Neurobiological bases of quetiapine antidepresant effect in the bipolar disorder

INTRODUCTION

Bipolar disorder is considered one of the ten major public health problems in the world and one of the conditions having the greatest disease burden. Its pharmacological treatment is complex. The treatment regimes used are often modified according to the disease phase and, in the clinical practice, multiple therapy with three or more drugs is very...

Bases neurobiolóxicas del efecto antidepresivo de quetiapina en el trastorno bipolar

El trastorno bipolar constituye un importante problema de salud pública en el mundo, siendo la fase depresiva la más importante en términos de frecuencia, duración y afectación de la calidad de vida. El tratamiento habitual de la depresión bipolar suele incluir antidepresivos, eutimizantes y antipsicóticos en diversas combinaciones, sin que ninguno de ellos disponga de la indicación para ello. La quetiapina se ha convertido en el primer fárma...
frequently used. These, on the other hand, generally belong to different therapeutic groups and, consequently, have different action mechanisms. One of these therapeutic groups is antipsychotics, whose presence in the treatment of bipolar disorder is increasingly more common.

The depressive phase of bipolar disorder is the most important in terms of frequency and duration. Different studies have shown that patients with bipolar disorder spend more time in the depression phase than in the manic phase, and that the depressive phases have a greater impact than any of the other phases of the disease, both on functioning and quality of life of the patient as on the risk of suicide.²⁻⁵ Judd et al.³ found that the patients with type 1 bipolar disorder had depressive symptoms three times longer than those with manic/hypomanic symptoms. In the case of type 2 bipolar disorder, this value increases, reaching the time with depressive symptoms of 40 times that of those with hypomanic ones.¹ The clinical importance of these findings directly affects the therapeutic management. Furthermore, a significant percentage of patients have subsyndromic symptoms after remission of the acute episodes, fundamentally depressive type, which have been associated to worse symptoms after remission of the acute episodes, fundamentally depressive type, which are likely to influence the therapeutic management. Furthermore, a significant percentage of patients have subsyndromic symptoms after remission of the acute episodes, fundamentally depressive type, which have been associated to worse symptoms after remission of the acute episodes, fundamentally depressive type, which are likely to influence the therapeutic management.

In spite of the enormous impact of the depressive symptoms on the course of the disease, until recently, there was no drug available with a specific indication for the treatment of bipolar depression. The drugs used most in the clinical practice to treat this phase, as the antidepressants and some mood stabilizing drugs, have some limitations, such as their slow action onset, side effects, absence of response in a part of the patients, etc.

Bipolar depression has been treated traditionally with antidepressants, known for their efficacy in the treatment of unipolar depression.⁴,⁷ Standing out among them is the use of selective serotonin reuptake inhibitors (SSRI) and dual serotonin-norepinephrine reuptake inhibitors (SNRI). However, the use of antidepressants in short and long term monotherapy in bipolar depression is debatable, due to the risk of induction of shift to mania or rapid cycling.⁵,¹⁰ Although the clinical data on the efficacy of its use in combined treatment with mood stabilizers are limited, in the clinical practice this drug combination is the one used the most in the treatment of bipolar depression in Spain, even though there is no clear evidence on its benefits.¹¹ Thus, in the STEP-BD study, in which the use of antidepressants as adjuvant therapy to mood stabilizers versus placebo was compared, no differences were found in terms of duration of the recovery, although the proportion of shifts also did not increase.¹²

In regards to the mood stabilizers commonly used, the most important data that support the use of lithium, although it lacks a specific indication in bipolar depression, is based on a meta-analysis of 32 randomized clinical trials that compared lithium vs placebo and other drugs in the management of mood disorders in the long term. This meta-analysis concluded that the patients treated with lithium have a lower risk of death by suicide than patients who received an alternative treatment, whether placebo or another treatment.¹³ However, in the studies on bipolar depression, lithium presents a long latency of this effect (6–8 weeks). This is an important limitation for its use.¹⁴,¹⁵ On the other hand, the two studies performed with valproic acid in acute depression showed positive results. However, the sample size was so small (N=25 and N=18, respectively) that great care must be used when interpreting the results.¹⁶,¹⁷ In regards to lamotrigine, of the five studies carried out in the acute depressive phase, only one was able to demonstrate significant differences compared to the placebo. In the remaining four, the results were not significant,¹⁸ this being a reason why lamotrigine has no therapeutic indication for the acute phase of bipolar depression.

