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Schizophrenia treatment. Critical review on the drugs and mechanisms of action of antipsychotics

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Schizophrenic treatment was developed during the second half of the last century, mainly within the context of the development of antipsychotic drugs. Even though there has been significant progress due to the availability and use of multiple drugs, these can still be classified into three basic groups of antipsychotic drugs (atypical antipsychotics, typical antipsychotics and dopamine partial agonist antipsychotics). Their primary antipsychotic mechanism is still the action on the dopamine systems. Many of the second-generation antipsychotics are believed to offer advantages over first-generation agents in the treatment for schizophrenia. However, the drug properties that provide the different therapeutic effects from those of the first generation are not clear and some adverse effects may still affect the patient's health and quality of life. Furthermore, the efficacy of the antipsychotics is limited. This has led to the use of adjuvant medications to strengthen the treatment effects. On the other hand, work is being done on the development of new research lines to develop new non-dopaminergic antipsychotic drugs, with not very successful results.

The aim of this paper is to make a brief review on the current therapeutic armamentarium for schizophrenia, the strategies to develop drugs, and theories of mechanisms of action of antipsychotics. Emphasis is placed on the new therapeutic targets for the development of future treatments

Key words:
Schizophrenia. Antipsychotics. Dopamine partial agonist.

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Tratamientos para la esquizofrenia. Revisión crítica sobre la farmacología y mecanismos de acción de los antipsicóticos

El tratamiento de la esquizofrenia ha evolucionado a lo largo de la segunda mitad del siglo pasado, principalmente gracias al desarrollo de los fármacos antipsicóticos. A pesar del gran avance realizado, que ha permitido la disponibilidad y uso de nuevos y diferentes fármacos, éstos continuan constituyendo tres grupos básicos (atipsicóticos típicos, atípicos y agonistas parciales dopaminérgicos), y todos ellos tienen como principal mecanismo de acción, la actuación sobre los sistemas dopaminérgicos. Se cree que una gran parte de los antipsicóticos de segunda generación (antipsicóticos atípicos y agonistas parciales dopaminérgicos) ofrecen ventajas añadidas a los de primera generación en el tratamiento de la esquizofrenia. No obstante, las propiedades farmacológicas y terapéuticas que confieren respecto a los de primera generación no están claras, y ciertos efectos colaterales pueden todavía, afectar a la salud y calidad de vida del paciente. Además, la eficacia de los antipsicóticos es limitada, lo que ha llevado a la utilización de medicaciones adyuvantes para potenciar los efectos del tratamiento. Por otro lado, se ha trabajado en el desarrollo de nuevas líneas de investigación para el desarrollo de nuevos fármacos antipsicóticos no dopaminérgicos, siendo los resultados poco exitosos.

Este artículo realiza una breve revisión crítica sobre el actual arsenal terapéutico para la esquizofrenia, estrategias de desarrollo de fármacos, y teorías sobre los mecanismos de acción de los antipsicóticos, centrándose en las nuevas dianas terapéuticas para el desarrollo de futuros tratamientos.

Palabras clave:
Esquizofrenia. Antipsicótico. Agonista parcial dopaminérgico.

INTRODUCTION

The therapeutic armamentarium for schizophrenia was developed in the second half of the century beginning

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with the introduction of chlorpromazine and the onset of the pharmacological era in psychiatry. The reintroduction of clozapine represented another advance and has allowed for proliferation of the atypical or second generation antipsychotics (SGAs), that include risperidone, olanzapine, quetiapine, ziprasidone, sertindole and zotepine.[1] In fact, there is growing evidence that most of the new drugs offer some advantages over the typical or first generation antipsychotics (FGAs), such as greater improvement of the negative symptoms, cognitive deterioration, prevention of relapses, functional capacity and improvement of the quality of life such as a lower grade of extrapyramidal symptoms (EPS) and tardive dyskinesia.[2] However, these differences are not necessarily substantial. On the contrary, other side effects such as weight gain, hyperglycemia and dyslipidemia have been observed. We are currently working to describe the clinical profiles of the new agents regarding the extension of their therapeutic effect and adverse effects on aspects such as cognition, suicide, social and affective response, cost-effectiveness, etc.[3]

In spite of the intense research performed, the pharmacological mechanisms underlying the therapeutic properties have still not been identified. Furthermore, the limitations of these drugs to act on all the dimensions of the disease (such as negative effects, cognitive deficits and social skills problems) have led to the search for drugs that can be used as adjuvants together with the antipsychotics. These drugs, that include benzodiazepines, lithium, anticonvulsants, antidepressants, beta-blockers and dopaminergic agonists, have been used to enhance the effect of the antipsychotics or to treat the residual effects and comorbid conditions of schizophrenia. However, there is little empirical evidence to support this practice.[4]

CURRENT TREATMENT FORMS: FIRST GENERATION AND SECOND GENERATION ANTIPSYCHOTICS

The treatment strategies and forms of schizophrenia vary based according to the phase and severity of the disease. Although several psychosocial therapies, such as cognitive-behavioral therapy or psychoeducation, have been developed, they are useful as adjuvants to the drug treatment, and all require the drug treatment to achieve their maximum effectiveness.[5] Even though all of the existing drug treatments have limitations regarding their efficacy and they are related with undesirable adverse effects, it is a demonstrable fact that antipsychotics can improve the psychotic symptoms of schizophrenia and prevent relapses.[6,7]

We currently have typical and atypical antipsychotics. The typical ones, although effective, are not an optimal treatment, since only a small percentage of patients respond to them and they cause a significant amount of acute and chronic adverse effects. At present, the only group of patients in whom these drugs are clearly preferred are those for whom there is a clear indication of injectable preparations or who have a background of an excellent response to them with minimal side effects.[8,9]

The new antipsychotics, together with benzamides and aripiprazole, seemed to provide important advances regarding the side effects and efficacy in this group of drugs. However, the atypical antipsychotics and the benzamides have been related with different side effects that negatively affect the patient's quality of life, together with some limitations in regards to their efficacy. Thus, there is a continuing need for new and better drugs.

