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Advances in the treatment of mania: aripiprazole

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Aripiprazole is a dopamine partial agonist antipsychotic drug that has just been approved in Europe for its use in the treatment of acute mania and for the prevention of manic episodes in bipolar disorder. Its efficacy in mania is superior to that of placebo, both as monotherapy and as adjunctive therapy, and comparable to that of haloperidol and lithium. From the safety perspective it is remarkable that it is not highly sedative and does not impair the metabolic parameters. The advantages of a non-sedative and metabolically neutral antimanic drug are particularly relevant in the long-term, due to their impact on cognition and quality of life. The experience on its use in routine clinical practice indicates that in order to avoid phenomena such as activation, abrupt worsening or akathisia, it is recommendable to start treatment with low doses and to increase them progressively, especially in those patients who are already receiving other drugs; moreover, it is advisable not to stop abruptly any ongoing treatment, unless there is an emergency, to transiently prescribe a concomitant benzodiazepine, and to maintain the dose that proved efficacious during the short term treatment during maintenance therapy.

Key words:
Aripiprazole. Antipsychotics. Mania. Bipolar disorder. Lithium.

Actas Esp Psiquiatr 2008;36(3):158-164

Avances en el tratamiento de la manía: aripiprazol

El aripiprazol es un antipsicótico agonista parcial dopaminérgico que acaba de ser aprobado en Europa para su uso en el tratamiento de la manía aguda y para la prevención de episodios maníacos en el trastorno bipolar. Su eficacia en manía es superior al placebo, tanto en monoterapia como en asociación, y comparable a la de haloperidol y litio, y de su perfil de seguridad destaca la escasa sedación y el respeto de los parámetros metabólicos. Las ventajas de un antimaníaco no sedativo y metabólicamente neutro son especialmente visibles a medio y largo plazo por su potencial impacto en la cognición y la calidad de vida. La experiencia en su utilización en la práctica clínica habitual indica que para evitar fenómenos de activación, reagudización o acatisia, especialmente en pacientes ya tratados previamente con otros fármacos, es recomendable iniciar el tratamiento con dosis bajas, subir progresivamente, no interrumpir bruscamente el tratamiento previo salvo en caso de urgencia, asociar temporalmente una benzodiazepina y mantener las dosis eficaces en fase aguda durante el mantenimiento.

Palabras clave:
Aripiprazol. Antipsicóticos. Manía. Trastorno bipolar. Litio.

INTRODUCTION

During the last decade, treatment of acute mania has been enriched by the arrival of a significant number of new molecules, most of which belong to the group of antipsychotics, which has increased the therapeutic possibilities for acute treatment and in some cases maintenance treatment of bipolar disorder manic episodes. However, not all of the news has been good since some drugs have not met the expectations regarding anti-manic efficacy (basically the new anti-epileptic drugs) and other, while effective, are accompanied by adverse events related especially with weight and metabolic parameters that limit their clinical use. Aripiprazole is the first representative to reach the market from a group of drugs that is characterized by being partial dopamine agonists. Although its affinity receptor spectrum makes it similar to the rest of the second generation antipsychotics, its partial agonism grants it a unique characteristic regarding the other ones. In the following pages, we are going to try to express how these characteristics are translated from the clinical point of view. We will also review the short and long term studies conducted with this drug in the field of mania. We will reveal how it is possible for a substance having low sedative capacity to be useful in the treatment of a clinical picture accompanied by excitation, such

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as mania, and we will analyze the drug dosing under the usual clinical conditions from the practical point of view.

PHARMACOLOGY OF ARIPIPRAZOLE

Aripiprazole is a novel antipsychotic that belongs to the group of the so-called Second Generation Antipsychotics (SGA)[1]. Its chemical structure belongs to the quinolinone class. Although it has more characteristics in common than differences with the other ASGs, it has a complex receptor profile that differs from them. Aripiprazole is a partial agonist on the presynaptic dopamine autoreceptors and on the dopamine D2 postsynaptic receptors[1,2].