On the other hand, atypical antipsychotics have been used widely in the treatment of mania and practically all have a specific indication in this phase. The studies carried out with olanzapine made it possible for this antipsychotic to be approved for use in the prevention of recurrences of mania in patients who had previously responded to olanzapine in the acute mania phase. However, studies that were conducted in bipolar depression showed some anti-depressive efficacy, but they were based on the improvement of symptoms that are not considered core in depression, such as inner tension, sleep disorders, and appetite disorders.¹⁹ Olanzapine does not have a specific indication for the treatment of bipolar depression.²⁰

Recently, the Spanish Drug Agency has approved the use of quetiapine, both in its immediate release formulation and extended release one, for the treatment of depression within type 1 and type 2 bipolar disorder, converting it into the first drug in Europe to obtain this approval.

The clinical trials conducted with immediate release and extended release quetiapine in bipolar depression have demonstrated that it has short and long-term antidepressant activity, which is the basis for the previously mentioned indication. Furthermore, two already published clinical trials in maintenance phase (clinical trials 126 and 127)²¹,²² have shown that quetiapine is effective in the prevention of manic and depressive recurrences in the long-term treatment, and independently of the index episode of the patient (manic, depressive or mixed), thus demonstrating its potential long-term capacity for mood stabilization.

The recent updates of the clinical practice guidelines consider quetiapine as a drug of first choice in the treatment of bipolar depression, both in type I as well as type II bipolar disorder. One of these guidelines, the CANMAT of 2009,²³ which at this time has been assumed to belong to the In-
International Society for Bipolar Disorders (ISBD) after the incorporation of international experts, manifests that the level 1 of scientific evidence supported the use of quetiapine as a drug of first choice in bipolar depression in its 2007 issue (considering the results of the BOLDER I and II study).\textsuperscript{24,25} has been reinforced with the distribution of the new results (studies 002, EMBOLDEN I and II).\textsuperscript{26-29}

Parallelly to these results, an extensive analysis of the action mechanism of quetiapine and of its principal metabolite, norquetiapine, as well as the discovery that norquetiapine specifically blocks the norepinephrine transporter (NET), are findings that could contribute to explaining the differential profile of efficacy on depressive symptoms of quetiapine in the bipolar disorder compared to other atypical antipsychotics.

In summary, the efficacy of quetiapine in bipolar depression would be explained by its action on the dopaminergic and serotoninergic systems, common to other drugs of its class, but also thanks to a specific action on the norepinephrine system that it shares with other antidepressants. All of this grants it a unique multireceptorial profile that would provide it with clinical efficacy both in the manic phase as well as in the depression one and in the prevention of recurrences of both poles.

The purpose of this article is to review the pharmacokinetic and pharmacodynamic profile of the different formulations of quetiapine and its metabolites, and to provide a scientific basis that makes it possible to place this drug in the setting of depression and mood stabilization beyond its effect as an antimanic and antipsychotic drug.

**PHARMACOKINETICS**

Quetiapine is a dibenzothiazepine derivative for which there are currently two galenic formulations: an immediate release (IR), which is administered twice a day, and an extended release (ER), with a single daily administration.

The oral absorption of IR is rapid, reaching maximum serum concentrations (Cmax) at 1 to 2 hours after the administration of the dose.\textsuperscript{30,31} There are no absolute data on its bioavailability (unaltered fraction of the drug that reaches the system circulation) due to the absence of an intravenous formulation. However, it has been estimated that at least 70% of the oral dose is absorbed.\textsuperscript{30,32} In fact, the relative bioavailability of the tablets compared with that of a solution was approximately 100%\textsuperscript{30}.

The elimination half life (time that it takes for this serum concentration to be reduced by half, t1/2) ranges from 4 to 8 hours, according to the different studies,30 reaching the steady-state at approximately 48 hours. Quetiapine IR shows a linear pharmacokinetics in the range of the dose studied: 375 mg twice a day and 250 mg three times a day.\textsuperscript{30,31} It is approximately 83% bound to plasma proteins 83\%\textsuperscript{30}.

Quetiapine is mainly via hepatic metabolism, above all due to the action of the cytochrome P450 (CYP3A4), which can cause metabolic interactions in presence of enzymatic inductors or inhibitors that affect it (for example, phenytoin, ketoconazole or thioridazine).\textsuperscript{30,31} There are no genetic polymorphisms that clinically affect the functionality of CYP3A4, so that no inter-ethnical variations or the existence of different individual patterns having a genetic base are expected in the metabolism of quetiapine. Renal excretion is one of the secondary elimination pathways, approximately 1% of quetiapine or any of its metabolites being recovered after a dose of 400 mg.\textsuperscript{30}

Eleven metabolites of quetiapine, two of them active, have been described. Of these, the most important one is N-desalkylquetiapine (norquetiapine). These metabolites form rapidly and have a tmax similar to that of the original compound, as has been observed in a study performed in both a pediatric and adult population.\textsuperscript{31} Regarding norquetiapine, its elimination half-life was mildly superior to that of quetiapine (11 h vs. 7 h) in both populations.