THEORIES ON THE MECHANISM OF ACTION OF THE ANTIPSYCHOTICS

First generation antipsychotics

All of the FGAs have a high affinity for the D_2 dopamine receptor in common,[10] there being a strong correlation between the therapeutic doses of these drugs and receptor binding affinity.[11-14] The importance of the dopaminergic receptor occupancy as an indicator of antipsychotic response and adverse effects has been demonstrated.[15] Thus, it has been seen that a 65-70% striatal D_2 receptor occupancy is associated with the antipsychotic effects[16-19] while an occupancy greater than 80% significantly increases the risk of extrapyramidal effects. Therefore, a threshold between 60 and 80% [20] of occupancy seems to represent the therapeutic window to minimize EPS risk of the FGAs (this model was not absolute and has its limitations). Interestingly, low doses of haloperidol (2-5 mg/day) should induce 60-80% receptor occupancy. Instead, a dose of 5 to 20 times more is generally prescribed in the clinical practice. This is partially supported by the fact that the long-term treatment with FGAs induces an increase of the D_2 receptors, which seems to be associated with a dopaminergic D_2 supersensitivity. Thus, we could say that the dose must be increased in order to produce the same effect on the dopaminergic transmission.[21,22]

Benzamides

Benzamides are very selective antagonists of the D_2 and D_3 receptors, with little affinity for the D_1 receptors or non-dopaminergic receptors. Some studies have proposed that, when given at low doses, they would preferentially block presynaptic D_2 receptors, causing an increase in dopaminergic release and neurotransmission. On the contrary, higher doses would reduce some postsynaptic dopamine receptor mediated effects. This would correlate with the antipsychotic efficacy, but with very little or no in-

duction of catalepsy, which would reduce the risk of EPS.[23]

Amisulpiride is also characterized by its rapid dissociation from the D_2 receptor. Its moderate affinity for the striatal D_2 receptors and its preference for binding on the D_2 /D_3 receptors of the limbic cortex could explain its therapeutic efficacy and limited tendency to induce EPS.[24]

Second generation antipsychotics

The serotoninergic-dopaminergic antagonism theory proposes that a higher level of affinity of the drug for the serotonin 5-HT_{2A} receptor, compared with the affinity for the dopamine D_2 receptor could explain the «atypical characteristic,» and the greater efficacy and lower tendency to produce EPS of the SGAs.[25-27]

PET studies have shown that therapeutic doses of risperidone, olanzapine and ziprasidone showed D_2 receptors occupancy higher than 70%. This leads us to consider that a specific threshold of the D_2 receptor occupancy would be important in the production of the antipsychotic effects of these drugs. (Fig. 1) However, this correlation does not occur with clozapine, quetiapine and ziprasidone. Thus, the other pharmacological properties, in addition to the receptor occupancy threshold, affect the clinical efficacy.[28,29]

Clozapine, risperidone, olanzapine and ziprasidone occupy more than 80% of the cortical 5-HT_{2A} receptors in the therapeutic range in humans. Although 5-HT_{2A} antagonism is a candidate to be associated with the low incidence of EPS of the SGAs, risperidone produces EPS at higher doses. Furthermore, it is not clear which clinical effects are produced by the 5-HT_{2A} antagonism beyond that of mitigating the adverse effect of the striatal D_2 antagonism and the tendency to cause EPS.[30,31]

The fast-off D2 theory. There is no evidence that a drug can act as an effective antipsychotic is it does not have some degree of D_2 occupancy. Recent *in vitro* studies have demonstrated that the antipsychotics are dissociated from the D_2 receptors at very different rates, expressed as K_{off} value.[32]

The binding of an antipsychotic to a receptor is a dynamic process with continuous association and dissociation, and can be expressed as follows:

$$D + R \Rightarrow DR \Rightarrow D + R$$

The SGAs have higher values of K_{off} (faster dissociation rate) than the FGAs, but this measurement also varies among the different SGAs. Kapur and Seeman proposed that the dissociation from the D_2 receptor makes it possible for an antipsychotic drug to rapidly accommodate to the physiological dopamine transmission, permitting an antipsychotic effect without EPS, prolactin elevation and providing benefits on the cognitive and affective function and on the secondary negative symptoms. In accordance with this hypothesis, they suggest that high D_2 occupancy is not required for the antipsychotic action. Rapid dissociation of clozapine and quetiapine from the endogenous

