RECEPTOR PROFILES OF ATYPICAL ANTIPSYCHOTIC MOLECULES

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We present the pharmacological elements and the receptor profiles of the latest generation antipsychotics, directly related to the applicability in clinical practice; a study of the specialized literature in the molecular registry, the presentation of the neuropil, the mechanisms of interhemispheric and interneuronal disconnection involved in schizophrenia, refers to medical applications with pro-functionality effects versus adverse reactions of atypical antipsychotics located at the sedative or incisive pole. Various receptor profiles are presented, together with recent pharmacological molecules and their action in restoring the judgment (pro-cognitive effects) of the medication in schizophrenia versus the types of receptor involved in adverse reactions.

Keywords: antipsychotics, dopaminergic receptor, functionality, adverse reactions, negative phenomenology

1. Introduction

Antipsychotic drugs are very different, similar in class, but very different between classes.

It is known that depot injectable medication for patients with schizophrenia increases the quality of life [1]. However, there is a need to quantify, measure functionality, which has necessitated the design of a functional index of antipsychotics in schizophrenia.

The functionality index of an antipsychotic is a concept from 2019 and it expresses as a percentage the pharmacodynamic capacity (the one given by the mode of action on the receptors) corroborated with the comfort of administration against a maximum theoretically possible [2]. It considers how the molecule acts on the receptors, the degree of action and the comfort of administration.

The patient itself, even in the absence of any medication, also has a degree of functionality. With different medicines, we improve more or less of this functionality affected by the disease [3].

If the premorbid maximum is possible, we carry this potential as high as possible with the optimal drug. We refer to efficacy as well as adverse effects.

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In this direction, new antipsychotic molecules are currently being developed. There are clinical studies on animals, where much more rudimentary you can quantify the functionality [4].

Modern antipsychotics have been obtained starting from the idea of maximizing the incisive effects regarding the "attack" on psychotic productivity (action on D2 receptors), along with improving negative phenomenology (action mainly on D3 receptors and in subsidiary on D4 - whose function is less known), with the minimization of adverse reactions. Many modern antipsychotics are caused by the cutting of a chain (see Olanzapine derived from Clozapine by cutting of a side chain), the purpose being to cancel the effects that "hit" the corporality (predominantly the spinal cord - agranulocytosis).

2. Methods

We start from the study of the specialized literature that involves elements of pharmacology, pharmacodynamics and pharmacokinetics, mainly the multimodal study of the receptors involved in the action of atypical antipsychotics (with minimal reference to the typical ones - classical neuroleptics).

We follow the analysis of some clinical studies performed in recent years on certain atypical antipsychotics, presenting comparative results and references to molecules that involve variants of depot, the aim being to increase the functionality of the patient with schizophrenia and his quality of life.

The article also presents the modern literature of neuroanatomy and brain neurophysiology, with an emphasis on neuropil disruption, considering the glutamatergic toxicity, this being the topical concept in the pathology of schizophrenia, compared to previous years where the focus was exclusively on dopaminergic growth in the synaptic cleft.

The method used is the analysis of modern literature from a molecular perspective, passing through clinical pharmacology and reaching aspects of medical semiology encountered in schizophrenia, with reference to the area of tertiary prophylaxis, as a link between molecularity and outcome with applicability in recovery medicine.

3. Results

3.1. The receptor profiles of typical antipsychotics

Mechanisms of action: dopaminergic D_2 agonism, muscarinic cholinergic agonism, histaminergic H_1 agonism, alpha1 adrenergic antagonism

They act on D_2 receptors, but also on other dopaminergic agonists, thus talking about muscarinic cholinergic agonism, histamine H1 agonism, $alpha_1$ adrenergic antagonism.

Haloperidol blocks D_2 receptors, with the risk of acute dystonia, which is the incisive pole of the Lambert-Revol scale [5]. At the other pole there is Levomepromazine, respectively Chlorpromazine, which acts on M_1, H_1 and $alpha_1$, which causes sedation and hypotension ("1" receptors produce sedation).

Blocking M_1 receptors means improving extrapyramidal syndrome. Levomepromazine and Chlorpromazine have lower extrapyramidal effects than Haloperidol, the other important effect of these drugs being sedation.

The negative effects generated by M_1 receptor blockade are: sedation, cognitive impairment (because acetylcholine receptors are blocked, dry mouth feeling, constipation, visual disturbances, increased appetite, with weight gain (eg Levomepromazine, including Quetiapine, Olanzapine and Clozapine), dizziness, orthostatic hypotension (also from blocking $alpha_1$ receptors).

The positive effects generated by blocking H_1 receptors are: sedation and anxiolysis. If the blockage does not occur very suddenly, then we mainly have anxiolysis and not sedation.