In regards to the pharmacokinetic profile of the two formulations of quetiapine, according to Figueroa et al.,\textsuperscript{35} the Cmax of the ER is 13% less than that obtained with the IR and the time to reach it (tmax) is greater (5 h vs. 2 h). However, the AUC of ER quetiapine after a single dose was similar to the AUC of IR quetiapine with the same total does divided into two doses. This indicates that there are no significant differences in the bioavailability of both formulations. As with IR quetiapine, the pharmacokinetics is linear in the dose range studied (up to 800 mg). This means that the increases of the serum concentrations are proportional to the dose increases.\textsuperscript{33} The pharmacokinetic profile of ER quetiapine allows faster titration than with IR quetiapine in schizophrenia and mania, with administration of a single dose. This assures the maintenance of the plasma concentrations within a therapeutic range for a longer period, and without increasing the risk of concentration-dependent side effects.

The safety and tolerability data with ER are similar to those seen for IR quetiapine, both in schizophrenia and in mania, as well as in bipolar depression. In a study conducted with IR quetiapine treated patients who were switched to ER quetiapine, no significant differences were observed in these aspects.\textsuperscript{32,34} However, a recent study\textsuperscript{35} indicates the differential profile in the sedation pattern with both formulations. The results show that the initial sedation pattern would have less intensity and a later onset than with the extended release formulation.
PHARMACODYNAMICS

Effects on the dopaminergic system

Although the alterations of neurotransmission of these serotonergic and noradrenergic circuits are those classically related with the pathophysiology of depression, it can be concluded from the data currently available that the single action on these receptors is probably not enough to obtain optimum efficacy as the modulation of the dopaminergic activity is also important.\textsuperscript{36,37} It has been proposed that both an alteration of dopamine (DA) release and the sensitivity of the dopaminergic receptors could form a part of the pathophysiology of depression.\textsuperscript{37,38}

In affective disorders, there seems to be significant involvement of the mesocortical and mesolimbic pathways (figure 1). These pathways intervene in the regulation of the concentration capacity, working memory, motivation and experience of pleasure and reward. Therefore, it has been hypothesized that there is a DA deficit in these circuits which could explain part of the core symptoms of depression, as for example, anhedonia, social withdrawal, loss of motivation and psychomotor slowdown.\textsuperscript{37-40} Many authors consider that a DA deficit in the prefrontal cortex is related with the appearance of cognitive symptoms (through the dorsolateral projections) and affective symptoms (through the ventromedial projections).\textsuperscript{41} The antidepressant effect of the increase in DA release in the prefrontal cortex has been demonstrated in studies with pure dopaminergic agonists such as pramipexole.\textsuperscript{42}

Quetiapine and norquetiapine act as dopaminergic antagonists. \textit{In vivo}, they have demonstrated a relatively low affinity (Ki 100 nM – 1 μM) both for the family of the $D_1$ receptors (that include the $D_1$ and $D_2$ receptors) and for the family of the $D_2$ receptors (that include the $D_2$, $D_3$ and $D_4$).\textsuperscript{43-46} When each receptor is analyzed individually, it is observed that there is a greater affinity for the D2, for both quetiapine and the metabolite. Norquetiapine also shows a higher affinity than that of quetiapine by the $D_2$ receptors.\textsuperscript{47} Some affinity has also been observed by the $D_3$ receptors.\textsuperscript{48} The dopaminergic antagonism in the areas of elevated density of $D_2$ receptors, as the limbic system and basal ganglia, is directly related with the antipsychotic and antimanic effect of quetiapine. It probably decreases the risk of shift to mania when used in the treatment of bipolar depression and favors its efficacy in the prevention of relapses of mania in the maintenance phase.