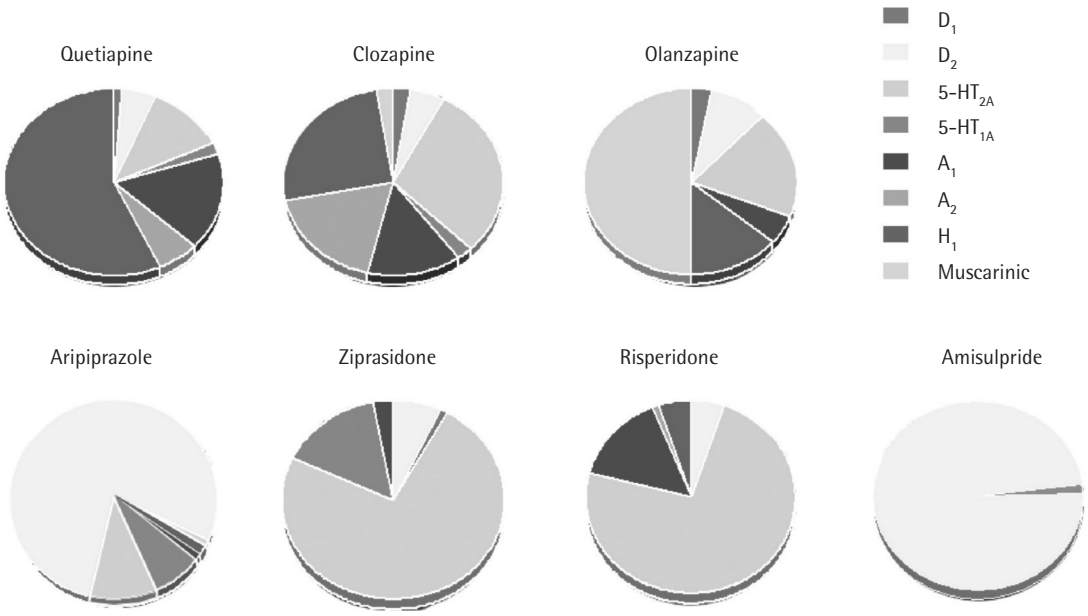

Figure 1 *Receptor profile in the second generation antipsychotics.*

dopamine D_2 receptors may lead to a faster clinical relapse after the suspension of the treatment. It is still not clear how long an antipsychotic needs to be bound to a D_2 receptor to maximize the therapeutic efficacy and minimize the risk of adverse effects related with D_2 occupancy.

In conclusion, the fast dissociation hypothesis proposes that the combination of a fast K_{off} and systemic transient occupancy of D_2 is sufficient to produce an atypical antipsychotic effect. It is not necessary to induce activity in other receptors. It suggests that the fast dissociation drugs, when used at adequately high doses that permit D_2 blockage, modulate the dopaminergic system so as to permit a more appropriate functioning of the physiological systems, which would lead to that currently called the atypical antipsychotic effect.[33]

Use of other neuroreceptors as potential therapeutic target. The SGAs, specifically clozapine, have many sites of action other than D_2 receptors, including D_1, D_3 and D_4 dopamine, sertonin 5-HT_{1A}, 5-HT_{2c}, 5-HT_6 and 5-HT_7, muscarinic cholinergic and histamine receptors. Among them, it has been proposed that the partial agonist activity of clozapine at the 5-HT_{1A} receptors could contribute to its efficacy against anxiety, depression and cognitive and negative symptoms of schizophrenia.[34,35] Even more, it has been proposed that the 5-HT_{1A} agonism contributes to the increased release of prefrontal dopamine. This could be related with its potential efficacy for the negative symptoms and the cognitive dysfunction of the schizophrenia. Finally, some SGAs, but not FGAs, may increase the release of acetylcholine in the prefrontal cortex, which could be a contributing factor to the cognitive improvement in schizophrenia.[36,37]

Interactions of the antipsychotics with the glutamatergic system. The ability of NMDA receptor antagonists to induce a spectrum of positive, negative and cognitive symptoms such as those of schizophrenia has led to the hypothesis that hypofunction of the NMDA receptors is involved in the pathophysiology of schizophrenia.[38,39] It has been suggested that the therapeutic mechanisms of action of the SGAs could be involved in counteracting the effects of the NMDA receptor hypofunction. However, the mechanism by which these effects are mediated is unclear, since none of the SGAs have a direct affinity for the glutamatergic receptors, including NMDA. More studies are needed to determine if the inhibition of the antagonist effects in NMDA by the SGAs entail molecular changes in the glutamate receptors. On the contrary to the acute effects, chronic treatment with both the FGAs and SGAs produces adaptive changes that seem to lessen the effects of the NMDA antagonists. Many studies in animals have demonstrated increases, decreases, or absence of change in the glutamatergic receptor action sites in different areas of the brain after chronic administration of antipsychotics. Thus, it is not known if these changes reflect an increased or decreased function of the glutamate receptors after chronic antipsychotic treatment.[40-45]

