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# Ziprasidone: from pharmacology to the clinical practice. One year of experience

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More than a year after the marketing of the atypical anti-psychotic ziprasidone, data from research studies and clinical practice have provided a fair amount of useful information for its practical use in the treatment of schizophrenia. Its pharmacodynamical characteristics and the results from clinical trials with a flexible dose seem to justify the need to administer doses in a range higher than what was initially foreseen, with an initial minimum of 120 mg per day and a fast titulation up to 160 mg per day. Such doses make it possible to achieve sufficient plasma concentrations to occupy at least 60% of the $D_2$ receptors from which the anti-psychotic effect derives. Moreover, its anti-depressive activity and its non-sedative profile have been confirmed, with a favorable effect on attention and other cognitive functions of the patient, according to its high affinity for $5HT_{1A}$ and $D_1$ receptors and the inhibition of serotonin and noradrenaline re-uptake.

Finally, the low affinity of this drug for α-adrenergic, histaminergic and muscarinic receptors favors a good tolerability profile, with a neutral effect on weight, and a lack of anti-cholinergic effects. Results from different clinical trials show that the use of doses in the higher range is associated to a faster and more pronounced clinical improvement without adding a higher risk of adverse events.

**Key words:**
Ziprasidone. Schizophrenia. Doses. Tolerability.

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## Ziprasidona: de la farmacología a la práctica clínica. Un año de experiencia

Transcurridos más de 2 años desde la comercialización del antipsicótico atípico ziprasidona los datos procedentes de estudios de investigación y de la práctica clínica han proporcionado abundante información útil para su manejo práctico en el tratamiento de la esquizofrenia. Sus características farmacodinámicas y los resultados de los estudios clínicos con dosis flexible parecen justificar la necesidad de administrar dosis en el rango superior de las inicialmente previstas, con un mínimo inicial de 120 mg/día y una rápida titulación hasta 160 mg/día. Dichas dosis permiten alcanzar concentraciones plasmáticas que permiten ocupar al menos el 60% de los receptores $D_2$ del que se derivará el efecto antipsicótico. Además, se confirma su actividad antidepresiva y su perfil no sedante, con un posible efecto favorable sobre la atención y otras funciones cognitivas del paciente, en relación con la elevada afinidad frente a receptores $5HT_{1A}$ y $D_1$ y la inhibición de la recaptación de serotonina y noradrenalina.

Por último, la escasa afinidad de este fármaco frente a receptores α-adrenérgicos, histamínicos y muscarínicos favorece un buen perfil de tolerabilidad, con un efecto neutro sobre el peso y falta de efectos anticolinérgicos. Los resultados de diversos ensayos clínicos muestran que el uso de dosis en el rango superior se asocia a una mejoría clínica más rápida y pronunciada que dosis inferiores, sin añadir un mayor riesgo de efectos adversos.

**Palabras clave:**
Ziprasidona. Esquizofrenia. Dosis. Tolerabilidad.

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## INTRODUCTION

Schizophrenia is a very complex disease that has serious repercussions in the patient's functioning. As a consequence, it may affect his/her family, work and social setting. It is characterized by the presence of a large diversity of positive, negative and affective symptoms that are shown over an underlying cognitive deficit. It has a chronic course that occurs with exacerbation and remission periods. The symptoms, that cannot be attributed to alterations of a single neuroanatomical or neurochemical system, vary greatly during the disease course and among different patients. At present, the repercussion of the symptomatic spectrum and cognitive deficit on the patient's functioning, treatment compliance and its long term results, evaluated in terms of quality of life and social reintegration, are aspects considered to be essential in the therapeutic approach to the disease.

Drug treatment consists in the administration of at least one of the so-called antipsychotic drugs that tend to be classified as first (typical) or second generation (atypical). It seems clear that the latter have accounted for a significant improvement of the therapeutic options as it is effective in the control of the positive and negative symptoms, with less risk of adverse effects, especially of extrapyramidal syndromes (EPS)[1].

Within each generation of antipsychotics and especially within second generation ones, there are important differences in the chemical structure of the different components. They justify the presence of different action mechanisms, pharmacokinetic properties and adverse effects profile. Any of these differences may be important when selecting treatment to adapt it best to the needs of each patient and thus favor the final therapeutic result.

Ziprasidone is the most recent second generation antipsychotic agent marketed in Spain (January 2003) for oral and intramuscular treatment of schizophrenia and control of the acute agitation of this disease. More than one year since this new antipsychotic has been on the market, accumulated experience has made it possible to profile some characteristics that were not perfectly defined when it was first marketed, a frequent fact in the case of almost all the new antipsychotics. In this sense, it is well to remember that the strict inclusion and exclusion criteria and controlled conditions under which clinical trials usually take place may lead to an important difficulty for the extrapolation of its results to the population of patients who receive treatment in the usual medical practice. The history of antipsychotics is marked by examples in which the daily clinical experience has conditioned changes in the drug management (for example, in the dose used) and even new data regarding the efficacy or safety profile of the antipsychotic.

This article aims to use a wide perspective to analyze accumulated experience with ziprasidone, going from its action profile to the receptor level to the results from the studies conducted during both the clinical development phase and those of the publications after its marketing. This review aims to stress, above all, aspects of clinical relevance and propose a series of recommendations for the drug management that are useful for the clinician who chooses this therapeutic option in the daily clinical practice.

## DIFFERENTIAL PHARMACODYNAMIC CHARACTERISTICS OF SECOND GENERAL ANTIPSYCHOTICS

### Action on dopaminergic and serotoninergic receptors

First generation or conventional neuroleptics have demonstrated that they are effective in the control of positive symptoms of schizophrenia over many years. These symptoms have been related with the existence of an excess of dopamine in the synapsis of the mesolimbic system. In fact, it is still considered that the antipsychotic effect is measured by the central blockage of the postsynaptic receptors of the $D_2$ family in the mesolimbic level[2-4]. It should be remembered that the study of dopaminergic receptors have made it possible to characterize 2 different families: $D_2$ (that includes the $D_2$, $D_3$ and $D_4$ receptors) and $D_1$ (with the receptors $D_1$ and $D_5$ receptors).

It has been stated that at least 60% of the $D_2$ family central dopaminergic receptors must be occupied to achieve adequate control of psychotic symptoms. Furthermore, the incidence of extrapyramidal symptoms (EPS) is also related with the absolute levels of $D_2$ occupancy, in this case, in the nigrostriatal level. This can occur after an occupancy threshold of 74%-82% and is more frequent when the $D_2$ receptors exceed 85%[6].

First generation neuroleptics have not been shown to be effective in the treatment of the primary negative symptoms and may also favor the appearance of negative symptoms secondarily to the presence of extrapyramidal symptoms and affective symptoms related with the treatment. On the other hand, its dopaminergic antagonist action on the mesocortical level could contribute to worsen the cognitive deficit of the patients.