Clozapine ($C_{18}H_{19}ClN_4$) (see Fig. 1 - Clozapine's pharmacological and binding profile) [2] acts on majority of receptors (on 23 receptors). It blocks 60% of them, while also having a rapid dissociation capacity. It has gentle action on D_2 receptors, which makes it indicated in late dyskinesia.

Dissociation means that it "blocks and leaves quickly", hence the indication in acute dyskinesia (the other antipsychotics block 80% of the receptors). Clozapine ratios with the other receptors are ideal, has maximum efficacy, unfortunately not maximum tolerability.

Clozapine is ideal for patients with suicidal ideation. There are studies in this regard, especially on schizophrenic patients with suicidal ideation. It has pro cognitive effects from its receptor profile, but these are blocked by sedative effects.

D_2 receptor blocking is at a lower level. There are many receptors acting at over 60% (with partial agonism effect).

Including actions on M_1, H_1 and $alpha_1$ receptor, means sedative effect and diminishing the pro-cognitive effect of Clozapine.

The champion regarding the metabolic risk is Olanzapine ($C_{17}H_{20}N_4S$) as the number of patients. As absolute value of the extra kilos taken by the patient is Clozapine, but the number of patients treated with Clozapine is not so great. Clozapine causes dyslipidemia over time.

Aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$) (see Fig. 2 - Aripiprazole 's pharmacological and binding profile) [6] Many psychiatrists have in recent years raised the problem of giving up Clozapine for Aripiprazole, even though after many years of Clozapine patients are no longer as sedated, but on the contrary, are active, with work, family, children, etc. compared to patients on other molecules. At one point, under Clozapine, problems appeared in the instinctive sphere. Hence

the need for Aripiprazole, which is a minimal agonist on D receptors. When patients had complaints due to sedation, Aripiprazole was proven effective.

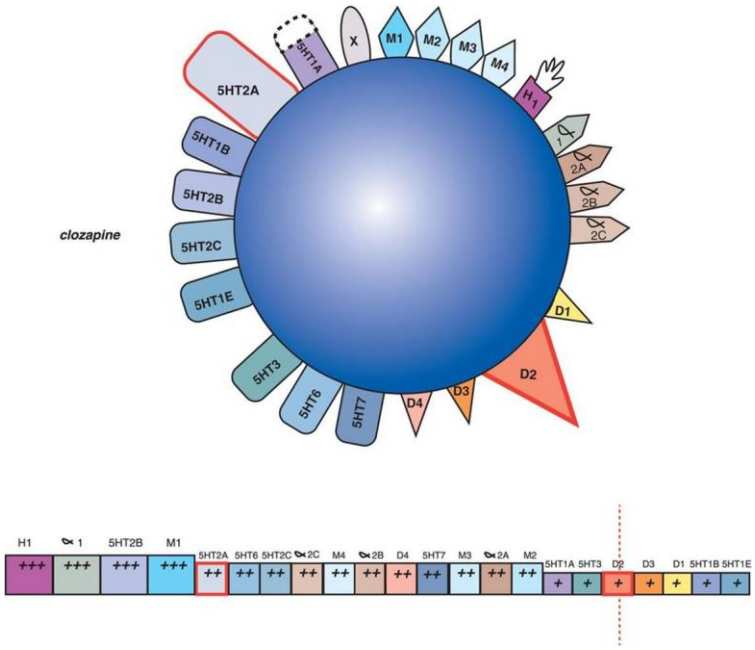
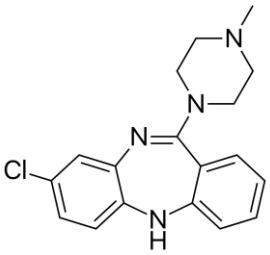


Fig. 1 - Clozapine's pharmacological and binding profile



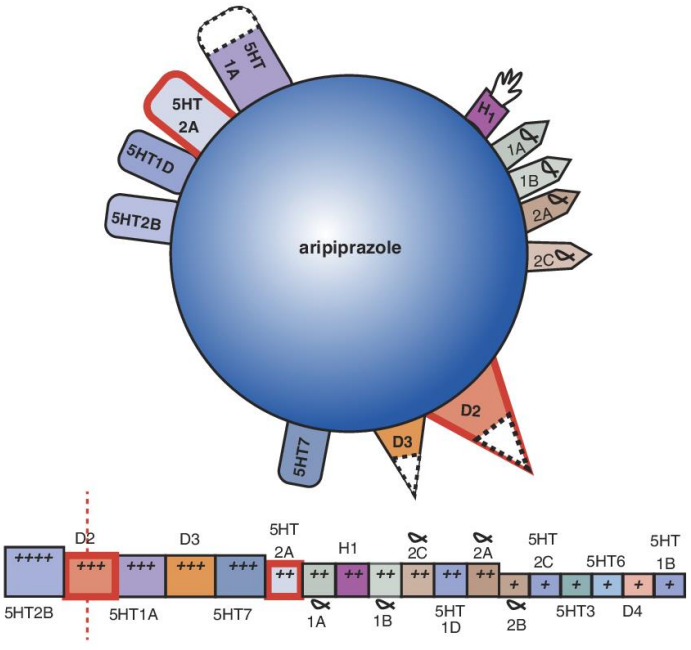
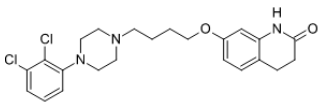