Quetiapine, as other second generation antipsychotics, exerts an action on the serotonergic receptors, also modulating in this way the concentration of synaptic DA: - Quetiapine and norquetiapine have a moderate to high affinity for the 5-HT\textsubscript{2A} (Ki= 38 nM and 2.93 nM receptors, respectively), on which they act as antagonists.\textsuperscript{49} One of the characteristics that is attributed to second generation antipsychotics is antagonism on 5-HT\textsubscript{2A} receptors that is relatively more potent than that exerted on the D2.\textsuperscript{43,48} The 5-HT\textsubscript{2A} antagonism would modulate the effects derived from the D2 blockade in the different areas of influence. Thus, while in the mesolimbic pathway, the 5-HT\textsubscript{2A} antagonism would not interfere with the antipsychotic action when the patient is in the manic phase, it would provide a certain grade of dopaminergic function on the nirostriatal, tuberoinfundibular and mesocortical level.\textsuperscript{41} This idea has been confirmed after observing that quetiapine produces a marked increase of the extracellular concentrations of DA in the areas of mesocortical projections.\textsuperscript{49} The importance of this finding is dual: on the one hand, the increase of the release of DA in the prefrontal cortex and in the hippocampus would be important in regards to the effect of quetiapine on depressive, negative and cognitive symptoms. On the other hand, it would at least partially explain that the therapeutic effect of quetiapine occurs with a dose associated to low frequency of extrapyramidal symptoms (EPS) and scarce hyperprolactinemia.\textsuperscript{48}

- It has been demonstrated that quetiapine decreases the density of 5-HT\textsubscript{1A} receptors in the prefrontal cortex\textsuperscript{43,49} while exerting an antagonist action on them.\textsuperscript{47} In this way, it minimizes the inhibition that the serotonergic neurons exerts on the release of DA and makes it possible for the DA concentration to increase in the prefrontal cortex.\textsuperscript{41} The relevance of these findings is that it has been observed that the decrease of the density of the 5-HT\textsubscript{1A} receptors is an endogenous adaptive phenomenon that occurs in depressed individuals, and it has been proposed as an important mediator in the success of the antidepressant treatment.\textsuperscript{50}
In turn, and as we will explain in more detail in the following, quetiapine increases DA release in the prefrontal cortex through the partial agonism on 5-HT$_{1A}$ receptors and of the modulation of the norepinephrine (NE) levels in the areas in which the DA transporter is present.

Within the second generation antipsychotics, quetiapine has a favorable profile of tolerability in relationship to the EPS. Its dissociation constant of the D$_2$ receptor is very low (K$_D$ = 0.64 nM). This implies that the velocity with which the molecule binds and dissociates from this receptor is elevated. The consequence is that quetiapine, as clozapine, but on the contrary to other antipsychotics, makes it possible for the receptor to be available for endogenous DA, so that the physiological transmission of DA continues in an attenuated way. The rapid dissociation of the D$_2$ receptor is related with the scarce appearance of EPS that is absorbed with quetiapine and clozapine. This is probably because a rapid $K_D$ would avoid the supersensitivity of the D$_2$ receptors, thus preventing the number of D$_2$ receptors in the striatal area from increasing (a phenomenon that is observed with the classical drugs).

In summary, a deficit of mesolimbic DA, and above all, of mesocortical DA seems to play a part in the pathophysiology of bipolar depression. Quetiapine, through its interaction with serotoninergic receptors (5-HT$_{1A}$ antagonism, decrease in the density of the 5-HT$_{3A}$ receptors, 5-HT$_2A$ antagonism, partial 5-HT$_1A$ agonism) could favor dopamine release in the prefrontal cortex and contribute to the improvement of the affective symptoms. On the other hand, the excess of DA in certain brain regions has been associated to the appearance of the manic pole of the bipolar disorder. Quetiapine could decrease the risk of a shift to mania by blockade of the D$_2$ receptors and the interruption of the dopaminergic signal in the areas with elevated density of the D2 receptors, such as the limbic system and the basal ganglia. It must be remembered that treatment of bipolar depression with antidepressants may entail a greater risk of shift to mania, but on the contrary to other antipsychotics, makes it possible for the receptor to be available for endogenous DA, so that the physiological transmission of DA continues in an attenuated way. The rapid dissociation of the D$_2$ receptor is related with the scarce appearance of EPS that is absorbed with quetiapine and clozapine. This is probably because a rapid $K_D$ would avoid the supersensitivity of the D$_2$ receptors, thus preventing the number of D$_2$ receptors in the striatal area from increasing (a phenomenon that is observed with the classical drugs).

Finally, the rapid dissociation of the D2 receptor would explain the low incidence of EPS compared with other antipsychotics that exert a more potent D2 blockade, as olanzapine.