Second generation antipsychotics produce a relatively potent antagonist effect on the $5HT_{2A}$ serotinergic receptors associated to a weaker antagonism of the $D_2$ family receptors. For some authors[7], the key to the differences in the effects with the first generation antipsychotics would be found in this characteristic. The $5HT_{2A}$ antagonism would make it possible to modulate the effects generated by the $D_2$ dopaminergic blockage in the different areas of influence. Thus, while the $5HT_{2A}$ antagonism in the mesolimbic pathway would not interfere with the antipsychotic action, the nigrostriatal and tuberoinfundibular level would facilitate a certain degree of dopaminergic function. This would reduce the risk of EPS and those due to prolactin release, respectively. In addition, increase of dopamine release in the prefrontal cortex and hippocampus could condition a favorable action on the negative symptoms and cognitive function.

Studies performed have demonstrated that pure $5HT_{2A}$ antagonists, such as setoperone or MDL 100.907[9] lack antipsychotic effects. However, when they are combined with conventional antipsychotics that only produce $D_2$ antagonism, they are capable of improving the control of positive and negative symptoms in schizophrenia and also of reducing EPS incidence.

As has been mentioned, the capacity of second generation antipsychotics to stimulate dopaminergic activity in the prefrontal cortex may be related with a favorable effect on cognitive function. In fact, it has been demonstrated in monkeys that this neuronal system is important in the opti-

mum performance of psychomotor functions through $D_1$ receptor activation[10]. Atypical antipsychotics may favor an increase of acetylcholine in prefrontal cortex due to different mechanisms. This could also favor cognition improvement[11].

*In vitro,* ziprasidone has shown better affinity for $5HT_{2A}$ receptors (Ki = 0.39 nM) than over the $D_2$ (Ki = 3.1 nM). Thus, it has a high quotient of $5HT_{2A}/D_2$ affinity, as is shown in table 1[12,13].

Several studies have analyzed the occupancy of $D_2$ and $5HT_{2A}$ receptors with ziprasidone, in vivo, using neuroimaging techniques (SPECT and PET). One of them that was recently published simultaneously analyzed the occupancy of $D_2$ and $5HT_{2A}$ receptors using PET in patients with schizophrenia or with schizoaffective disorder (SAD) treated with different doses of ziprasidone (20, 40, 60 and 80 mg every 12 hours)[14]. The results confirm the previous findings obtained in other studies with neuroimaging conducted in healthy voluntary subjects[15-18] since the percentage of occupancy of $D_2$ and $5HT_{2A}$ receptors showed a clear direct correlation with the plasma concentrations reached with ziprasidone (fig. 1). Occupancy of the $5HT_{2A}$ receptors exceeded that of $D_2$ over the entire range of plasma concentrations. The elevated quotient of $5HT_{2A}/D_2$ occupancy previous observed in vitro was confirmed *in vivo.* One of the most interesting aspects of this study was the demonstration that plasma concentrations of ziprasidone over 50 ng/ml, a concentration that is only obtained with the administration of doses over 120 mg/day of this drug, are needed to reach the threshold occupancy percentage of efficacy of the $D_2$ family receptors. This study establishes the need to administer this dose at least daily to guarantee antipsychotic efficacy. In addition, it confirms the elevated $5HT_{2A}/D_2$ quotient of ziprasidone and thus the possibility that this drug has a reduced incidence of EPS and certain efficacy in negative and cognitive symptoms.

The $5HT_{2A}/D_2$ antagonism profile is present in almost all the new antipsychotics except amisulpride, that only has a more specific antagonistic action on the $D_2$, $D_3$ and $D_4$ receptors. It has been stated that its atypical drug profile and thus its belonging to the second generation antipsychotic agents could be due to a greater affinity for the extrastriatal receptors ($D_3$), and to a lower occupancy of $D_2$ on the striate body level[19]. In a recent study that uses the SPECT to analyze the occupancy of $D_2$ family receptors with ziprasidone in patients with schizophrenia[20], it has been postulated that the efficacy of ziprasidone in positive symptoms and its lower risk of producing EPS than haloperidol could be due to a more effective blockage of $D_2$ family receptors on the limbic level ($D_3$) than the striatal one ($D_2$).

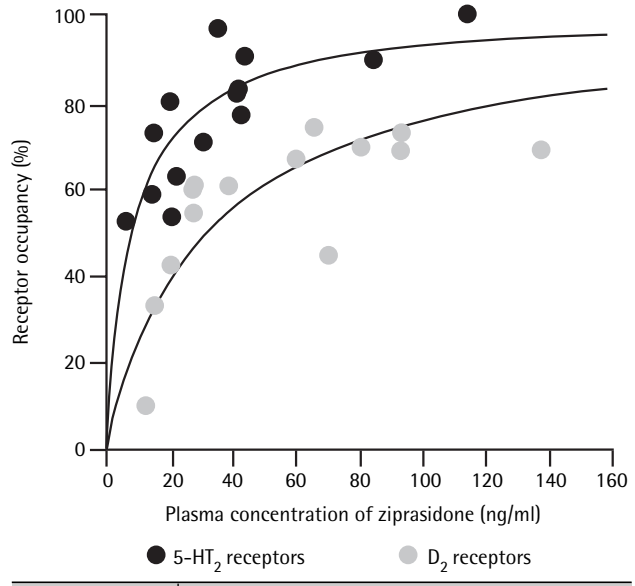


**Figure 1** | *Plasma concentration ratio/% of $D_2$ and $5HT_2$ receptors[14].*

Another hypothesis of interest has stated that the «atypicity» of the antipsychotic agents could arise from a rapid dissociation of the drug from the $D_2$ receptor, a theory applicable to the case of clozapine and quetiapine, but that cannot be transferred to the remaining second generation antipsychotics[21].

In summary, considering the results provided by the pharmacodynamic studies conducted with ziprasidone, use of doses under 120 mg/day to achieve an optimum efficacy seems to be recommendable. Accumulated experience during clinical development and in the daily use of this drug supplies the necessary evidence to support this statement.

**Table 1** | **Ki (nM/l) and $5HT_{2A}/D_2$ ratio[12]**

| Ki (nM/l) | $D_2$ | $5HT_{2A}$ | $5HT_{2A}/D_2$ |
|---|---|---|---|
| Ziprasidone | 3.1 | 0.39 | 7.95 |
| Clozapine | 36 | 4 | 9 |
| Haloperidol | 0.82 | 28 | 2.02 |
| Olanzapine | 20 | 3.3 | 6.06 |
| Quetiapine | 69 | 82 | 0.84 |
| Risperidone | 2.2 | 0.29 | 7.59 |

Ki: inhibition constant.

## Action on other serotininergic receptors and on α-adrenergic, histaminergic and muscarinic receptors

Beyond the $5HT_{2A}/D_2$ antagonisms, second generation antipsychotics act on a myraid of receptors that condition important differences in its efficacy and tolerability profile.