Fig. 2 - Aripiprazole's pharmacological and binding profile



The combination of Clozapine with Aripiprazole is a very good one (Clozapine in the evening, up to 100 mg, in combination with Aripiprazole depot).

Clozapine requires to repeat the blood tests for the risk of agranulocytosis. Collaboration with the hematologist is sometimes necessary, even for patients who have not accused anything in the area of granulocytopenia and who do not require dose changes. There are patients who have very low neutrophil (neutrocytes) values, not associated with major clinical symptoms, but for whom supplementation with B vitamins and corticosteroids is necessary. Great attention should be paid to this subgroup of patients that present only leukopenia or exclusively grananolithopenia.

Patients older than 15 to 20 years in treatment with Clozapine have decreased granulocytes approximately twice a year, when it is required to remain at 50 - 100 mg, up to 150 - 200 mg of Clozapine.

When trying to give up Clozapine completely, some patients ask to receive 25 mg of Clozapine back for sleep action. In such cases, a combination of Trazodone with another sleep inducer may be proposed instead of Clozapine.

Olanzapine ($C_{17}H_{20}N_4S$) (see Fig. 3 - Olanzapine 's pharmacological and binding profile) [6] is derived from Clozapine, by removing a chain. It is the most prescribed molecule in Romania as an indication in schizophrenia. It has rapid action, sedation (which we follow in the initial stages of a disorder episode), and in time produces cognitive deficiency.

The atypical mechanism is simpler than in Clozapine, which is why it is not indicated in active dyskinesia. If we overcome the blockade in more than 80% of the receptors, which may be possible only at more than 20 mg Olanzapine per day, then the effects of dyskinesia appear.

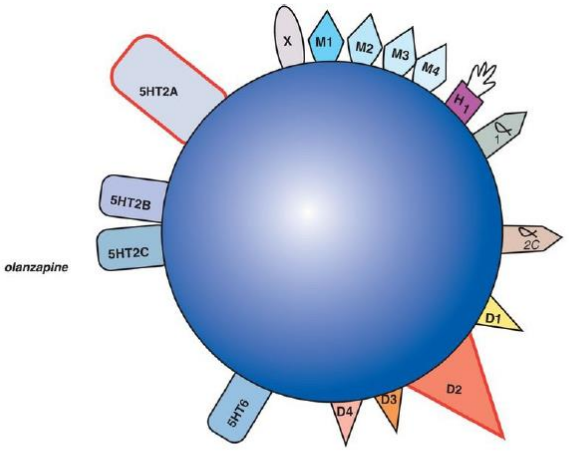
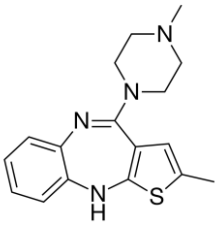
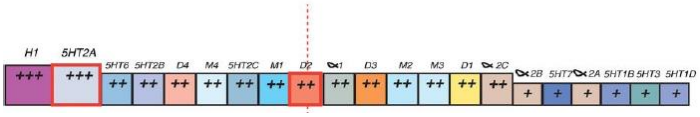


Fig.3 - Olanzapine's pharmacological and binding profile.





The sedative effects are beneficial by blocking the three receptors, which produces a very good sleep, but the risk is that the patients wake up at night and eat (the unfortunate metabolic effects of Olanzapine). From this perspective, Olanzapine is the "champion" of metabolic effects.

The advantage over its class is that it has a long action. Although in this case there were post-administration syndromes.

3.2. Functional perspective of patients with schizophrenia under different antipsychotic molecules

Quetiapine ($C_{21}H_{25}N_3O_2S$) (see Fig. 4 - Quetiapine 's pharmacological and binding profile) [6] blocks 60% of the receptors, with rapid dissociation, as does Clozapine too. Consequently, it has indication in late dyskinesia.