**Effects on the serotoninergic system**

Antidepressants exert their action on the serotoninergic pathway, increasing the synaptic concentrations of serotonin by several mechanisms such as inhibition of the transporter, modulation of the 5-HT$_{1A}$ receptors (pre- and postsynaptics) or inhibition of the 5-HT$_{3A}$. The latter two are shared by quetiapine.

As has been mentioned previously, quetiapine and norquetiapine have a moderate to high affinity for the 5-HT$_{1A}$ receptors (Ki= 38 nM and 2,93 nM, respectively), on which they act as antagonists. The 5-HT$_{1A}$ antagonism would modulate the effects derived from the D$_3$ blockage, so that quetiapine has demonstrated that it favors a significant increase of the extracellular concentrations of DA on the mesocortical level, which would contribute to its effect on depressive, cognitive and negative symptoms.

Both quetiapine and norquetiapine behave as partial agonists of the 5-HT$_{1A}$ receptors for which they show a low to moderate affinity (Ki= 720 nM and 191 nM, respectively).

The 5-HT$_{1A}$ agonists have been involved in the efficacy of the treatment of depression and anxiety. This efficacy would be mediated, at least partially, by an increase of serotoninergic transmission. The greatest densities of this receptor are in the hippocampus, dorsal and median raphe nuclei, frontal cortex, rhinal cortex and amygdala. The role of the hippocampus within depression has been widely studied since it has been seen that there seems to be an atrophy of this organ in depressed individuals and that the increase of the serotoninergic neurotransmission could stimulate its morphogenesis. Within the hippocampus, principally, but also in the previously mentioned structures, the postsynaptic 5-HT$_{1A}$ receptor is considered crucial in the antidepressant response. The increase of sensitivity to 5-HT of the post-synaptic 5-HT$_{1A}$ receptors and the increase of density of the receptor binding sites improve the serotoninergic neurotransmission, as has been demonstrated in studies with tricyclic antidepressants and with electroconvulsive therapy. Quetiapine improves the serotoninergic transmission by the increase of the density of the 5-HT$_{1A}$ receptors in the prefrontal cortex, presenting some regional specificity when exerting its action preferentially on said area, hardly affecting the nucleus accumbens. Quetiapine also produces some increase in the density of the 5-HT$_{1A}$ receptors in the rhinal cortex, a structure that is closely related with the hippocampus by afferent and efferent projections. The agonism on the 5-HT$_{1A}$ receptors is also associated to a dose-dependent DA increase in the prefrontal cortex. This effect is also favored by the combined antagonism of D2 and 5-HT$_{3A}$, which generates a functional 5-HT$_{1A}$ agonism. Besides increasing the DA, quetiapine also increases the acetylcholine (Ach) by stimulation of the 5-HT$_{1A}$ receptors in the prefrontal cortex, a region in which there is a large number of these receptors in the neocortical glutamatergic pyramidal neurons involved in the cognitive function. It is considered that the Ach plays an important role in the synaptic plasticity related with learning and memory. Thus, the modulation produced by quetiapine would contribute to the improvement of these functions.

Norquetiapine also acts as antagonists of the 5-HT$_{1A}$ receptor, for which it has a high affinity (Ki= 18,5 nM). It...
is thought that this, together with 5-HT₂₆ blockage, would be related with the properties of quetiapine to improve and stabilize the cognitive function and mood status.⁴⁷ The antagonism on the 5-HT₂₆ receptors is related with the increase in the release of NE and DA in the prefrontal cortex, secondary to the inhibition of the GABAergic interneuron of the brainstem.⁴¹ The deficit of DA in the ventromedial area of the prefrontal cortex is related with the appearance of affective and negative symptoms, so that the increase of DA secondary to the antagonism of quetiapine on the serotonergic receptors would be translated into an improvement of these symptoms both in the context of schizophrenia and in the mood disorders.⁴¹

Quetiapine does not have any action on the seroton transporter.⁴⁷

### Effects on the noradrenergic receptors

Quetiapine shows a moderate affinity for the adrenergic α₂ receptors (Ki= 617 nM) while norquetiapine has a low affinity (Ki= 1290 nM). Functionally, they act as antagonists, increasing noradrenergic and serotonergic transmission by a blockade of both the α₂ auto- and heteroreceptors.⁴⁷ In animal models, it has been demonstrated that systemic administration of quetiapine increases the extracellular concentration of NE in the prefrontal cortex.⁵⁰

Different studies in depressed subjects have demonstrated greater density and functionality of both peripheral as well as cortical α₂ adrenergic receptors in comparison with healthy individuals.⁶¹⁻⁶³ It has been observed that the electrical activity of the noradrenergic neurons of the locus coeruleus, involved in the pathophysiology of depression, as well as the concentration of NE in their areas of projection increase after the administration of the α₂ adrenergic antagonist drugs.⁶⁴ The blockade of the presynaptic α₂ adrenergic receptors, together with the post-synaptic 5-HT₂₆ receptors, would contribute to the increase of the concentration of NE but also of DA and 5-HT, in the synaptic cleft.⁴⁸ The intrasynaptic increase of these three neurotransmitters would be related with the quetiapine mediated antidepressant action.