**Table 2** Inhibition constant on different receptors[22]

| | $D_1$ | $D_2$ | $5HT_{2A}$ | $5HT_{2C}$ | $5HT_{1A}$ | $5HT_{1D}$ | $5HT_7$ | R. Inh. 5HT | R. Inh. NA | $Alpha_1$ | $Alpha_2$ | $H_1$ | $M_1$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ziprasidone | 130 | 3.1 | 0.39 | 0.44 | 2.5 | 2 | 4.9 | 50 | 50 | 13 | 300 | 47 | 5,100 |
| Clozapine | 53 | 36 | 4 | 5 | 710 | | | | | 3.7 | 51 | 17 | 0.98 |
| Haloperidol | 15 | 0.82 | 28 | 1,500 | 2,600 | > 5,000 | 490 | 1,800 | 5,500 | 7.3 | 1,600 | > 730 | 570 |
| Olanzapine | 52 | 20 | 3.3 | 10.1 | 2,100 | 540 | 120 | 15,100 | 2,000 | 54 | 170 | 2.7 | 4.7 |
| Quetiapine | 390 | 69 | 82 | 1,500 | > 830 | | | | | 4.5 | 1,100 | 21 | 56 |
| Risperidone | 580 | 2.2 | 0.29 | 10.4 | 210 | 170 | 3.3 | 1350 | 28,000 | 1.4 | 5.1 | 19 | 2,800 |

Ki: inhibition constant; R. Inh.: reuptake inhibitor.

Table 2 describes the affinity constant, expressed in ng/ml, presented by the atypical antipsychotics for different receptors[22]. This parameter is essential to compare the action of different antipsychotics on different receptors and could extrapolate the possible effects that may be derived from this action.

Evaluation of this parameter should be done considering that it expresses the concentration at which the drug is capable of binding to the receptor and exerting its effect. Thus, the lower its value, the greater the drug's capacity to bind to the receptor. On the contrary, very high values indicate that large concentrations, that never reach the recommended doses *in vivo,* are required to produce an effect on this receptor.

Considering the values described in table 2, it can be stated that there are important differences between the different antipsychotics that are mentioned in the following.

Ziprasidone has greater affinity for the $5HT_{2C}$ receptor than the remaining second generation antipsychotics. The antagonism of this type of receptors conditions disinhibition of noradrenergic and dopaminergic neurons in the cortex, producing an increase in norepinephrine and dopamine release. This effect may contribute to improvement in the cognitive function and of the affective symptoms described with the administration of this drug[23,24]. However, the $5HT_{2C}$ antagonism could also contribute to the lack of sedation and increase in alert state described in some patients treated with ziprasidone. This is what differentiates it from the typically sedative effect of other second generation antipsychotics (olanzapine, quetiapine, clozapine). This effect has been related with a predominance of the antagonism on the $5HT_{2C}$ receptors versus the $D_2$ one, that would occur with reduced plasma concentrations of ziprasidone. To understand this question, it should be remembered that the affinity of this drug for $5HT_{2C}$ receptor is greater (Ki inferior) than for $D_2$. Consequently there is the real possibility that the reduced concentrations of the drug would be capable of occupying $5HT_{2C}$ receptors without occupying the $D_2$ ones. There is some evidence on the presence of restlessness or agitation states when the $5HT_{2C}$ antagonism is not accompanied by concomitant $D_2$ receptor antagonism[24].

Another mechanism that has been involved in the improvement of the motivational level of the patients and of the negative symptoms is the presynaptic blockage of $D_3$ receptors, as indicated by some studies done with amisulpride at 50 to 100 mg/day dose[25].

Thus, there is another argument that newly indicates the need of using ziprasidone doses situated in the higher range to try to avoid the presence of adverse effects of activation. It must be remembered that doses superior to 120 mg/day must be administered to reach the best profile of the $D_2$ antagonism with ziprasidone. The patients and family should be informed on the possible activating effect of ziprasidone and if this occurs, and is not desirable, the dose administered, adherence to treatment, should be reviewed and benzodiazepine added, if necessary[26].

Ziprasidone is also capable of binding to 5HT1 receptors, with an agonist effect on $5HT_{1A}$ receptors[27] of greater intensity than that of the remaining antipsychotics. The action on this receptor has been associated with favorable effects on the cognitive function and on the depression and anxiety symptoms[28,29]. Furthermore, it has been described that the $5HT_{1A}$ agonist action may improve negative symptoms and decrease EPS[30].

On the other hand, and within the scope of the serotoninergic receptor family, Ziprasidone carries out a significant action against $5HT_{1D}$ receptors, a presynaptic receptor whose stimulation inhibits serotonin release. The possible consequence of the effect is an increase in serotonin release that may have antidepressive and anxiolytic effects 824). This effect is not produced by any of the remaining antipsychotic drugs.

Within the characteristics of ziprasidone, its capacity to inhibit serotonin and norepinephrine reuptake[24], from which an antidepressive and anxiolytic effect can be derived, stands

out. Again, as in the previous case, it is a unique pharmacological property among the presently available antipsychotic drugs.

Finally, and on the contrary to other atypical antipsychotics, ziprasidone has a reduced affinity for alpha$_1$ adrenergic receptors. This justifies a lower likelihood of producing orthostatism, sedation and sexual dysfunction phenomena. Furthermore, affinity for the $H_1$ histaminic receptors is even lower, so there is a very reduced likelihood that there will be weight gain and sedation. Finally, affinity on the $M_1$ muscarinic receptors is minimum. This explains the reduced incidence of undesired anticholinergic effects such as salivation, sedation, constipation and absence of iatrogenic cognitive alterations[31].

All these actions describe the profile of the clinical effects characteristic of ziprasidone when it is used at adequate doses (more than 120 mg/day), including clinical efficacy in the treatment of positive, negative and affective symptoms of schizophrenia, with a favorable repercussion of the cognitive function, reduced sedating activity and low EPS incidence, hyperprolactinemia, weight gain, orthostatism and sexual dysfunction. Naturally, each and every one of the nuances derived from the action mechanism should be ratified in comparative studies against other antipsychotics and in the daily care practice.

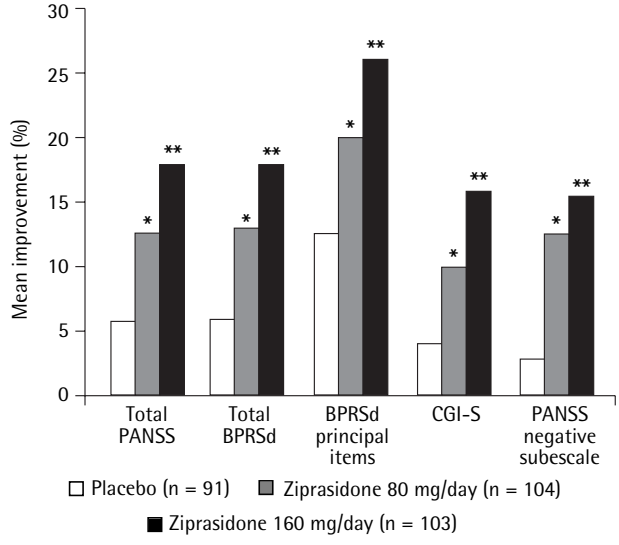


**Figure 2** *Mean improvements of total psychopathology, positive symptoms and negative symptoms regarding baseline time: 6 week study in comparison with placebo. Reproduced with authorization of Daniel et al.[32] *p<0.05 regarding placebo; **p<0,001; BPRSd: Brief Psychiatric Rating Scale (derived from PANSS); CGI-S: clinical global impressions scale-disease severity; PANSS: positive and negative symptoms scale.*

## CLINICAL EXPERIENCE WITH ZIPRASIDONE

### Clinical experience with ziprasidone and dose adjustment

The clinical trials done comparing different doses of ziprasidone versus placebo have demonstrated what doses are more effective and the existence of a dose-response relationship.