Aripiprazole has been available on the market since the end of 2003, initially in the USA and since 2004 in most of the European countries. The studies conducted up to now confirm that it is an antipsychotic drug with a reasonably good profile of side effects, with mild extrapyramidal side effects (although with some incidence of akathisia), little sedation and minimum weight gain. It has different types of presentations (oral solution, oral-disintegrating tablets, intramuscular preparation) which, although not all are available on the European market, facilitate its administration. The latter, added to its prolonged half life that avoids the problems related with a possible discontinuation syndrome, makes aripiprazole a drug having great interest for new applications.

In a series of neuroimaging studies conducted with Positron Emission Tomography (PET), Kapur et al. studied the binding of antipsychotics to dopamine receptors and they contributed data on the receptor characteristics and side effects of the ASGs[3,4]. According to said studies, an occupation of dopamine receptors (D2) greater than or equal to 60% is necessary to obtain therapeutic benefit with APGs, while occupation over 75% is associated to the appearance of extrapyramidal side effects. The pharmacological profile of aripiprazole is a special and differs from that of the remaining antipsychotics since it has a partial agonist at dopamine D2 and serotonin 5-HT1A receptors, with 5-HT2B inverse agonism and 5-HT2a antagonism[1,2,5,6]. The results obtained in a recent study on receptorial occupation of aripiprazole conducted with PET in 15 healthy subjects are consistent with the action mechanism proposed as partial agonist of the dopamine receptors[7]. At doses of 2 mg/day, aripiprazole occupied 70%-80% of the striatal D2 dopamine receptors. When the aripiprazole doses were increased to 30 mg/day, the estimated occupation of the dopamine receptors was 95%, which would originate important extrapyramidal side effects if it was a pure agonist. This profile has been recently confirmed in an animal model with PET with aripiprazole. In that study, a dissociation between the high affinity D2 receptor and absence of catalepsy in rats was demonstrated[8]. The elevated D2 dopamine receptor binding in absence of the appearance of extrapyramidal effects or hyperprolactinemia confirms the role of aripiprazole as partial dopamine agonist. In addition, it has a neuromodulator effect on the dopamine system thanks to the partial agonism on the 5HT1A serotoninergic receptor and antagonism on the 5-HT2A receptor. This makes it possible to explain the relative low incidence of extrapyramidal side effects of aripiprazole and perhaps its activity on mood[9]. In relationship to its profile of binding to other neuroreceptors, aripiprazole has a minimum histamine, muscarinic and alpha-1 adrenergic antagonism[2,5].

In terms of pharmacokinetic profile, the absorption of aripiprazole is rapid, it is highly bound to plasma proteins and has an approximate half life of 75 hours. Aripiprazole is metabolized by hepatic microenzyme system and may be influenced by drug interactions or by other drugs whose metabolism involves the hepatic microenzyme CYP3 group (i.e., ketoconazole, quinidine). This could produce an elevation of the aripiprazole plasma levels. In addition, hepatic inducing drugs (i.e., carbamazepine) may decrease bioavailability of aripiprazole in plasma. Recent data suggest that these pharmacological interactions can be solved by minimum daily dose adjustments of aripiprazole. Co-administration of aripiprazole with lithium or valproic acid has been studied and seems to be safe and effective[9,10].

Finally, the bioequivalence in terms of aripiprazole dose with other ASGs is still unclear, as is the minimum effective dose in mania. The only fixed doses trial in mania was the only negative trial of aripiprazole in that indication, so that it is not clear if doses below 30 mg/day are clinically effective from the scientific point of view. As we will see later on, the acquired clinical experience can respond to this question and it is clear that there are patients who respond to lower doses, such as 15 mg/day, and that many more would benefit from initiating treatment at an even lower dose (between 5 and 10 mg/day) that could be increased up to 30 mg/day or even more in very specific cases.