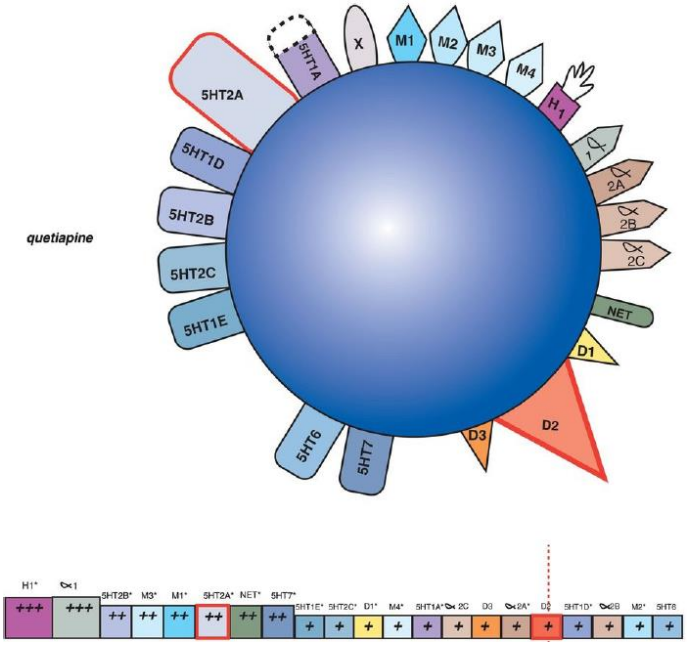
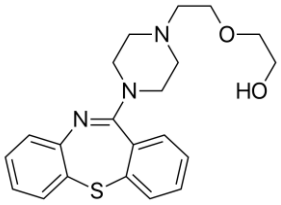


Fig.4 - Quetiapine 's pharmacological and binding profile.



In the US, Aripiprazole is also discussed in late dyskinesia. We are talking about late dyskinesia in which synaptic lesions are very important. The atypical mechanism of Quetiapine is similar to Clozapine: rapid dissociation of D_2 receptors and rapid action on serotoninergic receptors, which implies many antidepressant effects.

We ask the question Quetiapine is a "lost" antidepressant among antipsychotics? Norguetiapine (Quetiapine metabolite) inhibits noradrenergic recapture, hence the antidepressant effect.

Pro-cognitive effects exist, but they are also limited here by sedation. By moving to prolonged release, the problem of sedation was solved. At low doses there are only anxiolytic effects.

The metabolic risk of Quetiapine is intermediate. It acts on the same receptors, but in a smaller modality.

In what concerns the Risperidone ($C_{23}H_{27}FN_4O_2$) (see Fig. 5 - Risperidone 's pharmacological and binding profile) [6], blockage of D_2 receptors is in a much more important area than in the "-pine" class.

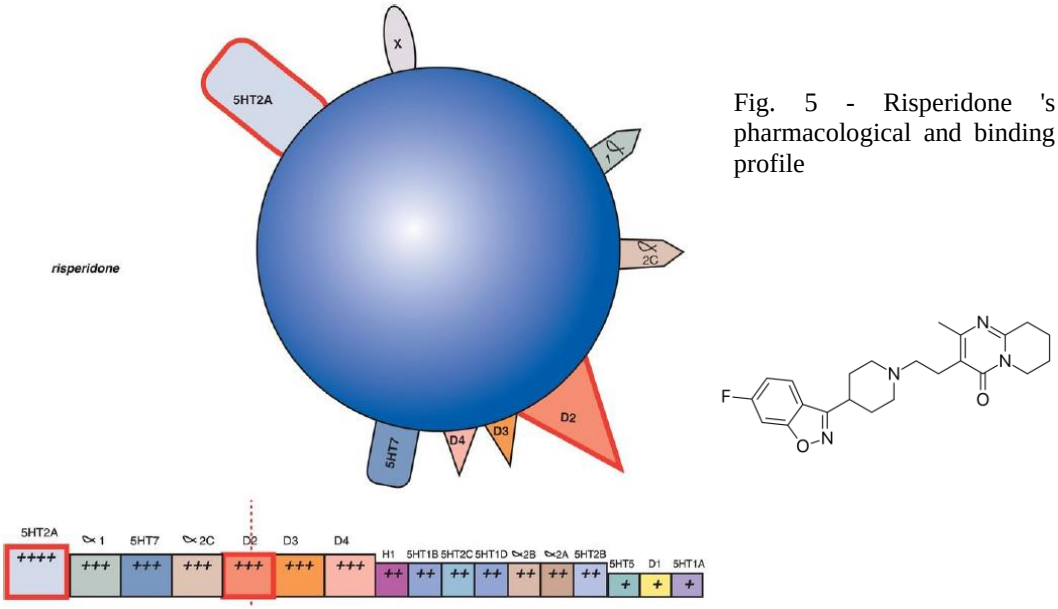


Fig. 5 - Risperidone 's pharmacological and binding profile

The action on D_2 receptors is more important, thus the antipsychotic effect is higher. Adverse effects are also superior, resulting also from the action on D_2 receptors (extrapyramidal effects and effects on prolactin).