In a 6 week long clinical trial conducted in a sample of 302 patients with schizophrenia or schizoaffective disorder in acute exacerbation phase[32,33], fixed doses of ziprasidone of 80 mg and 160 mg/day were compared to placebo. Although both doses of ziprasidone were shown to be more effective in the control of the symptoms of the disease than the placebo, significantly improving the total score in the clinical efficacy scales from the first week (total PANSS, BRPS, CGI-S) and the positive and negative symptoms scale (measured with BPRS nuclear symptoms and negative subscale of the PANSS), the significance level was greater with the 160 mg/day dose (fig. 2). A significant improvement in the affective symptoms measured with the MADRS scale in patients who had depressive symptoms in the baseline assessment (MADRS ≥14) was also observed with this same dose (160 mg/day) (fig. 3).

In another 4 week long clinical trial[34], efficacy and tolerance of fixed doses of 40 mg and 120 mg/day of ziprasidone were evaluated in comparison with placebo in a sample of 139 patients. Ziprasidone, at a dose of 120 mg/day (and not with 40 mg/day dose) showed a significantly greater clinical efficacy than the placebo in the BPRS and CGI-S

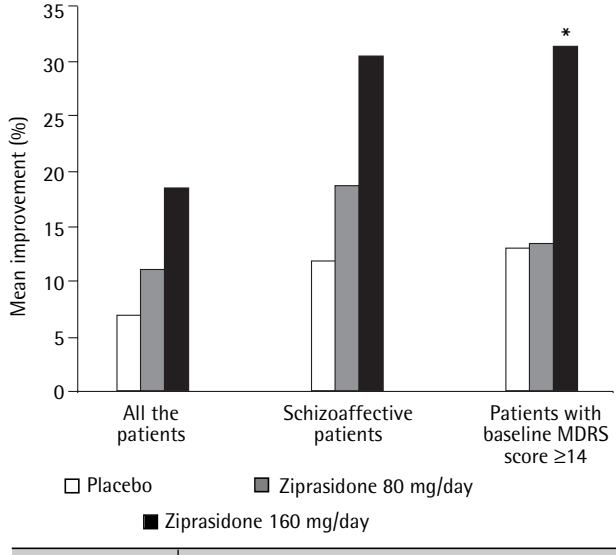


**Figure 3** *Improvements of mean total score of the MADRS versus baseline: 6 week study in comparison with placebo. Reproduced with authorization of Daniel et al.[32] *p < 0.05 regarding placebo; MADRS: Montgomery-Asberg Depression Rating Scale.*

scales ($p<0.05$). The patients who had depressive symptoms in the baseline assessment showed a significant decrease in the score of the anergy and depression subscales of BPRS ($p<0.05$) when they received the 120 mg/day dose (fig. 4).

The long term studies against placebo also demonstrated a greater clinical benefit in patients treated with higher doses of ziprasidone. Thus, in a 1 year long clinical trial[35] conducted in 278 patients with chronic schizophrenia and predominantly negative symptoms, fixes doses of ziprasidone at 40 mg (n=71), 80 mg (n=68) or 160 mg/day (n=67) or placebo (n=71) were administered. A Kaplan-Meier survival analysis was made to estimate the likelihood of relapse in the different groups. The relapse was defined as a score on the CGI-I of ≥6 (much worse) or a score of ≥6 in the hostility (P7) or lack of collaboration (G8) items of the PANSS. All the ziprasidone doses were significantly more effective than the placebo in the prevention of relapses. The likelihood of relapse at one year of follow-up was 77% in the patients treated with placebo versus 43%, 35% and 36% with 40, 80 and 160 mg/day ($p=0.002$, $p<0.001$, $p<0.001$) of ziprasidone respectively. All the ziprasidone doses showed a significantly more favorable repercussion than the placebo on the negative symptoms. This was observed by the changes in the PANSS negative subscale score, the most important improvement being reached with the 160 mg/day dose versus that obtained with 80 and 40 mg/day (a decrease in the score of 2.8, 1 and 1.9 versus an increase of 1.4 with placebo $p<0.001$, $p=0.011$ and $p<0.001$ respectively). Using a Path analysis, it was observed that part of the improvement in the negative symptoms was attributable to a direct effect of the medication and not secondary to other factors, such as improvement in the positive, depressive or extrapyramidal symptoms.

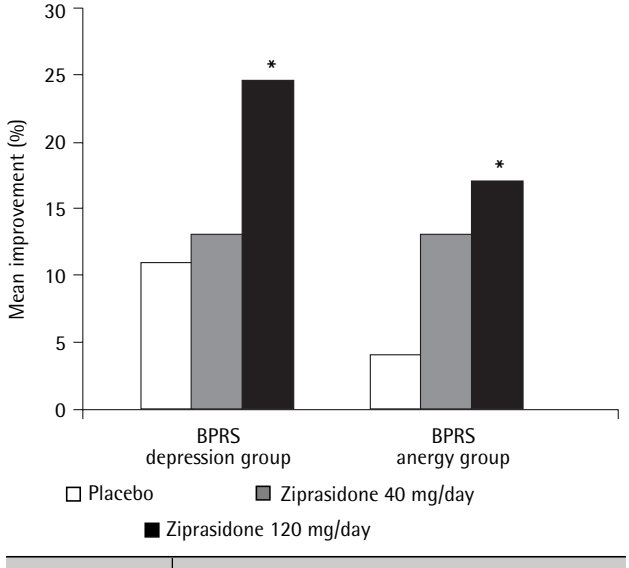


**Figure 4** *Mean percentage improvement of the scores of the depression and energy groups of the BPRS: 4 week study in comparison with placebo. Adapted with authorization of Keck et al.[34] The values of the BPRS depression group indicate improvement in the patients with baseline scores ≥ 18. *p<0.05 regarding placebo; BPRS: Brief Psychiatric Rating Scale.*

A joint analysis of four clinical trials done with fixed dose of ziprasidone (569 patients) versus placebo (273 patients) and haloperidol (85 patients) for 4-6 weeks showed that 120-160 mg/day doses are associated to a rapid and better improvement in all the symptomatic spectrum of schizophrenia than lower doses[36]. The statistically significant improvement in the BRPS was observed from week 1 in patients treated with 120-160 mg/day. On the contrary, a significant improvement was reached with 80 mg/day after the fourth week of treatment. Doses of 120-169 mg/day had a greater effect in the total BPRS score, corrected with the placebo effect, compared with the 40-80 mg/day doses (table 3). The effect of the initial dose of ziprasidone on the frequency of drop-outs due to lack of clinical efficacy was also examined and it was observed that there was a lower incidence of drop-outs due to lack of efficacy between the patients initially treated with 120-160 mg/day doses than between those treated with lower doses (fig. 5).