EFFICACY OF ARIPIPRAZOLE IN THE TREATMENT OF MANIA

In recent years, there has been an enormous increase in the number of clinical trials with ASGs in single drug therapy and in combination with mood stabilizers for acute and maintenance treatment of bipolar disorder[11]. At present, olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole have received FDA approval for treatment of acute mania. Studies are currently being completed in other antipsychotics, such as paliperidone or asenapine. In addition, olanzapine and aripiprazole are the only two ASGs that now have FDA approval for maintenance treatment of bipolar disorder. Until recently in Europe, most of the drugs had not followed a centralized procedure. Thus, there are large variations between countries. However, the situation is similar to that of the United States, with a slight delay in the approval of indications. On the other hand, in the treatment of bipolar depression, the combination of olanzapi-

ne/fluoxetine[12] in the USA has obtained this indication. Furthermore, quetiapine has also been demonstrated to be clinically effective in the treatment of bipolar depression in a multicenter, randomized double blind study called BOLDER I, whose results have currently been replicated in another study called BOL-DER II [13,14]. The data on aripiprazole in bipolar depression are disconcerting because there was a significant improvement during 6 weeks that did not continue up to the 8 weeks of the two placebo compared studies performed[15]. It is possible that aripiprazole accelerates the antidepressive response although it is not successful in maintaining it in long term single drug therapy.

ARIPIPRAZOLE IN ACUTE MANIA

There are several studies that evaluate effectiveness and safety of aripiprazole in patients with bipolar disorder. These studies were initially of short duration and focused on acute treatment of mania[11]. Aripiprazole is currently the antipsychotic drug having the most controlled trials in acute mania, with a total of 7 trials, 6 of which were placebo controlled.

The first study in which antimanic properties and tolerability of aripiprazole were observed was a double blind, three week long study[16] in patients (n=262) with acute mania. In this study, aripiprazole demonstrated a significant improvement in the total scores on the Young Mania Rating Scale (YMRS) between the baseline and final situation of the study compared with the placebo (–8.2 vs. –3.4; $p < 0.001$). The proportion of responding patients (≥50% reduction in YMRS) with significant clinical improvement who received aripiprazole at the end of the study was double (40%), compared with the patient control group who received placebo (19%; $p<0.001$). The clinical improvement was observed after the 4th day of treatment and was maintained during the 3 weeks of the treatment duration. Similar results were confirmed in the later study which had the same characteristics: In that study, a significant reduction was observed in the manic symptoms day 4 after the study onset[17]. In both studies, the doses of aripiprazole used ranged from 15 to 30 mg/day.

There is little data on the minimum effective dose in the treatment of acute mania. In another unpublished short term placebo-controlled trial, the percentages of responses found (about 40%-45%) were not very different among the patients who received 15 mg/day or 30 mg/day doses and there was also an elevated response rate (38%) in the placebo group[18]. This negative trial is, up to date, the only study that has evaluated the efficacy and safety of two different doses of aripiprazole (15 and 30 mg/day) for the treatment of acute mania. Given the technical deficiencies of the study, only minimally reliable conclusions can be obtained regarding tolerability.

In another long trial (12 weeks), effectivity of aripiprazole versus haloperidol was compared in a sample of 338 patients with acute mania[19], with more flexible doses of aripiprazole (mean dose of 21 mg/day). Aripiprazole was shown to be comparable to haloperidol in terms of efficacy, which is a good indicator of antimanic potency. The primary result was the number of responding patients (improvement ≥50% in the score of YMRS from the baseline time point) and that they were under treatment for 12 weeks. At the end of the follow-up period, the number of responding patients was significantly greater with aripiprazole than with haloperidol (49.7% vs. 28.4%; $p<0.001$). Furthermore, the continuation rates were significantly different (aripiprazole 50.9% vs. haloperidol 29.1%) with greater appearance of extrapyramidal effects in the haloperidol treated group. As the authors themselves indicate[19], the study design did not make it possible to administer the anticholinergic drugs and this could explain the greater rate of treatment drop-outs in the haloperidol group. In addition, the haloperidol dose was relatively elevated (15 mg/day) so that the results should be cautiously interpreted.

Recently, 2 more trials with aripiprazole in mania that followed the model required by the European Drug Agency have been completed: 2 arms, one placebo and another with an active comparator and 12 weeks in duration. In one, the active comparator was lithium[20] and in the other, it was haloperidol[21]. Aripiprazole was shown to have similar efficacy as lithium and haloperidol and a greater one than the placebo. There are also preliminary data on its efficacy in adolescents[22].