Partial dopamine agonists. Aripiprazole is a high-affinity partial agonist at the D_2 and D_3 receptors and thus acts in both presynaptic and post-synaptic D_2 receptors.[46,47] The partial agonist activity at D_2 receptors could stabilize the dopamine system while avoiding hypodopaminergic that could limit the efficacy of the FGAs. Furthermore, aripiprazole has a partial 5-HT_{1A} agonist and 5-HT_{2A} antagonist effect. It has also been proposed that aripiprazole induces functionally selective activation of the G-protein coupled receptor, explaining its unique clinical expression. It has a very high affinity for the D_2 receptor (greater than its 5-HT_{2A} affinity). This makes it unlikely that it would have a fast K_{off}. PET studies in normal humans indicate that aripiprazole occupies 90% of the striatal D_2receptors at clinical doses, and does not produce EPS, suggesting that its inherent agonism may be responsible for a mechanism that protects against the excessive blockage of the D_2 system. This hypothesis proposes aripiprazole as a possible new treatment form for schizophrenia thanks to its action as a partial dopamine receptor agonist.[48]

PHARMACOLOGICAL CLINICAL PROFILES OF THE ANTIPSYCHOTICS

First generation antipsychotics

FGAs are equally effective in the treatment of the positive symptoms and in the prevention of recurrences. However, approximately 30% of the patients with exacerbated acute psychotic symptoms have little or no response to the FGAs, and up to 60% of the patients only have a partial response to the medication. FGAs are generally less effective against negative than against positive symptoms of schizophrenia. They also cause inconsistent small effects on the cognitive function. Cognitive deterioration may worsen with the use of adjuvant anticholinergic medication, that are often needed to treat the FGA-induced EPSs.[49,50]

Furthermore, the preventive efficacy of the FGAs for the prevention of recurrences is limited by the scarce therapeutic compliance and the fact that even with total compliance, approximately 20% of the patients may relapse.

In regards to the adverse effects, all the FGAs may produce EPS at therapeutic doses, including Parkinsonism, dystonia, akathisia and tardive dyskinesis in varying degree, and increase serum prolactin concentration in the usual range of the clinical dose.[51]

When these EPSs occur, they may be unpleasant for the patient and often entail an important reason for abandoning the medication.[52]

Benzamides

A meta-analysis comparing amisulpiride with FGAs or placebo demonstrated that amisulpiride was significantly more effective than the FGAs for the global and negative symptoms of schizophrenia. The drug also demonstrated its therapeutic benefit with scarce or null EPS, less use of antiparkinsonian medication and lower rates of drop-out due to the adverse effects in comparison with the FGAs. Its principal adverse effect is the substantial increase of the prolactin. More studies are needed to clarify if amisulpiride is really more effective for the primary negative symptoms.[53]

Second generation antipsychotics

Efficacy. Many double-blind studies that compare the efficacy and tolerability of the SGAs with the FGAs for acute and maintenance therapy of schizophrenia have been carried out. In general, the SGAs seem to be at least as effective as the FGAs for psychotic symptoms. However, there is considerable disagreement regarding the clinical superiority of the SGAs over the FGAs.[54,55]

In a meta-analysis, comparing new antipsychotics with FGAs, it was concluded that the superior efficacy observed of some SGAs may be due to the negative effects produced by the excessively high doses of the FGA compared.[56]

A third meta-analysis that compared FGAs with SGAs concluded that there was no evidence that the FGA dose would affect the results. We should mention that these three meta-analyses did not have available information to evaluate the remaining clinical dimensions (for example, affect, quality of life and cognitive function), that currently receive greater attention. In addition, the fact that most of the studies included in these reviews were clinical trials sponsored by pharmaceutical companies that used limited types of measurements or data analysis methods and whose duration was relative short could limit the capacity of evaluating the comparative effects of the two drug groups.[57,58]

Efficacy on negative effects. Although the SGAs have been shown to be more effective than the FGAs in the treatment of the negative symptoms, there is on-going debate regarding whether these therapeutic effects are secondary to a reduction of the EPS or other symptoms, or to a direct effect on the primary negative symptoms.[59] The secondary negative symptoms may be associated with positive symptoms, EPS, depression and environmental deprivation, but most of the clinical studies on SGAs do not distinguish between primary and secondary negative symptoms. Furthermore, the adverse effects of the SGAs on most of the negative symptoms may be moderate or mild compared with placebo or FGAs. One work group concluded that the FGAs are superior in terms of the totality of the negative symptoms, but its impact on the specific components is still being studied.[60]

Efficacy on the cognitive function. Studies on the effects of the SGAs on the cognitive function are limited and the results have been inconsistent. It is not clear if this effect is dependent on or independent of the treatment effect on the psychotic symptoms.[61,62] Most of the global cognitive function with the SGAs could be secondary to a lower degree of EPS and its greater efficacy in the treatment of the negative symptoms. In general, the SGAs have demonstrated superior efficacy then the FGAs in verbal fluency tests, motor function and executive function. Since all the tests measure behavior during a certain period of time, this reinforcement on behavior with SGAs could lead to a partial reduction of the Parkinsonian adverse effects. In a double-blind trial on the treatment of cognitive deterioration of schizophrenia in the early phases, risperidone and olanzapine produced significantly greater improvements in verbal fluency compared with haloperidol, and olanzapine was superior to risperidone and haloperidol regarding their effects on motor skills, non-´verbal fluency and immediate memory.[63,64] This result, however, is complicated by the high incidence of anticholinergic administration prior to the final cognitive evaluation and by other methodology problems. There is ongoing debate about whether the SGAs have a pro-cognitive efficacy or produce less cognitive deterioration.[65]

