski, histaminski, adrenergički i kolinergički sustav te posredno i na gama-aminomaslačnu kiselinu i glutaminski sustav. Sve to čini mehanizam djelovanja antipsihotika izrazito kompleksnim. Postoji više različitih podjela antipsihotika, a u kliničkoj praksi najčešća je podjela na tzv. tipične i atipične. Tipični antipsihotici koji svoj mehanizam djelovanja ostvaruju blokadom D2 receptora pokazuju učinkovitost u liječenju pozitivnih simptoma shizofrenije ali u liječenju negativnih, afektivnih i kognitivnih simptoma imaju puno manji učinak. Oni nerijetko imaju značajne nus pojave. Atipični antipsihotici djeluju i na pozitivne i negativne simptome psihoza. Kod teških oblika psihoza oni su često nedovoljni u liječenju pozitivnih simptoma pa smo prisiljeni na kombinaciju antipsihotika. Iako je monoterapija antipsihotikom idealna terapija u praksi smo nerijetko prisiljeni kombinirati dva ili više antipsihotika, kao i kombinirati antipsihotike s drugim skupinama psihofarmaka. Nije jednostavno odgovoriti jesu li kombinacije antipsihotika korisne ili nisu. Ključ uspjeha je individualnom pristupu, pažljivu izboru vrste i doze antipsihotika te uključivanje psiho i socioterapijskih metoda koje su indicirane u svakom slučaju individualno.

Ključne riječi: antipsihotici, izbor, suvremene spoznaje.

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