Until recently, the existing data on the concomitant use of aripiprazole with mood stabilizers were scarce[11] and were limited to studies conducted in patients with schizophrenia or schizoaffective disorder and purely pharmacokinetic studies that evaluated the safety and interactions of aripiprazole with lithium or valproate[9]. However, a randomized, double blind placebo controlled 6 week follow-up study[10] that demonstrates that the combination of aripiprazole with lithium or valproate is superior in efficacy to single drug therapy with lithium or valproate (plus placebo) has recently been concluded. The trial shows that aripiprazole contributes an added value to the treatment with stabilizers without affecting tolerability. However, it is true that the subgroup of aripiprazole with lithium showed somewhat higher rates of akathisia than the combination with valproate or single drug therapy with stabilizers.

MAINTENANCE TREATMENT OF MANIA

Keck et al.[23] initially evaluated the efficacy and tolerability of aripiprazole compared with placebo in the prevention of type I bipolar disorder in a 26 week double blind study that was later extended to 74 weeks[20], that is, to a total of 100 weeks. The patients who had presented a recent manic or mixed episode first went through a clinical stabilization phase, this being defined in YMRS values ≤10 and MADRS <13 in four consecutive visits or during 6 weeks, during which they ran-

domly received aripiprazole at a dose of 15-30 mg/day for 6-18 weeks. Once this phase was achieved, the patients went on to a second phase in which they were assigned by double blind method to the placebo or aripiprazole group for 26 weeks. In this second phase, the cut-off was the relapse time (appearance of affective symptoms). The patients who completed these 26 weeks continued until completing the 74 weeks of the study where efficacy, relapse and tolerability were evaluated. A total of 161 patients met the stabilization criteria and were then assigned to treatment with aripiprazole and others to placebo (p=0.02). At 100 weeks, the time to relapse was greater with aripiprazole (p=0.01). On the other hand, aripiprazole was superior to placebo, delaying relapse in the manic phase (p=0.05). However, no significant differences were observed between the two groups in the time to relapse in a depressive phase. The most frequently mentioned adverse effects with aripiprazole were akathisia, tremor and dry mouth as well as hypertension, weight gain, vaginitis, confusion, pharyngitis, and flu picture[20,24]. Efficacy of aripiprazole in the prevention of bipolar disorder relapses and its good tolerability explain why the FDA approved aripiprazole for maintenance treatment of patients with bipolar disorder. From the clinical point of view, aripiprazole could be a drug having an optimum profile in the prevention of relapses in bipolar patients with predominantly manic polarity[25,26].

ARIPIPRAZOLE IN MIXED STATES

The mixed episodes are not only difficult to diagnose but also to treat. Drugs such as lithium are less effective in this type of episodes and the use of antidepressants is generally not recommendable due to the worsening they induce in the clinical condition. On the contrary, some atypical antipsychotics and antiepileptics seem to be good alternatives, both in single drug therapy and in combined treatment[27]. In fact, recent data collected from different studies indicate that aripiprazole in single drug therapy has a significant advantage over placebo for the treatment of the mixed states[28]. Even more, only the trials conducted with aripiprazole, ziprasidone and olanzapine had sufficient statistical power to demonstrate their efficacy in the mixed states[27].

SAFETY AND TOLERABILITY OF ARIPIPRAZOLE

In general, aripiprazole is a well-tolerated drug as has been observed in studies conducted in patients with affective disorders[16,17,23,29,30]. Special mention should be given to the low incidence of extrapyramidal side effects and scarce weight gain. However, a greater incidence of akathisia than with the placebo has been observed in some patients (11%-18%)[30-32] but one lower than with haloperidol[19]. In the clinical practice, the use of lower doses of aripiprazole or addition of a short half life benzodiazepine may be effective measures to alleviate this side effect. In principle there is no evidence of an increase in the incidence of tardive dyskinesia in short and long duration studies with aripiprazole, although it may be too soon to state this.