The results of the preliminary analysis of the ZIS study[37,38] (ziprasidone in schizophrenia), open, prospective, non-comparative and multicenter post-marketing study conducted in Spain in schizophrenia subjects seen as outpatients and treated with flexible doses of ziprasidone show the effectiveness and tolerability of the treatment in the clinical practice. At 6 months of treatment, 46.2% of the patients (n=648) showed a decrease of ≥30% in the PANSS score ($p<0.001$). The changes were significant from the first control at 2 weeks. Mean dose of ziprasidone at the end of the treatment was 124.4 mg/day (± 36). Patients treated with ziprasidone showed a favorable changed in the global attitude towards the medication and in relationship with the tolerability to the treatment dose seen with the DAI-30.

Considering the accumulated clinical experience, it seems clear that higher doses of ziprasidone (120 mg/day or 160 mg/day) are associated with a faster response on the general psychopathology and with lower drop-out rates due to inadequate clinical response[36]. Thus, efficacy of ziprasidone in the daily clinical practice may be conditioned by the dose used, the use of high doses being recommendable (120 mg/day or 160 mg/day).

## CLINICAL EXPRESSION OF THE MULTIRECEPTORIAL PROFILE OF ZIPRASIDONE IN COMPARATIVE CLINICAL TRIALS WITH OTHER ANTIPSYCHOTICS

Clinical trials conducted in patients with schizophrenia or SAD in acute exacerbation phase comparing ziprasidone with other antipsychotics have demonstrated that ziprasidone is at least as effective as haloperidol, risperidone, olanzapine and amisulpride in the control of all the disease

**Table 3** Effects of treatment with ziprasidone corrected with placebo on the total BPRS score based on week of visit in the placebo controlled studies, with fixed doses at short term[36]

| Time of assessments | Mean variation of the total BPRS score (95% CI) | | | | |
|---|---|---|---|---|---|
| | Ziprasidone | | | | Haloperidol |
| | 40 mg/d | 80 mg/d | 120 mg/d | 160 mg/d | 15 mg/d |
| Week 1 | −1.70 (−3.42 to 0.02) | −1.76 (−3.66 to 0.15) | −2.95** (−5.01 to −0.90) | −5.05*** (−7.33 to −2.76) | −4.90 (−7.58 to −2.95) |
| Week 2 | −1.51 (−3.55 to 0.54) | −0.62 (−2.89 to 1.65) | −3.14* (−5.58 to −0.69) | −5.62*** (−8.33 to −2.90) | −6.66 (−9.55 to −4.05) |
| Week 3 | −3.03** (−5.28 to −0.78) | −2.38 (−4.88 to 0.12) | −3.78** (−6.47 to −1.08) | −7.76*** (−10.75 to −4.76) | −7.18 (−11.38 to −5.20) |
| Week 4 | −2.95* (−5.31 to −0.60) | −1.90 (−4.52 to 0.72) | −4.39** (−7.21 to −1.57) | −6.78*** (−9.92 to −3.64) | −8.89 (−13.24 to −6.83) |
| Week 5 | −2.76 (−6.50 to 0.99) | −4.41* (−7.91 to −0.91) | −3.75 (−7.62 to 0.11) | −7.48*** (−10.97 to −3.98) | −8.78 (−12.38 to −6.56) |
| Week 6 | −3.60 (−7.39 to 0.19) | −3.91* (−7.45 to −0.37) | −4.42* (−8.34 to −0.51) | −7.17*** (−10.71 to −3.63) | −8.78 (−12.51 to −6.57) |
| Final assessment | −3.12* (−5.54 to −0.69) | −1.99 (−4.69 to 0.71) | −5.04*** (−7.95 to −2.14) | −6.13*** (−9.36 to −2.91) | −7.25*** (−10.62 to −3.89) |

*p<0.05; **p<0.01; ***p<0.001 vs placebo.

symptom spectrum. They have also manifested the existence of differences in the tolerability profile of ziprasidone versus other antipsychotics.

## Ziprasidone in comparison with conventional antipsychotics

Two clinical trials were conducted, comparing the efficacy of oral ziprasidone with short and long term haloperidol. In the first one, 90 patients were randomized to receive fixed doses of 4, 10, 40 and 160 mg/day of ziprasidone or 15 mg/day of haloperidol for 4 weeks[39]. The patients treated with ziprasidone with 160 mg/day doses showed decreases in the total BPRS scales, BPRS nuclear symptoms and CGI-S nuclear symptoms comparable to haloperidol. The percentage of patients who responded according to BPRS reached 47.1% with haloperidol and 45% with ziprasidone. The EPS incidence was greater among those treated with haloperidol, 52.9% of the patients of this group needing concomitant administration with benzotropin versus 15% of the patients treated with ziprasidone.

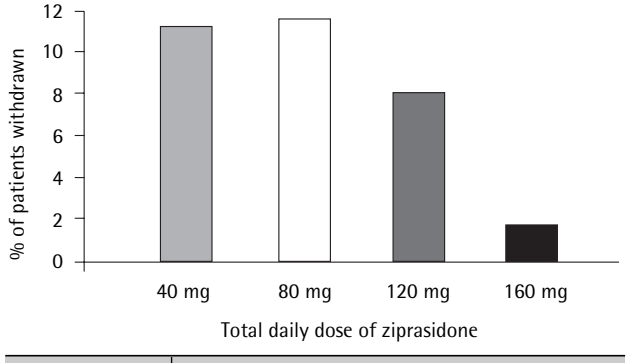


**Figure 5** *Percentage of withdrawals due to insufficient clinical response in the 14 days after initiation of ziprasidone in placebo controlled fixed dose trials[36].*

In another 28 week long clinical trial, in which a flexible dose of ziprasidone (80-160 mg/day) was compared with haloperidol (5-15 mg/day) in 301 patients with chronic schizophrenia[40], similar improvement percentages were observed. Mean dose of ziprasidone was 116.5 mg/day and of haloperidol 8.6 mg/day. A total of 45% of the patients treated with ziprasidone and 42% of those treated with haloperidol discontinued the treatment. The percentage of discontinuation due to lack of clinical response was 18% in both groups while that caused by adverse effects was 8% in the ziprasidone and 16% in the haloperidol one.

In the clinical trial conducted in patients with haloperidol treatment resistant chronic schizophrenia (resistance was defined as lack of response after 6 weeks of treatment with a dose of up to 30 mg/day of haloperidol), 307 patients were randomized to be treated with 80-160 mg/day of zi-

prasidone or 200-1,200 mg/day of chlorpromazine for 12 weeks[41]. Both treatments led to a significant and comparable improvement in the positive symptoms (measured with the BPRS nuclear symptoms and PANSS subscale of positive symptoms.) The mean dose of ziprasidone was 151 mg/day and that of chlorpromazine 706 mg/day. Improvement of the negative symptoms was significantly greater in the patients treated with ziprasidone ($p<0.05$) and there was also a greater reduction of the mean value of prolactin.