Furthermore, norquetiapine is a potent inhibitor of the norepinephrine transporter (NET) for which it has elevated affinity (Ki = 12 nM - 34.8 nM)⁵⁴,⁶⁷ (table 1). This is a mechanism by which some antidepressants (reboxetine, SRNI) act. However, it had not been observed up to now with any antipsychotic drug in therapeutic doses. In the prefrontal cortex, there is elevated density of NET and low density of DAT (DA transporter) so that it is the NET that is in charge of terminating the action of DA, by reuptake and then incorporating it into the neuron again.

With the inhibition of the NET in the prefrontal cortex, the amount of NE available in the synaptic space increases, but that of the DA also increases.⁴¹ On the other hand, the α₂ adrenergic antagonism, a receptor having presynaptic inhibitory character, potentiates the increase of the availability of NE induced by the blockade of the NET.⁶⁶ The antidepressant effect initiated secondary to the blockade of NET induced by norquetiapine could be accelerated as the inhibitory effect of the α₂ adrenergic receptors will cancel the antagonist properties on these quetiapine and norquetiapine receptors.⁶⁴

Thus, the elevation of DA and NE produced by quetiapine and norquetiapine through the inhibition of NET and of the α₂ adrenergic antagonism would, in practice, be trans-

<table>
<thead>
<tr>
<th>Drug</th>
<th>NET Kᵢ (nM)¹</th>
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<tbody>
<tr>
<td>Quetiapine</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>Norquetiapine ²</td>
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</tr>
<tr>
<td>Clozapine</td>
<td>3168</td>
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<tr>
<td>Olanzapine</td>
<td>&gt;10000</td>
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<tr>
<td>Duloxetine</td>
<td>1.17 – 20</td>
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<tr>
<td>Venlafaxine</td>
<td>1.060 – 6.310</td>
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</tbody>
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¹ Data obtained from the NIMH Psychoactive Drug Screening Program (http://pdsp.med.unc.edu/pdsp.php).
² Data obtained from Jensen et al., 2008⁶⁵.

lated into an antidepressant affect and an improvement in cognitive function.

### Effects on other receptors

The possible role of antipsychotics on other receptors such as the glutamatergics or GABAergics is still being studied.

Tascedda et al.⁶⁶ evaluated the effects produced by quetiapine on the glutamate NMDA and AMPA receptors and compared them with those observed with haloperidol and clozapine. The results indicated that quetiapine did not affect the expression of NMDA in the striate, contrary to haloperidol, whose extended exposure produces an increase in the mRNA levels that code for the NMDA receptor in this cerebral region. It is thought that these receptors would
play some excitotoxic role associated to the appearance of extrapyramidal effects with the classic antipsychotics.\textsuperscript{66} In the nucleus accumbens, the results with quetiapine are also different since, on the contrary to haloperidol, it is capable of producing adaptive changes in the expression of the different subunits of the NMDA receptor. Exposure to haloperidol, clozapine and quetiapine shows an increase of immunoreactivity in the nucleus accumbens, which indicates that this region is a target of these drugs. However, quetiapine, as clozapine previously, but not haloperidol, reduced the mRNA levels for some subunits of the NMDA receptor (NR-1 and NR-2). It has been proposed that the decrease of the expression of the subunits of the NMDA receptor in this region could contribute to restoring normality of the glutamategic neurotransmission. This study also revealed that quetiapine produces a significant elevation of the GluR-B and GluR-C subunits of the AMPA receptor in the hippocampus of rats, a finding that was not reproduced with haloperidol or clozapine. The levels of mRNA for the GluR-B subunit are reduced in the hippocampus of schizophrenic patients. Therefore, this finding could be relevant in the cognitive deterioration observed in these patients.\textsuperscript{66,67}