The most common side effects are nausea, vomiting, dyspepsia, somnolence, agitation and anxiety. These are generally resolved within one week in most of the patient, although at some time 3% of the patients report somnolence that lasts more than one week[16,32].

According to the current scientific evidence, aripiprazole hardly seems to be associated to weight gain, on the contrary to most of the antipsychotics used in mania[11]. In the clinical trials conducted in patients with mania, weight gain was minimum[16,17,19]. In a long duration clinical trial, mean weight gain after randomization was 0.5 Kg[23]. Abdominal circumference values, body mass index (BMI) and fat mass were significantly greater in those adolescents who received either risperidone, olanzapine, quetiapine, or ziprasidone. The effect of aripiprazole in these indexes was undetectable. Low risk of metabolic or endocrine side effects was also significant. In this sense, the American Diabetes Association (ADA) in collaboration with the American Psychiatric Association and the American Association of Endocrinologists have summarized the scientific evidence up to now on the induction of related diabetes and metabolic disorders for each ASG[33]. All the data up to date indicate that both aripiprazole and ziprasidone have a lower risk of producing these side effects compared with the other ASGs[1,28].

In relationship to other side effects, there is no evidence of elevation of the prolactin levels (but rather in inverse) and there is also no evidence of significant cardiac alterations in the corrected QT prolongation (QTc) during treatment with aripiprazole[16,32]. Regarding the hematological profile, risk of agranulocytosis and seizures is extremely low, being comparable with that of first generation antipsychotics (FGA). As has occurred with all the new antipsychotics, some clinical cases of possible appearance of malignant neuroleptic syndrome with aripiprazole have been recorded from the time that the drug appeared on the market up to date[34,35]. In general, if the possible phenomena of akathisia and activation that may occur during the first days of treatment, especially in patients previously treated with other antipsychotics, are avoided, the long term safety profile of the drug can be qualified as excellent.

PRACTICAL ASPECTS

This review on the pharmacological and clinical profile of aripiprazole makes it possible to anticipate and stress the growing and important role of aripiprazole in the acute and maintenance treatment of mania and in affective disorders in general. Partial dopamine agonists may decrease dopamine release in hyperdopaminergic states, as occurs in the acute psychotic, acute mania and agitation episodes. In addition, they can increase dopamine release in the mesolimbic region[36,37] during those situations of hypodopaminergia as occurs in the schizophrenic negative syndrome or in bipolar and unipolar depressions. In this sense, aripiprazole is an antipsychotic drug with proven effectiveness in the acute ma-

nia episodes and has sustained long term antimanic activity at doses between 15 and 30 mg/day. Its profile of side effects is characterized by its low risk of extrapyramidal effects and tardive dyskinesia, absence of elevation of prolactin levels and low risk of weight gain and metabolic syndrome. In any case, the possible incidence of akathisia «motor activation syndrome» (a type of reaction with mania symptoms that may be difficult to distinguish between akathisia and a simple relapse) creates the incognito about whether the clinicians are capable of correctly managing it (either by adjusting the dose or with coadjuvant therapy). The coadjuvant and transitory use of benzodiazepines may be useful at the onset of treatment to prevent this problem. More time and practice may be needed for the clinicians to become familiarized with non-sedative antipsychotics such as aripiprazole whose anti-manic efficacy is independent of a sedative effect[38]. Although sedation is not recommendable at any time of the treatment, the therapeutic approach of the acute mania episode with a non-sedative drug may be a challenge for the clinician. Treatment dose and regime in acute mania depend on the baseline situation of the patient. In those patients where it is necessary to switch from the antipsychotic that they were taking previously, it may be convenient to use a dose escalated regime, beginning with lower doses than the final ones and without suddenly interrupting the previous treatment. On the contrary, in acute patient with severe symptoms and without previous treatment, the dose administered initially should be somewhat closer to the maximum effective dose and thus it would not be necessary to increase the dose so slowly, although they could also benefit from a conadjuvant benzodiazepine during the first weeks of treatment. If a picture of akathisia or activation appears, it would be advisable to reduce the dose of aripiprazole, add a benzodiazepine and propanolol and in some cases combine the antipsychotic with a drug such as valproate. After remission of the picture, if necessary, many patients tolerate well an increase in the aripiprazole dose as long as it is done progressively. Table 1 shows a list of practical advice for the effective use of aripiprazole in mania.