Efficacy in treatment resistant schizophrenia. Clozapine has consistently demonstrated its efficacy against psychotic symptoms in treatment-refractory patients in comparison with other SGAs and with the FGAs. In a meta-analysis, it was seen that clozapine is superior to the FGAs in regard to psychopathology, EPS and dropout rates. Controlled sequential trials of new drugs in treatment-resistant patients are necessary in order to study this question in greater depth.[66]

Safety. The principal difference of the SGAs compared with the FGAs is the lower incidence of EPS and tardive dyskinesia. Most of the SGAs have mild EPS or none, while risperidone has less at lower doses, and higher doses may produce EPS compared with those of the FGAs.[67]

The increased risk of weight gain, diabetes mellitus, QTc interval elongation and the possible secondary cardiovascular complications have been widely studied and observed. These adverse effects are associated, on the one hand, to a potential risk to the health of these patients in the long run and on the other hand, to a decrease of treatment compliance and eventually could favor recurrence.[68]

Among the SGAs, clozapine and quetiapine have demonstrated minimum risk of producing EPS or hyperprolactinemia with the therapeutic dose range. On the other hand, risperidone may cause dose-dependent EPS. Except for akathisia, the incidence of EPS or hyperprolactinemia with olanzapine and ziprasidone is not significantly different from its incidence with placebo.

Important differences have been observed in the risk of weight gain, diabetes or hyperlipidemia among the different SGAs. Thus, some analyses have shown a greater risk of weight gain with clozapine and olanzapine, intermediate risk with risperidone and quetiapine and minimal weight gain with ziprasidone.[69]

FUTURE STRATEGIES IN THE DEVELOPMENT OF DRUGS

Dopaminergic agents

Dopamine D_1 receptor agonist or antagonist. Scientific evidence suggests an important role of the Dopamine D_1 receptors in the pathophysiology of schizophrenia.

In contrast with the lack of efficacy of the D_1 antagonists in the treatment of schizophrenia, low doses of full agonists of the D_1 receptor have shown a reinforcing effect on the cognitive function in non-human primates. [70] Decreased binding to the D_1 receptor has been found in treatment-resistant schizophrenics and a correlation regarding the decrease of the prefrontal D_1 receptors and the severity of the negative symptoms and cognitive alteration. It has been postulated that both excess as well as deficit of D_1 receptor stimulation are detrimental for the cognitive function of the prefrontal cortex. Thus, an optimal level of D_1 receptor activation is needed for normal cognitive function.[71] The role that has been attributed to the D_1 receptor agonists of improving work memory suggests that these drugs may provide a new way of treatment for the negative and cognitive symptoms of schizophrenia.[72]

Dopamine D_4 receptor antagonist. There are several research lines that propose that selective D_4 receptor antagonists could be a new antipsychotic treatment. For example, clozapine and some clinically effective antipsychotics have a relatively high affinity for the D_4 receptors Further, an increase of the D_4 receptors in the brains of schizophrenics has been observed.[73,74]

An initial clinical trial with a highly selective D_4 antagonist failed to demonstrate any antipsychotic activity in the treatment of schizophrenia. This drug seemed to worsen the symptoms. Thus, this information raises serious doubts about whether the D_4 antagonism, in isolation, is, alone, associated with clozapine efficacy, and on whether the selective D_4 antagonists may have any therapeutic efficacy in schizophrenia.

Dopamine D_4 receptor partial antagonist or agonist. Most of the antipsychotics have a relatively high affinity for the D_3 receptor In a post-mortem study, elevation of the D_3 receptors in the striatum-limbic system of untreated schizophrenic patients was demonstrated while the expression of the D_3 receptor in patients treated with antipsychotics was normal. These findings have given rise to great interest about the D_3 receptor as a possible therapeutic target of the antipsychotic activity.(75) Currently, the role of the D_3 antagonism in antipsychotic activity is not clear. Thus, controlled clinical trials with selective D_3 antagonists are needed.

Glutamatergic agents

Positive allosteric regulators of the NMDA receptor. If the decreased function of the NMDA receptor has been involved in the pathophysiology of schizophrenia, then we could consider the drugs that enhance the NMDA receptor function as possible therapeutic agents or as adjuvants to the conventional antipsychotic treatments.[76]

Glycine is a positive allosteric modulator and obligatory coagonist at the NMDA receptor. This allosteric regulation is a potential target for the drugs that would increase the NMDA-mediated neurotransmission. The agonists of the glycine action site seem to be effective in reducing the negative symptoms and the cognitive deterioration in patients with schizophrenia when they are added to antipsychotic treatment, except for clozapine. Their beneficial effects on the positive and depressive symptoms are not as clear. Within the agonists of glycine, D-serine seems to be the most promising agent.[77]

Glycine reuptake inhibitors. Some pre-clinical findings suggest that the glycine reuptake inhibition could be a possible and feasible option to enhance the NMDA receptor mediated neurotransmission and possibly for the treatment of schizophrenic patients.[78]

Glutamate reuptake inhibitors. Post-mortem studies in schizophrenic patients showed alterations in the genetic expression of the glutamate transporters. Furthermore, preclinical studies demonstrated that chronic treatment with clozapine or haloperidol may underregulate the EAAT3 glutamate transporter in the infra-limbic and hippocampal cortex. Thus, glutamate reuptake inhibitors such as the EAAT3 antagonists may increase the synaptic availability of glutamate and increase the glutamatergic action in the postsynaptic neuron and consequently it may produce therapeutic effects in some symptoms, following the model of the decrease in glutamatergic activity in schizophrenia.[79,80]