In summary, it can be stressed that the studies that have compared ziprasidone with conventional antipsychotics have demonstrated similar efficacy in the control of positive symptoms. In the case of the negative symptoms, ziprasidone seems to offer advantages over conventional neuroleptics. However, it seems to be necessary to clarify if the improvement only explains a favorable action on the secondary negative symptoms or also on primary negative ones. Finally, ziprasidone causes less incidence of EPS, which among other consequences, generates a reduction in the concomitant use of anticholinergics, the increase of prolactin being significantly less.

## Ziprasidone vs atypical antipsychotics

*Ziprasidone vs olanzapine*

In a 6 week long clinical trial, conducted with patients having schizophrenia or SAD in acute exacerbation phase, and in which flexible doses of olanzapine (5-15 mg/day) ($n=133$) were compared with ziprasidone (80-160 mg/day) ($n=136$)[42,43], a rapid improvement of the symptoms (total BPRS, CGI-S and total PANSS) and more specifically, in the positive and negative symptoms, measured with the BPRS nuclear symptoms and PANSS subscales of positive and negative symptoms was observed in both groups. Clinical efficacy reached did not show significant differences between both treatments. Improvement in the depressive symptoms measured with the Calgary Depression Scale for Schizophrenia (CDSS) was also seen, without significant differences between both. The mean doses administered were 11.3 mg/day of olanzapine and 129.9 mg/day with ziprasidone. Patients treated with olanzapine experienced weight gain of 3.57 kg compared to 0.93 kg of increase among those treated with ziprasidone ($p<0.0001$). Furthermore, there was a mean increase of 20 mg/dl and 12 mg/ml of total cholesterol and LDL concentration, respectively, in the olanzapine group. Among the patients treated with ziprasidone, the increase in both parameters was 1 mg/dl, the differences being statistically significant. Treatment with olanzapine was also associated with a significant increase of the serum insulin levels by 36% ($0<0.001$) and of the HOMA IR index ($\text{HOMA IR} = \text{Ins} \times \text{Glu}/22.5$) —an insulin resistance indicator— of 11% ($p<0.001$). This did not occur among the patients treated with ziprasidone[44].

The continuation study was extended until completing 6 months and included 133 patients who had shown satisfactory clinical response (defined as a decrease ≥20% in the PANSS or a CGI-S ≤2 (much better) during the previous phase). The mean doses were 12.2 mg/day with olanzapine and 136.9 mg/day with ziprasidone. Controls were made with all the scales used during the previous phase. No significant difference was observed in the efficacy between both groups. Weight gain persisted with olanzapine, reaching 4.7 kg versus weight loss with ziprasidone of 1.3 kg ($p<0.001$). Furthermore, significant changes in the insulin plasma concentrations, total cholesterol and LDL-C persisted with olanzapine[45].

*Ziprasidone vs risperidone*

Efficacy and tolerability of ziprasidone was compared with those of risperidone in an 8 week long clinical trial conducted in 296 patients who had acute exacerbation of schizophrenia or SAD[46,47]. The patients were randomized to flexible doses of 6-10 mg/day of risperidone or 80-160 mg/day of ziprasidone. The mean daily doses reached were 7.4 mg in the case of risperidone and 114.2 mg for ziprasidone. At the end of the follow-up, the patients treated with risperidone and ziprasidone showed similar decreases in the score of the total PANSS and CGI-S scales and also on the PANSS positive and negative subscales. Incidence, duration and severity of the extrapyramidal symptoms were assessed with the Movement Disorder Burden Score (MDBS) scale. The score on this scale was significantly less with the patients treated with ziprasidone compared to those with risperidone ($p<0.05$). A 1.36 kg mean weight gain in men and 2.27 kg in women was observed in those treated with risperidone while the weight change with ziprasidone was <0.45 kg in both genders. Prolactin experienced a mean increase of 18 ng/ml with risperidone and a decrease of 9 ng/ml with ziprasidone, from the baseline visit to the end. Furthermore, a larger incidence or deterioration of the sexual function in the patients treated with risperidone was observed.

In the continuation study made until completing 52 weeks[48] in the 139 patients who showed adequate clinical response after 8 weeks of treatment, improvement in the clinical efficacy scales did not show differences between both groups. Patients treated with risperidone experienced an additional increase of prolactin during the follow-up while no additional variations were observed with ziprasidone, a drug that was associated with less weight gain and lower EPS incidence than risperidone.

*Ziprasidone vs amisulpride*

A single 12 long clinical trial was made to compare the efficacy and tolerability of ziprasidone (80-160 mg/day) with amisulpride (100-200 mg/day), antipsychotic that has stood out for its good efficacy in the treatment of negative symptoms[49]. A total of 123 patients with chronic schizophrenia who had a predominance of negative symptoms

(PANSS SN ≥6 over the PANSS SP score) were chosen. Mean dose of ziprasidone and amisulpride was 112 and 138.5 mg/day, respectively. No significant differences were observed between both treatments in the change of PANSS SN score nor in the remaining efficacy variables (total PANSS and CGI-S).

*Conclusions: ziprasidone vs atypical antipsychotics*

Comparative studies with other second generation antipsychotics show that ziprasidone is a drug having similar efficacy in both the control of positive and negative symptoms. It is important to state that on the contrary to other second generation antipsychotics, ziprasidone does not generate weight gain or alterations in the patients' lipid and glycemic profile.

Mean dose of ziprasidone used in all short term comparative studies with flexible doses was greater than 120 mg/day.

## STUDIES ON COGNITIVE FUNCTION AND SOCIAL REINTEGRATION

Cognitive deficit is a nuclear manifestation of schizophrenia and is progressively becoming the focus of greater attention as a clinical efficacy variable in the treatment of this disease. It has been documented that the cognitive deficit predicts the functional result of the patients and consequently their work and social reinsertion capacity with greater force than the positive and negative symptoms[50]. A metaanalysis of 37 studies identified verbal memory, immediate memory attention and executive function as the cognitive functions most closely related with the functional state of schizophrenia patients[51].

The effects of ziprasidone on the cognitive function have been assessed in three antipsychotic treatment substitution studies done with identical design and in a comparative clinical trial with olanzapine.

In the treatment substitution studies, a total of 270 patients[52] with schizophrenia or stable SAD who had shown secondary effects or inadequate clinical response with the previous antipsychotic treatment consisting in conventional antipsychotics (108 patients), olanzapine (104 patients) or risperidone (58 patients) were included. Treatment duration with ziprasidone in these studies was 6 weeks. Cognitive function of the patients was assessed with a battery of 18 tests that were used to analyze the different domains of the cognitive function. Cognitive, depression/anxiety subscales and PANSS prosocial subscale were also assessed. In order to analyze the results using a factorial analysis, the 18 cognitive function variables were grouped into 3 domains: verbal skills, attention and short term memory and executive function.