CONCLUSIONS

The action mechanism of aripiprazole as a partial dopamine agonist has been shown to be clearly effective in the acute treatment of mania episodes and in their long term prevention. If the clinicians become familiarized with its management, it is a drug which, although lacking a sedative profile, improves agitation, manic symptoms and hostility. It can be foreseen that aripiprazole will have a wide use not only in the short term treatment but will also have a very relevant role in the long term maintenance treatment in the coming years since that is where its principal benefits are obtained: limited weight gain and metabolic effects, low incidence of sedation, good profile on cognitive functions, absence of rebound effect due to momentary forgetting to take the medication and, of course, long term sustained efficacy. The most important challenge to obtain the long term benefits is to become familiarized with its dosage and with the techniques of switching from an antipsychotic aripiprazole, to learn to avoid akathisia and the activation syndrome and to make a rational use of the coadjuvant drugs, such as benzodiazepines, anti-seizure drugs or lithium. In the coming years, we will be seeing an

Table 1 **Practical aspects of the use of aripiprazole in mania**

Whenever possible, make a progressive introduction to the drug, especially in out-patients and in those who have already taken other antipsychotics (for example, beginning with 5 or 10 mg/day)
Sedation is not the same as antimanic efficacy. The benefits of an effective treatment without sedation are observable from the first days, but they may be different and require some clinical observation ability
The target dose in acute mania is approximately 30 mg/day, but there are many patients who respond to lower doses, and, rarely, some patients require higher doses
Do not suddenly interrupt the treatment with other antipsychotics or with lithium when initiating aripiprazole; many apparent adverse events are really due to sudden discontinuation of the previous treatment
Special care must be taken in patients who are stabilized with an antipsychotic treatment but who need to switch due to poor tolerability (for example, weight gain) since in the case of olanzapine and clozapine and also lithium, treatment discontinuation should be slow to avoid sudden relapse
Associate a benzodiazepine such as lorazepan or equivalent at moderate doses during the day and before going to bed at the onset of the treatment
The association with valproate has been shown to be safe and effective; with lithium, the efficacy is also good but should be monitored for possible greater incidence of akathisia, and with carbamazepine, it may be necessary to increase the dose of aripiprazole. The combination of lamotrigine is also possible although this has not been studied as much
If akathisia or activation appears, it is recommended to reduce the dose of aripiprazole, increase the benzodiazepines, and associate propranolol or an antihistamine
After remission of the acute symptoms of mania, it is convenient to maintain the same dose for the prevention of relapses. It has been demonstrated that the patients who maintain the treatment for at least 2 years have a better condition than those who interrupt it
The advantages in cognitive aspects related with a low sedative treatment can be seen but the patients may not be aware of its relationship with the treatment. Indicating them may help compliance
Psychoeducation is useful to help the patients to understand the benefits and risks of the treatments. In the case of aripiprazole, this is the long term advantages of the treatment in maintaining their physical and mental health

increase in the interest for providing integral care to the bipolar patient[39], seeking acute efficacy but also safety, care of the general health and prevention of the allostatic load[40], and complementing drug treatment with psychosocial care[41], for a better prognosis that is not only clinical but also functional[42]. This is the challenge for the next decade.

ACKNOWLEDGEMENTS

The authors thank the Ministry of Health, Instituto de Salud Carlos III, CIBERSAM and Stanley Medical Research Institute, for their help in the Research Program of Bipolar Disorder of Barcelona.

Potential conflicts of interests: Dr. Vieta has received financing for the investigation and has collaborated as advisor for the following pharmaceutical companies: Almirall, Astra-Zeneca, Bial, Bristol-Myers-Squibb, Eli Lilly, Forest Research Institute, Glaxo-Smith-Kline, Janssen-Cilag, Jazz Pharmaceuticals, Merck Sharpe & Dohme, Lundbeck, Novartis, Organon, Otsuka, Pfizer, Sanofi-Aventis, and Servier.

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