AMPA/kainate receptor antagonists. Some findings suggest that the AMPA/kainate receptor may have an antipsychotic effect and that it would be useful in the treatment of cognitive deficits when hypofunction is suspected in the NMDA receptor.[80]

Ampakines. Ampakines are a type of compound that allosterically enhance the function of the NMDA receptor. They have been proposed as a potential adjuvant treatment for schizophrenia. Some preliminary findings propose that the chronic administration of an ampakine may improve the negative and cognitive symptoms in schizophrenic patients who have also received clozapine.[81]

Glutathione precursor. Glutathione is the principal non-enzymatic antioxidant. A decrease in glutathione levels in the cerebrospinal fluid and in the medial prefrontal cortex of treatment-resistant schizophrenic patients has been observed. Glutathione supplements with glutathione precursors could be an interesting strategy in schizophrenia in terms of preventing oxidative stress and enhancing neurotransmission in the brain NMDA receptors. The latter is due to the fact that glutathione enhances the response of the NMDA receptor to glutamate, thanks to the redox regulation of the action site.[82]

Noradrenergic agents

Alpha-2-adrenergic receptor agonist or antagonist. Norepinephrine plays an important role in the cognitive function of the prefrontal cortex due to its action on the alpha-2-adrenergic receptors situated there. Clonidine (alpha-2 agonist) improves the mediated cognitive dysfunction in the prefrontal cortex in schizophrenia. Another selective alpha-2 agonist, guanfacine, demonstrated its efficacy and safety in a double-blind controlled study as adjuvant treatment of the cognitive deterioration in schizophrenia. The patients who received guanfacine combined with risperidone showed significant improvement in the areas of work memory and attention in comparison with those who received FGAs plus guanfacine. The potential capacity of the alpha-2 agonists to improve cognitive behavior in prefrontal cortex dependent areas seems to have great importance in the search for a new drug approach for schizophrenia.[83,84]

Clozapine and risperidone have potent antagonic properties on the alpha-2 receptors, that seem to be involved in the functional actions of clozapine in humans and that contribute to mood improvement.[85]

COMT inhibitors. Studies on mice with COMT (catechol O-methyl-transferase) deficiency have shown that the dopamine levels are increased in the prefrontal cortex but not in striatum nucleus. Alterations of the prefrontal dopamine function associated with work memory seem to be important features of schizophrenia and some alleles of the COMT gene act in families with a high incidence of the disease.

Tolcapone, a selective inhibitor of COMT has been demonstrated to improve work memory in rodents as well as the cognitive dysfunction in advance Parkinsonian disease if it is associated to therapy with l-DOPA. However, it has been removed from the market in Europe and Canada due to its higher risk of severe hepatic dysfunction and in the United States, the level of the hepatic enzymes must be monitored, which limits the use of this drug to a large degree.[86,87]

Cholinergic agents

Alpha-7 nicotinic receptor agonist. Nictonic receptors of acetyl choline have been implicated in the cognitive function and formation of the sensory processing. Genetic studies that associate the alpha-7 nAChR gene with sensory processing deficits in schizophrenia, together with decreases of the receptor in specific zones of the brain of schizophrenic patients, propose that this receptor could be a relevant therapeutic target in schizophrenia. Agonists of the alpha-7 nAchR hour being developed in clinical trials on schizophrenia, without exactly knowing if these agonists have any benefit on the different symptoms and the long-term use of these drugs could induce desensitization of the receptors, giving rise to tolerance and thus limiting the duration of their efficacy.[88,89]

Alpha-4-beta-2 nicotinic receptor agonist. It has been proposed that these receptors play an important role in many of the behavioral actions of nicotine. A selective agonist of the alpha-4-beta-2 receptor has been demonstrated to stimulate dopamine, norepinephrine and acetyl choline release in the prefrontal cortex and hippocampus in rats. These findings suggest that the agonist of this receptor could produce a therapeutic benefit in the treatment of cognitive deficits and schizophrenia.[90]

Allosteric modulators of nicotine receptor and acetylcholinesterase inhibitors. The presynaptic nAChRs receptors are capable of regulating acetylcholine release and other neurotransmitters, such as glutamate, serotonin, and GABA, which could contribute to the schizophrenia symptoms. In cases studies, it has been proposed that the adjuvant administration of galantamine, a positive allosteric modulator, improves the negative symptoms in patients with treatment resistant schizophrenia.

Different case studies and an open label trial of the adjuvant donepecil, a reversible AcHe inhibitor, have demonstrated some of its beneficial effects on cognitive deterioration in schizophrenia.[91,92]

Muscarinic receptor agonist. The SGAs clozapine and olanzapine are partial agonists of the cholinergic receptors M_1, M_2 and M_4. In animal models, muscarinic agonists have activity on the negative symptoms, cognitive dysfunction and affective disorders, thus proposing the potential utility of these agents in the treatment of schizophrenia. One example, xanomeline, has shown its positive effects on the cognitive and psychotic symptoms in Alzheimer's disease. Different findings propose that partial muscarinic agonists could be effective in the treatment not only of the positive symptoms but also of the negative and cognitive symptoms of schizophrenia.[94,95]