Verbal skills significantly improved in the patients who had changed from conventional antipsychotics, olanzapine and risperidone, to ziprasidone. Attention and short term memory improved in the three groups, although they only reached significant differences in the group previously treated with risperidone. Finally, the executive function also significantly improved in the latter group. PANSS cognitive and anxiety/depression subscales improved in all the groups, the differences being significant in patients who had previously been treated with conventional neuroleptics and risperidone. The social reinsertion subscale showed a significant improvement in all the groups once the change to ziprasidone was made. As a whole, change of treatment to ziprasidone had a favorable repercussion in the patients' cognitive function of social readaptation.

In a comparative 6 week long study of ziprasidone versus olanzapine conducted in 269 patients hospitalized due to exacerbation of the psychotic symptoms[53], cognitive function was assessed on the first day after discontinuation or the previous medication and at the end of the follow-up period. Measurements of attention/alertness, executive function, learning/memory and verbal fluency were included in the assessment. This study's results showed a significant improvement in the two patient groups in the attention, visomotor speed, executive function and learning/memory tests. In the extension study made until completing 6 months in patients who had shown an adequate clinical response during the initial phase, significant improvements were observed with ziprasidone and olanzapine in almost all the cognitive tests[54,55] (table 4).

In all, these studies suggest that ziprasidone improves a wide range of cognitive functions in patients with schizophrenia or SAD in both the stable and unstable phase of the disease. In the clinical practice, many of the patients who take ziprasidone experience an increase in the alertness state and concentration capacity. This may favor a better grade of functioning and consequently reintegration to family, work and social life. These aspects, and their repercussion in the patients' and caretakers' quality of life, must be evaluated in larger studies with a longer follow-up[56].

## TOLERABILITY PROFILE

In the joint analysis of the 4-6 week long clinical trials done in patients with schizophrenia or SAD[57] in acute exacerbation phase treated with fixed doses of ziprasidone of up to 200 mg/day (n = 702) or with placebo (n = 273), the global incidence of adverse events was similar in both groups (79.6% with ziprasidone and 79.9% with placebo). Most of the adverse effects associated with ziprasidone had mild to moderate intensity. A total of 4.1% of the patients treated with ziprasidone and 2.1% of those treatment with placebo dropped out of the treatment due to side effects. Headache was the most frequent adverse effect (22% for both groups). Standing out among the adverse effects re-

**Table 4** Comparative study of ziprasidone (80-160 mg/day) vs olanzapine (5-15 mg/day) 6 months duration (n = 126)[55]

| Cognitive f. | Ziprasidone | | | Olanzapine | | |
|---|---|---|---|---|---|---|
| | Baseline-final difference | Effect size | Significance | Baseline-final difference | Effect size | Significance |
| RAVLT | 11.67 | 0.97 | p<0.001 | 7.77 | 0.70 | p<0.001 |
| Delayed recall | 3.58 | 1.06 | p<0.01 | 2.15 | 0.72 | p<0.01 |
| TMT A | –32.64 | 0.60 | p<0.004 | –10.17 | 0.63 | p<0.004 |
| CPT | 0.33 | 0.50 | p=0.01 | 0.40 | 0.63 | p=0.002 |
| TMT B | -42.67 | 0.61 | p<0.002 | –49.48 | 0.97 | p<0.0001 |
| WCST | –9.09 | 0.66 | p=0.004 | –3.68 | 0.33 | p=0.14 |
| Letter fluency | 4.06 | 0.64 | p<0.001 | 3.53 | 0.36 | p=0.04 |
| Category fluency | 0.58 | 0.56 | p=0.002 | 4.32 | 0.09 | p=0.618 |

Measurement of verbal memory and learning (Rey Auditory Verbal Learning Test [RAVLT] and Delayed recall), attention and alertness (Continuous Performance Test [CPT] and Trail Making Test A [TMT A]), executive function (Trail Making Test B [TMT B] and Wisconsin Card Sorting Test [WCST]) and verbal fluency (Letter Fluency Test and Category Fluency Test).

ported by more than 55 of the patients treated are somnolence. This was reported in 14% of the patients treated with ziprasidone versus 7% of those treated with placebo. These had a mild to moderate intensity and transitory character (table 5). Ten percent of the patients treated with ziprasidone and 7% of those treated with placebo had nausea. Other adverse effects related with the CNS were akathisia and dizziness, with an 8% incidence in both cases with ziprasidone versus 6% and 7% with placebo. The SAD incidence was 5% with ziprasidone and 1% with placebo. Akathisia and SAD were a drop-out reason in only 3 patients. Use of benzotropine and beta blockers, drugs used to treat SAD, was similar in the patients treated with ziprasidone and placebo (22% required benzotropines at some time with ziprasidone vs 18% with placebo and this occurred in the case of beta blockers in 7% and 6% respectively[57]. The incidence of other adverse effects was low with ziprasidone: tachycardia (1.6% vs 1.1%), orthostatic hypotension (1.3% vs 0.4%), prolongation of the QTc >500 ms (1.2% vs 1.4%), weight gain (0.4% vs 0.4%), impotency (0.3% vs 0.4%).

Treatment with ziprasidone does not seem to be associated to a sustained increase of the prolactin concentrations. During the treatment with ziprasidone 40-160 mg/day[32], the mean serum concentrations of prolactin returned to baseline values in the 12 hours following the drug administration in patients with schizophrenia or SAD in a 4 week study. On the contrary, the mean concentrations of prolactin significantly increased during the treatment with 15 mg/day of haloperidol and continued to be elevated 12 hours after the dose administration. Mean prolactin concentrations decreased from 30.4 to 23.6 µg/l in patients with schizophrenia who received ziprasidone for 1 year[35].

**Table 5** Summary of adverse events (AE) (for all causes) that appear with treatment in ≥5% of the patients who received 80-160 mg/day of ziprasidone, and with greater frequency than with placebo in 4 to 6 week long placebo controlled clinical trials with fixed doses

| | Ziprasidone (n = 702) | Placebo (n = 273) |
|---|---|---|
| Men/women | 73,5%/26,5% | 74%/26% |
| Exposition (days) | 19.940 | 6.743 |
| With AE | 79,6% | 79,9% |
| Withdrawn due to AE | 4,1% | 2,1% |
| **Adverse events** | | |
| Asthenia | 5% | 3% |
| Constipation | 9% | 8% |
| Diarrhea | 5% | 4% |
| Dyspepsia | 8% | 7% |
| Nausea | 10% | 7% |
| Akathisia | 8% | 7% |
| Dizziness | 8% | 6% |
| Extrapyramidal syndrome | 5% | 1% |
| Somnolence | 14% | 7% |
| Respiratory disorder* | 5% | 1% |

* Described as cold symptoms, not nasal congestion. Adapted from[57].