In another study performed by Tarazi et al. to evaluate variations in the density of the glutamategic receptors produced with olanzapine, risperidone and quetiapine and compare them with those produced by clozapine or haloperidol, it was observed that the three drugs decreased the density of the NMDA receptors in the caudate-putamen while increasing the density of the AMPA receptors in this same region, without significant changes in the cortical or limbic regions. The concentrations of the kainate receptors were not significantly modified in any region, possibly because of the low affinity shown by these drugs.\textsuperscript{66} These results were similar to those obtained previously with clozapine, but not with haloperidol.\textsuperscript{66} The authors propose that the changes observed in the NMDA receptors could emerge indirectly from the neurochemical changes produced by the interaction of these drugs with other neurotransmitter systems, as the serotoninergic and the dopaminergic ones, which are modulators of the dopaminergic neurotransmission. The changes in the 5-HT cortical receptors could suppress the neurotransmission in the corticostriatal projections that innervate the caudate and the putamen, and lead to a reduction in the expression of the striatal NMDA receptors. Suppression of the activity of the NMDA receptors is related with the lower impact of these drugs on the extrapyramidal system.\textsuperscript{66} The changes observed in the AMPA receptors are associated to post-transcriptional changes, since the mRNA levels are not modified. The antipsychotic-induced increase of the AMPA receptors could restore the cortico-striato-limbic glutamategic neurotransmission by the normalization of the glutamategic activity. As with the NMDA, the indirect action of these drugs on the 5-HT system could contribute to the increase of the density of the AMPA receptors found in the caudate and putamen. The changes in the cortical 5-HT\textsubscript{1A} (increase) and 5-HT\textsubscript{2A} (decrease) receptors after a continued treatment with these drugs could alter the AMPA mediated corticostrial glutamategic neurotransmission and lead to an increase in the post-transcriptional expression of the postsynaptic AMPA receptors in the caudate and putamen.\textsuperscript{66}

The histamine H1 and \((\alpha_{1})\) adrenergic receptors also form a part of the quetiapine receptorial profile. The sedative effects of a drug have been related, above all, with the affinity for these two types of receptors,\textsuperscript{41} although it is also thought that the 5-HT\textsubscript{1A} participate, being involved in the control of the quality of sleep.\textsuperscript{29} Furthermore, it has been observed that the dose administered may influence the sedation grade. Quetiapine has a relatively low affinity for the H1 receptors and \((\alpha_{1})\) adrenoceptor in comparison with other drugs of its class such as olanzapine and clozapine.\textsuperscript{20} The blockade of the \((\alpha_{1})\) adrenoceptors is also related with the possible appearance of low blood pressure during the treatment with quetiapine.\textsuperscript{41} On the other hand, the antagonism on the H1 histamine and 5-HT\textsubscript{1A} serotoninergic receptors is associated to weight gain, above all, if this antagonism is potent and simultaneous on both types of receptors. Considering the profile of quetiapine, its associated risk of weight gain is less than that of olanzapine.\textsuperscript{41}

**NEUROPROTECTION**

The phenomenon of neurogenesis is initiated after conception, when the embryonic stem cells began to differentiate towards immature neurons. In adults, this process continues from the adult stem cells, but only in two regions: dentate gyrus of the hippocampus from the neuronal precursors of the subgranular zone and olfactory bulb from the precursors of the subventricular zone.\textsuperscript{41,71} These neurons would integrate into the hippocampal circuit and play an important role in learning and memory.\textsuperscript{41} Factors such as stress, aging and disease negatively affect the functions of the hippocampus while learning, psychotherapy, exercise, some factors of endogenous growth and certain psychodrugs stimulate the neurogenesis.\textsuperscript{41} One of these endogenous factors is the BDNF (brain-derived neurotrophic factor), a neurotrophic factor synthesized mainly in the neurons and widely distributed by the brain that provides support to the cholinergic neurons and that has demonstrated a role in the stimulation of the functioning and survival of the dopaminergic, GABAergic, noradrenergic and serotoninergic neurons. Multiple factors may play a role in its expression, such as stress, the action of the neurotransmitters and the second messengers cascades, including the AMPAc.\textsuperscript{71} Currently, it is well established that the drugs with antidepressant potentiality revert the inhibition of the neurogenesis processes associated to stress and depression.