The atypical mechanism is quite small. It additionally blocks the serotoninergic 2A receptors.

The pro-cognitive effects are more discrete, but slightly higher than the "pine" class due to the smaller sedation.

Risperidone is in the intermediate risk zone compared to "-pine" because it has less sedation.

Paliperidone ($C_{23}H_{27}FN_4O_3$) (see Fig. 6 - Paliperidone's pharmacological and binding profile) is an active metabolite of Risperidone, which implies rapid dissociation on D_2 receptors. Consequently, it has an additional atypical mechanism.

Antidepressant effects are on the same receptors, pro-cognitive effects are the same, the antidepressant effect due to blocking alpha$_2$ receptors is higher. So, we are talking about a dual antidepressant mechanism.

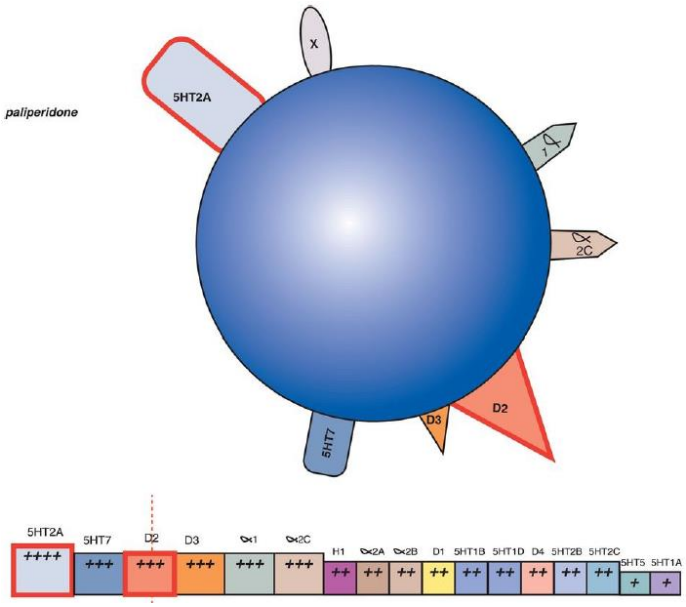
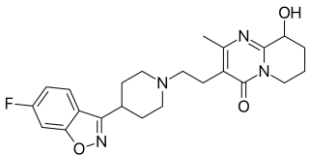


Fig. 6 - Paliperidone's pharmacological and binding profile



Postsynaptic alpha$_1$ receptor must not be blocked to achieve a superior antidepressant effect (such as, for example, Risperidone). The fact justifies the indication of Paliperidone in Schizoaffective Disorder, where the efficiency is not on the definitive antidepressant mechanism, but Paliperidone has an undoubted effect in this spectrum. There is also the long acting variant, which is an opportunity.

Ziprasidone ($C_{21}H_{21}ClN_4OS$) has a single atypical mechanism. It has some pro cognitive effects and some antidepressant effects.

Aripiprazole is part of the class of partial agonists and has an interesting receptor profile. It has four atypical mechanisms.

1) Partial agonism on D_2 receptors (when dopaminergic activity is increased, it binds instead of dopamine). The fact explains the cognitive and antidepressant effects. It becomes an intelligent molecule, which increases dopamine where it is low and lowers it where it is grown.

2) Rapid dissociation of receptors. It binds to D_2 receptors and leaves. Between bindings, receivers retain their properties. The properties of D_2 receptors remain intact and Aripiprazole does not cause synaptic damage.

3) It blocks the serotoninergic 2A receptors, also having an active effect on $5HT_{2A}$.

4) Increases the activity of D_2 receptors in the prefrontal area. It also has antidepressant effects, making patients more alert, more vigilant and more spontaneous. This fact is possible even if the patients have previously had several tried antipsychotics.

If we look at D_3 receptors, the action of Aripiprazole on them produces a pro-cognitive effect. Action on D_2 receptors means 90% binding, and binding to D_3 receptors is also 90%. The clinical correspondent is increasing motivation and preventing diabetes (in a class of medicines where most are at risk of producing diabetes).

It should be noted that Aripiprazole has important effects on D_3 receptors.

The other receptors produce glutamatergic stabilization (an upstream effect). The increased glutamate increases dopamine in the mesolimbic system (which produces productive symptoms) and decreases the dopamine in the prefrontal area (responsible for the negative and depressive symptoms).

