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Dopamine partial agonism in antipsychotic-induced sexual dysfunction

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Introduction. Sexual dysfunction is a frequent side effect associated with antipsychotic treatment. It is known to be caused by the hyperprolactinemia that results from the D2 receptor blockade that is characteristic of antipsychotic drugs.

The D2 partial dopaminergic agonism of aripiprazole could explain why its use does not usually cause this side effect, and may even revert it when added to another antipsychotic.

Case reports. We present the cases of two patients treated with D2 dopaminergic antagonists for a first episode of psychosis, who complained of amenorrhea and erectile dysfunction during follow-up. After the addition of aripiprazole to their previous antipsychotic treatment, these side effects reverted without a negative impact on treatment adherence or therapeutic efficacy.

Conclusions. Pharmacological treatments with the potential of reverting sexual dysfunction secondary to antipsychotic treatment can improve compliance and quality of life of our patients, especially in those who are younger and are being treated for a first psychotic episode. In the cases reported here, the use of aripiprazole as an adjunctive treatment resulted in the disappearance of the undesirable effects without affecting the efficacy already achieved with the previous antipsychotic treatment.

Key words: Adherence, Partial dopaminergic agonism, Antipsychotic, Sexual dysfunction, Hyperprolactinemia

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Agonismo parcial dopaminérgico en la disfunción sexual secundaria a antipsicóticos

Introducción. La disfunción sexual es un efecto secundario frecuente de los antipsicóticos. Ha sido relacionada con la hiperprolactinemia producida por el antagonismo dopaminérgico D2 propio de los fármacos antipsicóticos.

El agonismo parcial dopaminérgico D2 del aripiprazol podría explicar por qué su utilización no suele producir ese efecto secundario y que incluso lo revierte al añadirse aripiprazol al tratamiento con otros antipsicóticos.

Casos clínicos. Se presentan dos casos clínicos con un primer episodio psicótico en tratamiento con antagonistas dopaminérgicos D2, que desarrollan amenorrea y disfunción eréctil respectivamente. Tras añadir aripiprazol a su tratamiento antipsicótico previo remiten estos efectos secundarios manteniendo adherencia y eficacia terapéutica.

Conclusiones. Los fármacos que pueden disminuir los efectos secundarios en la esfera sexual pueden mejorar la aceptación al tratamiento y la calidad de vida, especialmente en pacientes jóvenes con primeros episodios psicóticos. En los casos presentados, el uso de aripiprazol como fármaco adyuvante, se tradujo en una mejoría en los efectos secundarios de la esfera sexual, sin comprometer la eficacia terapéutica.

Palabras clave: Adherencia, Agonismo parcial dopaminérgico, Antipsicótico, Disfunción sexual, Hiperprolactinemia

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INTRODUCTION

Antipsychotic agents are capable of blocking dopaminergic D2 receptors. Blockade of the mesolimbic pathway has been associated with the antipsychotic efficacy of these agents. However, receptor blockade of other dopaminergic pathways can cause undesirable effects. Among the potential adverse effects, those related with sexuality (amenorrhea in women, and erectile dysfunction in men)¹⁻⁴ have been associated with hyperprolactinemia caused by D2 receptor blockade in the tuberoinfundibular pathway.

Aripiprazole is a partial agonist of D2 and 5-HT1A receptors and an antagonist of 5-HT2A receptors. Binding to D2 receptors impedes dopamine binding and, due to its partial agonist capacity, aripiprazole stimulates the dopaminergic receptor, although to a lesser degree than endogenous dopamine. Consequently, aripiprazole acts as a D2 antagonist in areas of dopaminergic hyperactivity and as an agonist in regions of dopaminergic hypoactivity. This dual functionality is of key importance in aripiprazole's profile of therapeutic effects and adverse effects in the treatment of schizophrenia.

Replacement of the prior antipsychotic agent with aripiprazole lowers elevated prolactin levels,⁵ restores the menstrual cycle in women,⁶⁻⁹ and improves erectile dysfunction in men^{7,10-11} induced by previous antipsychotic treatment. Although there have been reports of improvement of adverse effects in the sexual sphere as a result of adding aripiprazole as an adjunctive to other antipsychotic agents,¹²⁻¹⁵ to date there have been no data on this issue with regard to patients experiencing their first psychotic episodes.