In the analysis of the placebo controlled clinical trials with short term ziprasidone, the mean weight gain regarding baseline value was 0.9 kg in all the subjects treated with ziprasidone and the mean weight loss in the subjects who received placebo was 0.4 kg. Clinically significant weight gain incidence (≥7%) in these studies was 9.8% with ziprasidone and 4.0% with placebo[57]. These data are more favorable than those recorded in the American data sheets of similar studies with risperidone[58] (18% versus 9% in placebo group), quetiapine[59] (23 versus 6% in placebo group) and olanzapine[60] 29.3% versus 2.7% in placebo group). As has been mentioned before presenting the clinical trial results versus the comparers, ziprasidone does not condition significant alterations in the lipid and glycemic profile of the patients[42-45]. The repercussion of some atypical antipsychotics on the metabolic profile in the patients with schizophrenia (weight gain, repercussion in glycidic and lipid profile) and its possible implications in increase of cardiovascular risk in this population have been progressively calling greater attention. This has given rise to the recent publication of a Consensus on antipsychotic drugs, obesity and diabetes (of the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists and North American Association for the Study of Obesity) in which practical recommendations are included on the adequate check-up of the patient and therapeutic management of antipsychotics in this study [61].

Ziprasidone is probably the antipsychotic that has the most detailed and systematic information of its effect on the QTc because its marketing was preceded by a growing sensitization of the FDA to this subject conditioned by the problems of QTc prolongation detected with other antipsychotics. The FDA demanded that ziprasidone demonstrate reliably its cardiovascular harmlessness with specific studies on QTc prolongation before its approval. It has been demonstrated that the effect of ziprasidone on the QT interval is mild and well characterized and that it is not modified by metabolic inhibition. Non-significant increases of the QTc of the following has been observed:

- 6-10 ms in ECG performed at random (with 40 to 100 mg/day of ziprasidone twice a day).
- 15-20 ms with the $C_{max}$ of ziprasidone (160 mg per day) both with and without the ketoconazole metabolic inhibitor.

Values of QTc > 500 ms (2/3095; 0.06% of the subjects) and in no case Torsade de Pointes have rarely been recorded during the clinical development program[62]. In a recently published study, the effects of ziprasidone 160 mg/d versus risperidone 6-16 mg/d, olanzapine 20 mg/d, quetiapine 750 mg/d, tioridazine 300 mg/d and haloperidol 15 mg/d on QTc in absence and presence of a metabolic inhibitor were compared, performing a control of the plasma levels. The mean effect of ziprasidone on the QTc interval did not increase after adding metabolism inhibitor. Plasma doses of ziprasidone of up to 434 ng/ml were reached, the mean plasma concentration of the pharmacokinetic data of 23 clinical studies being 71 ng/ml. No patient had a prolongation of QTcB greater than 500 ms[63].

The recommendation on the use of the dose in the highest margins of the therapeutic range recommended and even greater undoubtedly make it necessary to confirm the safety of the drug at these doses. Although the data existing with doses superior to 200 mg/day are limited, it is interesting to mention that it was observed in a recent study made in patients with schizophrenia that the QTc only experienced an increase of 3 msec against the mean increase recorded with 160 mg/day when the maximum recommended dose of ziprasidone was increased twice (up to 320 mg/day)[64]. On the other hand, in a retrospective analysis conducted in 51 patients with a history of treatment resistant schizophrenia and only partial response to 160 mg/day, in whom the ziprasidone dose was increased to ≥ 240 mg/day, reaching up to 320 mg/day in a step-up form (21 patients), 400 mg/day (3 patients) and 480 mg/day (2 patients), no adverse effects were reported in 83.3% of the patients. A total of 8.1% of the patients had sedation. One patient had Akathasia and restless legs and another involuntary orofacial movements, this abating in both cases after dose reduction. No electrocardiogram with a prolongation of QTc > 500 ms was observed[65].

## RELEVANT CONCLUSIONS FOR THE CLINICAL MANAGEMENT OF ZIPRASIDONE IN THE CLINICAL PRACTICE

Accumulated clinical experience with ziprasidone has made it possible to identify a series of aspects that may be useful for its management in the daily clinical practice and to optimize the therapeutic results:

- Neuroimaging studies show that ≥ 120 mg/day doses of ziprasidone are necessary to guarantee the threshold of occupancy of the $D_2$ family (> 60%) associated to adequate antipsychotic efficacy. Reaching doses of ziprasidone of at least 120-160 mg/day in a period of 3 days is recommended since the accumulated evidence shows that these doses are associated with a faster response in the global psychopathology of schizophrenia. They are also associated with less drop-outs due to lack of efficacy, without a greater incidence of side effects.
- Clinical trials that compare IM/oral ziprasidone with IM/oral haloperidol show that ziprasidone is at least as effective as haloperidol in the treatment of acute agitation and exacerbation of the schizophrenia and the long term one. Ziprasidone has a lower risk than haloperidol for the appearance of extrapyramidal symptoms and hyperprolactinemia. Consequently, it is associated to a lower concomitant use of anticholinergics and beta blockers.
- Clinical trials that compare ziprasidone with several atypical antipsychotics have demonstrated that it is at

least as effective as risperidone, olanzapine and amisulpride in the treatment of all the disease symptom spectrum (positive, negative and affective). Ziprasidone has also shown a better tolerability profile than risperidone in relationship with the appearance of SAD and hyperprolactinemia and lower incidence of sexual dysfunction. In comparative studies, ziprasidone shows a neutral profile on weight, on the contrary to olanzapine and risperidone. It is not associated to alterations in the glycemic and lipid profile of the patients, so it can be considered among the drugs of choice in patients with cardiovascular risk factors.

- On the other hand, on the contrary to other atypical antipsychotics, ziprasidone does not show a sedating profile and could increase the patient's degree of alertness. The risk that restlessness states or agitation appear is minimized with therapeutic doses of ≥ 120 mg/day. In any case, it seems recommendable to inform the patients and family on the possible activating effect of ziprasidone and that, if this occurs and is not desirable, the dose administered, adherence to treatment should be revised and benzodiazepine should be added. It has been observed that increase in alertness grade and activity of the patient may have a favorable repercussion on his/her cognitive functioning and social reintegration.
- The post-marketing studies conducted in Spain with oral ziprasidone (ZIS study) have shown its effectiveness in the long term treatment of schizophrenia under conditions of the usual clinical practice when using mean doses superior to 120 mg/day and that it is well-tolerated and accepted by the patients.

Future lines of investigation should be aimed at increasing knowledge of the disease and its treatment. It should study the different phases of the natural history of schizophrenia, from the prevention and management of the first episodes, to the treatment of exacerbations and maintenance. The repercussion of the antipsychotic treatment should be analyzed carefully in all the spectrum of symptoms of schizophrenia and in the functioning and quality of life of the patients. The risks that may be associated to treatment should be minimized as much as possible. Furthermore, the results of the studies conducted during the clinical development phase of the drugs must be compared with the evidence provided by its use in the usual clinical practice after marketing and should reflect the findings as practical orientations that facilitate its management. Finally, it is essential to perform specific studies on certain population groups (child, elderly, immigrants, etc.) and comparative studies between different drugs to facilitate the selection of the most adequate treatment and its optimum management.

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