Glutamatergic stabilization is quintessential in Bipolar Affective Disorder. Consequently, in bipolar affective disorder, Aripiprazole is effective at doses of 20-30 mg / day. In schizophrenia, 15 - 20 mg daily is sufficient. In bipolar affective disorder there is a tendency to use higher doses, whereas in schizophrenia the ideal dose is 20 mg [7].

The equivalent long acting dose is 21.2 mg daily for Aripiprazole Maintena 400 mg. Glutamatergic stabilization is performed at this dose. In schizophrenia, 15.9 mg daily is sufficient. Aripiprazole long acting is very well dosed for both indications.

The action on the two serotoninergic receptors:

For serotoninergic $5HT_{1A}$ receptors, low doses are sufficient to be blocked, while for $5HT_{2A}$ serotonergic receptors, they are less well blocked at 10 mg, with 20 to 40 mg of Aripiprazole required to produce complete glutamatergic stabilization. The effective thymostablishing effect is achieved by complete glutamatergic blockade.

Cariprazine ($C_{21}H_{32}Cl_2N_4O$) involves an atypical mechanism in three directions:

1) Partial agonist on D_4 receptors

2) Partial action on the two antidepressant receptors $5HT_{1A}$ and $5HT_{2A}$

3)The action on D_3 receptors is superior in terms of negative phenomenology, with Cariprazine is acting on motivation and affective symptomatology.

It has two active metabolites, one of them with long degradation, so the patient can skip doses and the effect remains.

The effect settles slower in the area of D_3 receptors, but undoubtedly the molecule acts on the negative register, on motivation and affectivity, but without yet having a long acting variant. There are also cognitive effects.

Brexpiprazole ($C_{25}H_{27}N_3O_2S$) is also a partial agonist, which has three atypical mechanisms, such as Cariprazine.

It is the partial agonist with the strongest action on D_2 receptors (decreased dopaminergic activity). Consequently, it is the most potent atypical antipsychotic with action on D_2 receptors.

In the opposite area is Cariprazine, then Aripiprazole.

Bifeprunox was still present, but only in clinical trials. It did not differentiate sufficiently, being the least partial agonist and staying close to placebo. It had antidepressant effects like Brexpiprazole, as well as pro-cognitive effects.

Amisulpride ($C_{17}H_{27}N_3O_4S$) is an atypical molecule between atypical medicines, a simpler molecule. Rapid dissociation of D_3 receptors is the main mechanism. At low doses it is partially agonist (below 300 mg), over 300 mg is dopaminergic blocker.

It has selectivity and goes to areas where dopaminergic activity is increased. It has a high risk of hyperprolectinemia.

Antidepressant effects may occur at lower doses (below 300 mg).

In the US, at 50 mg it has indication in dysthymia. Paradoxically, in the US there is no indication of schizophrenia.

It has pro cognitive effects, in the sense that it does not accentuate the negative symptomatology.

Sertindole ($C_{24}H_{26}ClFN_4O$) has action in two directions:

1) Rapid dissociation of D_2 receptors, which produces antidepressant and procognitive effects, along with discrete sedation.

2) Action on $alpha_1$ means sedation, but also dizziness, lowering your BP (blood pressure).

There is the "-pine" class which has an important effect on $alpha_1$ receptors. If we go to "-done", we have an intermediate action, and in the area of partial agonists, the action is inferior. The action on $alpha_1$ blocks some antidepressant receptors.

Blocking $alpha_2$ effects has antidepressant effect. The action is superior in the area of "-pines", intermediate to "-done" and among the last ones that maintain an action in the area $alpha_2$ is Aripiprazole. Adverse effects have been transformed from one class to another.

3.3. Presentation of the receptors. Molecular aspects

D_2: the antipsychotic effect is the main pursued and beneficial. Adverse effects are: extrapyramidal reactions, hyperprolactinemia, cognitive impairment, dystonia, anhedonia.

Functionality: all antipsychotics previously exposed, except Risperidone and Amisulpride.

D_1 receptors: pro-cognitive effect and improvement of negative symptomatology.

D_3 receptors: pro-cognitive effect, improvement of symptomatology related to motivation and functionality. Here comes Cariprazine and Aripiprazole.

D_4 receptors: unknown effects.

$5HT_{2A}$ receptors: blockade that produces antidepressant effects.

$5HT_{1A}$ receptors: hyperprolactinemia.

$5HT_{1D}$ receptors: the mechanism is not very clear.

$5HT_{2C}$ receptors: dopamine increases in the prefrontal area, which has an antidepressant and pro-cognitive effect.

When blocked with H_1 receptors, it causes weight gain.

We consider it a receiver in general functionality and not a good receiver for functionality if the H1 receivers are blocked simultaneously.