Others agents

CB_1 Receptor antagonists. The acute cannabis poisoning may reproduce symptoms similar to those of schizophrenia, including hallucinations, altered judgment, false beliefs and cognitive dysfunction and the long-term usage of cannabis often induces negative symptoms similar to those of schizophrenia. Furthermore, cannabis may precipitate psychotic

symptoms in schizophrenia and can increase the risk of developing the disease. A cannabinoid hypothesis of schizophrenia has been developed. It states that be cannabinoid receptors and their endogenous activator system could be deregulated in schizophrenia.endogenous cannabinoid system includes the CB_1 and CB_2 receptors. A selective CB_1 receptor antagonist can reduce the induced hyperactivity in gerbils by different stimulant drugs, including cocaine, amphetamine and morphine, known to produce or exacerbate schizophrenic symptoms. These findings suggest that the selective antagonists of the CB_1 receptor may be effective in the drug treatment of schizophrenia.[96,97]

Neurokinin 3 antagonist. The neurokinin 3 receptors seem to regulate the neuron dopamine activity of the midbrain. A non-selective NK_3 antagonist has been demonstrated in preliminary clinical trials to be effective in regards to placebo in the global evaluation of efficacy and in the measurement of positive symptoms and schizophrenia.[98]

Neurotensin agonist. The neurotensin is a neuropeptide that regulates the function of dopamine mesolimbic neurons and it has been involved in the pathophysiology of schizophrenia. The central administration of neurotensin induces behavioral and biochemistry of attacks that are very similar to the effects of the antipsychotics. Thus, there is great interest in the potential use of the neurotensin agonist as new antipsychotics.[99]

MAO-B inhibitors. It has been proposed that the negative symptoms of schizophrenia may be manifestations of regional deficit of brain dopamine activity, so that the increase of dopamine neurotransmission could be a beneficial treatment strategy. Selegiline is a MAO-B inhibitor that selectively enhances dopamine activity. Although different case series have shown the benefits of selegiline on the negative symptoms of schizophrenia, a double-blind controlled study of the drug as adjuvant to antipsychotic treatment failed to offer any therapeutic benefit. Up to now, there have not been any conclusive results regarding the effects of the MAO-B inhibitors in schizophrenia.[100,101]

PDE10 inhibitors. PDE10 is a recently identified cyclic phosphodiesterase and some studies suggest that its selective inhibitors may constitute a target for the development of new antipsychotic types.[103]

Nitric oxide synthase (NOS) inhibitors. Nitric oxide (NO) in an important inter- and intracellular messenger in the central nervous system. Preclinical studies have demonstrated that inhibition of nitric oxide synthase may lessen the hyperactivity produced by the NMDA antagonists, but not by amphetamines. In treatment resistant schizophrenia, methylene blue (a NOS inhibitor) moderately improves the symptoms. However, it must be pointed out that all of the available NOS inhibitors may produce serious adverse effects, including hypertension and cognitive dysfunction.[104,105]

Neurosteroids. Dehydroepiandrosterone: in chronic schizophrenics, significantly reduced levels of dehydroepiandrosterone (DHEA) are observed. Furthermore, there are some case reports that proposed that DHEA may be useful in the treatment of schizophrenia, especially for the negative symptoms. A recent study on DHEA as adjuvant to antipsychotic treatment of chronic schizophrenics with prominent negative symptoms suggests that it can improve the negative, depressive and anxiety symptoms characteristic of the disease, especially in women.

Pregnenolone: some findings have proposed that pregnenolone and pregnenolone sulfate may have therapeutic potential to improve the cognitive deficits observed in schizophrenia.[106,107]

Neutrotrophic factors. The role of the neurotrophic factors in the pathophysiology of schizophrenia is becoming an important subject of research. Neurotrophic factors such as the nerve growth factor (NGF), the brain-derived neurotrophic factor (BDNF) and neurotrophin may play a decisive role in the neurodevelopmental process. Thus, the pathological alterations of the neurotrophic factor system can entail poor neural development, migration deficits and disconnections, all of which have been defended as pathogenic factors characteristic of the hypotheses of neural development for schizophrenia.[108] The drugs that selectively stimulate the production of neurotrophic factors could represent a new possibility to prevent the progression of schizophrenia and increased morbidity.[109,110]

FUTURE LINES

Although a recent meta-analysis suggests that some SGAs are more effective then the FGAs, it cannot be accurately predicted which patients will respond better to a specific antipsychotic drug. Significant differences are being found between the new antipsychotics, so that the choice of the drug needs to be evaluated for each patient individually. It is very likely that the individual genetic differences are important determining factors in the efficacy and an adverse effects of the antipsychotic medication. Thus, the response to the drug can be improved for each patient by the identification of the polymorphisms of a single nucleotide in the DNA of the patients. Knowledge of the relationship between the specific genetic polymorphisms involved in the pharmacokinetics and pharmacodynamics of a drug may lead to a better design of the drug and to an individualized pharmacotherapy. The studies are becoming more and more sophisticated and provide detailed information on the individual morphological changes of the brain, the circuits and pathways involved in the different aspects and stages of schizophrenia.[111-113]

Up to now, there are no drugs without activity or affinity for the D_2 dopamine receptor that have been shown to have antipsychotic efficacy. Therefore, the development of new

compounds aimed at systems other than that of dopamine will probably be used as an adjuvant or in combined treatments used because the application that they may have in monotherapy.