We report two cases of patients with a first psychotic episode in whom D2 antagonist treatment caused sexual side effects that resulted in poor adherence in one case and low therapeutic compliance in the other. The addition of a D2 partial agonist to the previous treatment of these patients produced complete remission of these side effects.

CLINICAL CASES

Case 1

The case of a 35-year-old woman with a first psychotic episode and treated with risperidone 9 mg/day is presented. She presented adequate remission of the psychotic clinical manifestations in the first phase of treatment. During follow-up, her evolution was favorable but she complained of the occurrence of amenorrhea and extrapyramidal clinical manifestations. Due to these symptoms, the patient gradually reduced her treatment on her own account. Two months later, she presented exacerbation of her psychotic

symptoms and she was advised to start treatment with a depot antipsychotic. Poor control of symptoms and persistent side effects led to a hospital admission eight months later. During this admission, a decision was made to add aripiprazole to the previous treatment (risperidone 6 mg/day and zuclopenthixol 200 mg intramuscularly every 3 weeks), gradually increasing the dose to 30 mg/day. Four days later, the patient's menstruation had returned and her extrapyramidal symptoms had improved. She was discharged after 3 weeks with clear improvement of her psychotic clinical manifestations and good tolerance of treatment; the decision was made to discontinue zuclopenthixol administration. After six months of follow-up, the patient remained stable with the psychopathological improvement achieved, no side effects in the sexual sphere, and good adherence and therapeutic compliance.

Case 2

A 30-year-old man with no previous psychiatric history had a first psychotic episode with schizophreniform features. After starting treatment with amisulpride 600mg/day, his psychotic symptoms improved progressively and he was discharged after 20 days of hospitalization. One and one-half months later, the patient complained of erectile dysfunction and communicated his desire to discontinue treatment if this symptom persisted. It was decided to add 15 mg of aripiprazole to his previous treatment. One week after this change, the patient reported that his erectile dysfunction had remitted. Four months later, he remained psychopathologically stable and free of erectile dysfunction.

Discussion

The evidence of the negative consequences of antipsychotic-induced hyperprolactinemia¹⁻⁴ suggests the advisability of identifying antipsychotic agents with a favorable endocrine profile that can prevent or ameliorate these side effects. These side effects are one of the main factors that motivate patients to abandon treatment,¹⁶ especially young patients with the first psychotic episodes, which is a determinant of relapse occurrence, the number of hospitalizations, overall functionality and the prognosis of these patients.^{17,18}

Among the antipsychotics that have a favorable endocrine profile, several studies of aripiprazole show little or no elevation of prolactin levels in patients treated with this antipsychotic drug compared to patients treated with other second-generation antipsychotics, such as risperidone, olanzapine or quetiapine.^{12,19,20} There also is growing interest in the possible beneficial effects of aripiprazole as adjunctive therapy, associated with other antipsychotics associated with the induction of hyperprolactinemia.¹²⁻¹⁵

In case 1, after the introduction of aripiprazole the patient's amenorrhea resolved, and in case 2, the patient's erectile dysfunction disappeared. In both cases, the improvement took place without an increase in the incidence of other side effects while maintaining adequate control of the psychotic symptoms. Among the limitations of this study, it should be noted that it would be advisable to use scales to evaluate sexual function, such as PRSexDQ-SALSEX validated for Spain.²¹ Moreover, it would have been useful to have measurements of serum prolactin levels before and after drug treatment, which would have provided objective data to support the relationship between the pharmacological change and clinical improvement. In this regard, we believe that the improvement in the sexual sphere observed in both cases after the addition of aripiprazole, although highly suggestive of being a consequence of this change of treatment, does not allow a firm cause and effect relation to be established. In the last four years, a clinical trial¹² and several cases^{13,15} have been published in which the addition of aripiprazole to the previous antipsychotic achieved an improvement in sexual function and/or a decrease in prolactin levels. However, to date we know of no publications referring to patients treated for a first psychotic episode. In this sense, the two cases reported highlight how the rational combination of certain antipsychotic drugs may be a therapeutic option worth considering, even in patients with their first psychotic episodes. Further studies of this topic could lead to the development of therapeutic strategies that have a more positive impact on the quality of life and adherence to treatment of these patients.

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