$5HT_3$ receptors: anti-vomiting effects. Clozapine is a variant for this pathology. And Mirtazapine is good on serotonergic receptors 3.

$5HT_6$ receptors: pro-cognitive effects.

$5HT_7$ receptors: pro-cognitive effects and regulation of circadian rhythms.

Serotoninergic receptors are quite specific to Aripiprazole.

Inhibition of serotonin reuptake: We do not have an antipsychotic in Romania to act on this. The beneficial effect is the antidepressant, but there is a slight risk that serotonin levels will decrease slightly in the prefrontal area. So: antidepressants could cause cognitive impairment!!!

$Alpha_1$ receptors: side effects: dizziness, orthostatic hypotension, sedation. Good is the anxiolytic effect.

It is neutral or, rather, anti-functional.

The inhibitory effect of noradrenaline reuptake is beneficial. If it grows too much, we can see sweating, tremor, hypertension.

Quetiapine does not produce these effects, because of its wide receptor activity, it blocks its possible adverse effects alone.

When we are talking about Desvenlafaxine, Duloxetine, Milnacipran we are facing: constipation, tremor, high blood pressure, because these molecules do not have mechanisms to block these adverse effects alone.

Consequently, we can say that molecules such as Quetiapine and Norquetiapine are functional.

M_1 receptors: they improve the symptoms of extrapyramidal type (the "pine" class, compared to "done", has smaller extrapyramidal effects).

M_3 receptors: it alters insulin secretion, produces ketoacidosis, hyperosmolar hyperglycemia. This category includes molecules such as: Olanzapine, Quetiapine, Clozapine).

H_1 receptors: the anxiolytic sedative effect is a positive one (at the slower release molecules). The negative effects are: sedation, weight gain (on the extended release molecules).

It is an against-functionality receptor.

Metabotropic receptors: increase insulin resistance.

In conclusion, there are 11 receptors for functionality, 6 receptors against functionality and 1-2 receptors neutral regarding functionality.

The D_2 receiver is a controversial one. It counts the degree of receptor binding and the rate of dissociation (how fast a drug leaves a receptor).

The psycho-behavioral correspondent of the combined receptive action can be translated by the following intrapsychic foundations: the patient's ability to build goals, motivation for the world and life, curiosity, empathy, pleasure (versus risk of anhedonia), functional social interactions (absence of those described above) constituting the nucleus of deficit syndrome). The volitional motivational system also influences the interpersonal relationships, as well as the instrumental roles of an individual and the different aspects of his / her experiences vis-à-vis the surrounding staff.

It also counts the patient's initiatives or if he has the tendency to avoid and social withdrawal, if the person concerned can still keep a job, if he is educated or if he is domestic. The ability to carry out activities is analyzed, as well as the level of involvement that the person in question feels, if their capabilities are underestimated or if they feel under used. Sometimes it is important to evaluate trivial matters such as whether the patient still has bank or shopping cards, telephone, keys, if he is still driving alone or if he still drives the car, if he pays his bills or if he can still have other personal worries, in a word if it is still functional.

3.4. Brain morphological changes in schizophrenia

Post-mortem studies in patients with schizophrenia describe a multitude of morphological changes at the level of different brain structures: ventricular enlargement and cortical belt enlargement, changes in the limbic system (hippocampus and para hippocampus), characterized by reduced volume with cellular architecture disorders, changes in the level of the thalamus, characterized by the reduction of the volume and cellular losses, changes of the cellular architecture in the frontal and temporal zones, the absence of the structural asymmetry, normal in certain cortical regions [8]

Every psychotic episode is toxic. The glutamatergic excess is due to the fact that there is a defective GABA inhibitory neuron, which causes more glutamate to discharge. Thus, brain matter is lost. Under glutamate, calcium channels open and mitochondria detect and trigger apoptosis. Similar to stroke

situations. All cells in the surrounding penumbra area die. In schizophrenia cortical neurons are disconnected. All the structures disappear, and the neurons are left alone. The cortex is thinner, it loses brain matter.

In the early stage of the disease, the disappearance of the neuropil can be observed in the temporal parietal cortex, as well as in the lateral dorsal prefrontal cortex. Other changes that occur, are also interested in the structures around the lateral ventricles (hippocampus, thalamus). Under excitotoxicity, these structures suffer loss of brain matter. The lateral ventricles widen. In schizophrenia we talk about loss of interneuronal connectivity, low development of inhibitory circuits, excessive elimination of excitatory circuits, decreased myelination. The formation of neural circuits is based on the notion of neuropil and is based on the following mechanisms: proliferation, migration (these two taking place prenatally), arborization (formation of circuits) and myelination.

Neuropil is involved in the excitation-inhibition ratio including, besides the neuron, the synaptic syncytia between neurons along with the process of connectivity.