With the improvements in the drug treatment that have been observed in the last decade, the purpose of the therapy for schizophrenia has varied from relief of the psychotic symptoms to other psychopathological domains, including negative and emotional symptoms, cognitive deficits and functional deterioration that prevent the daily functioning of these patients, reintegration into the society, and recovery. At present, there is much work to do in the development of treatment strategies and the determination of their adequate use, together with adjuvant and psychosocial therapies.

DISCUSSION

The drug profile of the antipsychotic seems to have significant clinical importance, so that the professionals choose to change from one drug to another, «seeking efficacy where others have failed.» recent studies support the theory that the antipsychotics may modify the deteriorating course of schizophrenia,[114] considering that the psychotic symptoms, above all, the greater their duration, debut and period of time without receiving treatment, are associated to a worse prognosis, and to a progressively more deteriorating course.[115] If we take into account that these drugs act by inhibiting the symptoms of psychosis, we could probably say that the antipsychotics are also a little anti-schizophrenic in the sense that they may interfere with the deteriorating course of the disease, as has been seen in some studies in patients have not received medication *(Duration of Untreated Psychosis)* and with the hypothesis of neurotoxicity and synaptic connectivity.[116]

From the clinical point of view, it seems that there is a linear relationship between the effective clinical dose and the dopamine blockage, that is better observed in the first-generation antipsychotics (Fig. 2), while this linearity does not exist in the second-generation antipsychotics, as they have a very heterogeneous pharmacological profile. It could be stated that the first-generation antipsychotics would have a limited therapeutic window while the second-generation ones would have a wider therapeutic window.

However, in spite of all of this, the atypicality concept is still controversial, given that the typical/atypical classification is a highly clinical and basically qualitative one, that is only based on the atypicality that is presupposed to clozapine.

Psychopharmacological research efforts have focused on developing compounds with unique combinations of effects at different perisynaptic neurotransmission action sites. Future research efforts must move beyond the strategies that develop drugs that only focus on the modulation of the neurotransmission in the synapsis and develop agents that can affect other cell functions, including signal transduction, signaling pathways and gene expression. Furthermore,

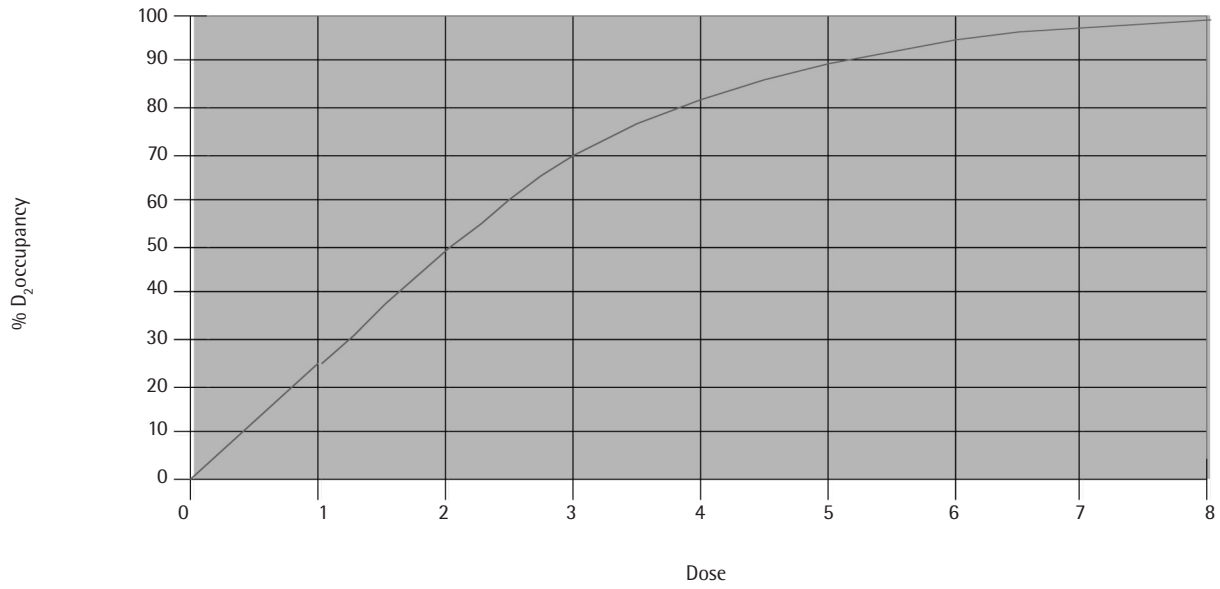

Figure 2 *Linear relationships between clinically effective dose and dopamine blockage.*

the efforts to identify genetic mechanisms that underline the mental disease will reveal new targets for the pharmacological development. One of the important objectives of the pharmacological research should be the development of new ideal antipsychotic agents with limited associated risk, rapid action, more effective treatment for the negative, affective and cognitive symptoms, an improvement in the recurrence rates and reduction or disappearance of the accumulated morbidity. An important aspect to keep in mind is that the patients with schizophrenia have elevated comorbidity with medical conditions, and this point should be kept in mind in order to avoid undesirable side effects that may worsen the medical condition.[117,118] The hope for better progress is found within the development of a number of different basic and clinical strategies in neuroscience. However, with these novelties it is likely that we will achieve this progress in the near future.

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