Several studies in animal models have demonstrated a beneficial effect of quetiapine on neurogenesis. This has led
to the consideration of a potential effect of improvement of the cognitive defects that schizophrenic or depressed patients may present.\textsuperscript{71-73} Xu et al.\textsuperscript{73} reproduced a state of decrease of expression of BDNF and the neurogenesis in an animal model subjected to a period of chronic stress. After, they examined the effects of different doses of quetiapine, venlafaxine and a combination of both on the hippocampal cell proliferation and the expression of BDNF. The results demonstrated that the administration of quetiapine or venlafaxine blocked the reduction of cell proliferation of the hippocampus that had previously induced the stress. Furthermore, the highest dose of both drugs also improved the expression of BDNF. Multiple post-hoc comparisons also demonstrated interactions between both drugs. The groups of quetiapine and of quetiapine + venlafaxine showed a cell proliferation superior to that of the group that only received the vehicle, while the group of venlafaxine was comparable to the vehicle group. When compared with the group that was not subjected to stress, the quetiapine + venlafaxine group obtained superior results in terms of cell proliferation and similar ones in regards to expression of BDNF.\textsuperscript{71} Luo et al.\textsuperscript{72} also studied the effects of quetiapine on cell proliferation in the hippocampus and the expression of the pCREB protein (phosphorylated cAMP response element-binding protein), which is located in immature neurons of the hippocampus and is linked with learning, neuronal survival and synaptic plasticity and whose activation stimulates the neurogenesis of the dentate gyrus of the adult. To do so, they used an animal model subjected to chronic stress. The experimentation subjects who received quetiapine demonstrated an increase of hippocampal cell proliferation and of the expression of pCREB. This led the authors to conclude that quetiapine has a neuroprotective potential that could contribute in humans to the therapeutic effect on the cognitive defects of patients with schizophrenia and depression.\textsuperscript{72}

Another cerebral protein related with stress is the heme-oxygenase-2 (HO-2). This is a constitutive protein whose gene does not respond to any stimulus except that of extended exposure to glucocorticoids, which has been demonstrated to reduce the immunoreactivity of HO-2 in the hippocampus. When several groups of rats were exposed to chronic stress and treated with quetiapine, venlafaxine or both, the results showed significant differences in the expression of HO-2 between the group that only received the control after exposure to stress and the one that received the combination of quetiapine + venlafaxine that were not reproduced in the groups with a single drug. According to the authors, the results suggest a synergic action of quetiapine and venlafaxine on the regulation of HO-2 and suggest the hippocampus as a target shared by both.\textsuperscript{73}

On the other hand, there are studies that also suggest a role of neural inflammation and immunogenetics in schizophrenia through the microglia, so that its activation would lead to the release of cytokines, nitrate oxide (NO) and reactive oxygen molecules that would mediate the inflammatory process, leading to, in the end, neuronal damage and apoptosis, directly affecting the neurogenesis of the adult hippocampus.\textsuperscript{74-76} In a study performed by Bian et al.\textsuperscript{74} with murine microglial cell cultures and the drugs of perospirone, quetiapine and ziprasidone to evaluate the anti-inflammatory effects on the activated microglia, it was observed that the three drugs significantly inhibited the NO concentration in a dose-dependent way. Furthermore, quetiapine and perospirone inhibited the release of TNF-α, also being dose-dependent, while ziprasidone increased it.\textsuperscript{76} The authors concluded that based on these data, an anti-inflammatory effect could be considered, above all, of quetiapine and perospirone, through the inhibition of the activated microglia, which in turn would be of advantage to neurogenesis and oligodendrogenesis.\textsuperscript{76}

**CONCLUSIONS**

This scenario demonstrated within this article reflects the complexity of treatment of a disease whose pathophysiology is multifactorial, with different therapeutic targets from the molecular point of view, which affect the principal neurotransmission pathways, that is, noradrenergic, serotonergic and dopaminergic.

Quetiapine has demonstrated its efficacy in the treatment of acute bipolar depression, based on an action on these three pathways. Both the inhibition of NET, a novel mechanism between drugs considered antipsychotics, such as the partial 5-HT\textsubscript{1A} agonism, and the 5-HT\textsubscript{2C} antagonism have been demonstrated to modify the mood state, through the increase of the concentrations of 5-HT, NE and DA in the prefrontal cortex. If we add the 5-HT\textsubscript{2A} antagonist action and the reduction of the density of the 5-HT\textsubscript{2A} receptors to this, which also contribute to the increase of the cortical DA, and the adrenergic α\textsubscript{2} antagonism, above all presynaptic, we obtain a fundamental profile to explain the anti-depressive effect of quetiapine, that no other antipsychotic or antidepressant drug on the market shares.\textsuperscript{75}

Furthermore, a promising field in which research has only just begun in recent years with encouraging results is still open, that of neuroprotection. Although some time is needed to confirm the findings obtained in animal models in humans, the data available up-to-date suggest a potential neuroprotective effect of quetiapine that could contribute beneficially in the long term treatment of bipolar disorder.

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