In schizophrenia the brain volume decreases, not the density, because the neurons remain there. Psychotic symptoms have an organic toxic effect on the brain with atrophic synaptic connections and impaired judgment and abilities.

From this perspective, the medication aims to reconnect to reality. Hyperdopaminergic effect is equivalent to a hyperstimulation of post-synaptic, glutamatergic neurons, glutamate being toxic in the situation where "neurons float in glutamate". It is not the neurons that are necessarily affected but the dendrites and the axon. The progressive loss of the ash substance in the parietal, frontal and temporal cortex together with the large lateral ventricles, cortical atrophy, decreased tonsil volume and hippocampus cause significant loss of judgment.

4. Discussions

4.1. Classification of receptors in terms of patient functionality

Table 1 [2]

For Functionality Receptors	
dopaminergic	D_2 (for amisulpride, risperidone, paliperidone is neutral and for neuroleptics it is negative) D_3
serotonergic	$5HT_{2A}$ $5HT_{1A}$ $5HT_{2C}$ (when the H_1 receptors are not locked simultaneously) $5HT_3$ $5HT_6$ $5HT_7$

	SERT
adrenergic	$Alpha_2$ NET
Neutral receptors regarding the functionality	
dopaminergic	D_2 (for amisulpride, risperidone, paliperidone)
cholinergic	M_1
Against functionality receptors	
dopaminergic	D_2 (for neuroleptics) D_1
histaminergic	H_1
adrenergic	$Alpha_1$
cholinergic	M_3
metabotropic	X

4.2. Clinical applicability

The period in which these anatomical changes occur, and the patient loses brain matter is the period of actively decreasing socio-professional and occupational functionality, the period lasting 5-10 years. Then there is the irreversible damage. You can extend this period from 5 to 10 years, but you cannot cancel the evolution.

Consequently, we are talking about symptomatic recovery. 51% of patients are in symptomatic recovery [9]. First, we see them in symptomatic functionality, then recover symptomatically and, later, recover functional, the percentages decrease to 23%. Patient recovered symptomatically, functionally and with a good quality of life. 4% of schizophrenics are here, although symptomatic recovery is 33%.

The relationship between social functionality and risk of relapse should be directly related to the reduction of the risk of hospitalization. If the patient is functional, he has a lower risk of relapse. With each new admission, the functionality decreases even more. Patients who maintain good functionality one year after the last hospitalization are those who still have high scores on the functionality scales in the hospital. On the GAFS scale [10], the risk of relapse when patients had low functionality at the time of discharge is double compared to patients with already high functionality at discharge.

A study [11] comparing Aripiprazole and Paliperidone, both in the long-action version, began with oral administration, then switched to the injectable forms. The study lasted 28 weeks.

The permitted doses of Aripiprazole were 300 or 400 mg per month. For Paliperidone 50 up to 150 mg per month (depot). Functionality evaluation was done with Carpenter Scale, the study was opened for the doctor, blind for the rater.

Deficiency syndrome was analyzed. The scale has received a threshold of 5.3 points from the beginning, otherwise we are in the area of mathematical variation and there is no obvious benefit. Both groups have improved. Those with Aripiprazole Maintena were improved over this threshold, with the conclusion that patients under 35 years of age performed very well. In those over 35 years of age, the difference between Aripiprazole and Paliperidone is not that significant. So, Abilify Maintena is good in the early stages of the disease, patients being improved on all four areas of the scale.

As a result, the sample with Abilify Maintena was extended to 52 weeks, demonstrating that the patients in question also had volitional motivational reserves that could be exploited receptively under this molecule. Thus, younger patients (the earlier forms of the disease) evolve better on clinical scales, reducing the risk of relapse.

From the third month of administration of Abilify Maintena the optimal plasma levels are reached. If, after six months of oral administration of Aripiprazole, the hospitalization rate was 38%, this dropped to 8%. When included in the study was performed the PANSS scale [12], subsequently finding improvements on both the positive and negative dimensions (the study was performed comparatively in Germany and in the UK).

5. Conclusions

Modern psychiatry would like to create new molecules that will act mainly on dopaminergic neurons in the lateral dorsal prefrontal cortex, but also in the hippocampal ones, the aim being to approach the disorganization dimension in the phenomenology of schizophrenic thinking (tangentiality, circumstantiality, weakening of logical associations, removal of the signifier from the signified, the construction of illogisms, the reversal of the effect with the cause, the deficiency of mentalization); the medication currently used in this area is having remarkable results in the psychotic productive area, but smaller results in the area of disorganization of thinking, language and behavior. Furthermore, antipsychotic medication expanded medical understanding of the role of chemical messaging in neurotransmission and reduced the stigma associated with mental illness.

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