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Spanish Working Group
for the Study of
Psychotropic-Related
Sexual Dysfunction

Observational, open-label, prospective multicenter study of sexual function in patients starting treatment with aripiprazole

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Introduction. Treatment with neuroleptics may be associated with secondary sexual dysfunction. Studies of sexual dysfunction induced by antipsychotic are important to establish the effectiveness of these agents in patients taking chronic treatments. The main objective of this study was to evaluate prospectively whether a 3 month course of aripiprazole produces changes in the sexual function of patients with schizophrenia.

Methods. The efficacy analysis was performed in the intention-to-treat population (41 patients) and the per protocol population (36 patients). The safety analysis was based on the total sample (42 patients).

Results. The incidence of sexual dysfunction after 3 months of treatment with aripiprazole was zero both in patients who switched therapy due to lack of efficacy and in those taking aripiprazole as a first antipsychotic. Aripiprazole led to an improvement in the symptoms of psychosis (score on the BPRS) and lower scores on the SALSEX questionnaire. The most remarkable improvement was in delayed ejaculation/orgasm.

Conclusion. During the 3 months of treatment, we observed an overall improvement in sexual performance, with a quicker recovery in men than in women, although recovery was similar in both at the end of treatment.

Key words:
Schizophrenia. Sexual Dysfunction (SD). SALSEX questionnaire. Aripiprazole.

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Estudio sobre la función sexual de pacientes que inician tratamiento con aripiprazol. Estudio naturalístico, abierto, prospectivo y multicéntrico

Introducción. El tratamiento con neurolepticos puede asociarse a disfunción sexual secundaria. Los estudios so-

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bre la disfunción sexual secundaria a antipsicóticos son importantes para poder establecer la eficiencia de estos fármacos en los tratamientos crónicos. El objetivo principal de este estudio ha sido valorar de forma prospectiva si el aripiprazol produce modificaciones en la función sexual de los pacientes con esquizofrenia 3 meses después de su instauración.

Métodos. El análisis de eficacia se efectuó en dos poblaciones, la población para intención de tratamiento (41 pacientes) y la población por protocolo (36 pacientes). El análisis de seguridad se ha realizado en la muestra total (42 pacientes).

Resultados. Incidencia nula de disfunción sexual a los 3 meses de tratamiento con aripiprazol, tanto en los pacientes que recibían aripiprazol como primer antipsicótico como en los que habían cambiado a aripiprazol debido a una falta de eficacia de otro antipsicótico. Además de producir una mejoría de los síntomas de psicosis (escala BPRS), el aripiprazol disminuyó la puntuación en la escala SALSEX, siendo el retraso en la eyaculación u orgasmo el que presentó una mejoría media más marcada.

Conclusiones. Mejoría global del funcionamiento sexual durante los 3 meses de tratamiento con aripiprazol, que muestra una recuperación más rápida en los hombres que en las mujeres, aunque ambos consiguen una recuperación similar.

Palabras clave:
Esquizofrenia. Disfunción sexual. Escala SALSEX. Aripiprazol.

INTRODUCTION

Treatment with neuroleptic or antidepressant agents is associated with the onset of sexual dysfunction,¹ unlike treatment with anxiolytics or mood regulators, which do not clearly affect sexual function, or only do so mildly and nonspecifically.² Thioridazine causes sexual dysfunction in 60% of patients, whereas with other antipsychotic drugs this figure is 25%.³ Sexual dysfunction includes conditions

such as decreased libido, difficulty initiating and maintaining sexual relations, and disorders of ejaculation, orgasm, erection, and vaginal lubrication. It can also include priapism, menstrual disorders, and gynecomastia (increased volume of the breasts in women or men).⁴⁻⁶ These disorders can be reversed by interrupting therapy, although priapism may require surgery.

Up to 89% of sexual problems in patients with chronic psychosis are related to the disease itself and to its effect on volition, relationships with others, affective deficit, or difficulty in finding and keeping a partner.⁷ The dissatisfaction caused by treatment-induced sexual dysfunction can make patients reluctant to take medication, thus worsening long-term prognosis.⁸

Although atypical antipsychotic drugs are better tolerated and more efficacious in terms of negative symptoms, they are not exempt from classic adverse effects such as weight gain, liver abnormalities, and anticholinergic symptoms.^{9,10} There are no systematic studies on the effects of antipsychotics on sexual function.

Human sexual function is affected by a substantial number of neurotransmitters,¹¹ including dopamine, serotonin, noradrenaline, acetylcholine, gamma-aminobutyric acid, oxytocin, arginine-vasopressin, angiotensin II, growth hormone-releasing hormone, substance P, neuropeptide Y, and cholecystikinin-8. The physiologic mechanism of a normal sexual response includes neurogenic, psychogenic, vascular, and hormonal factors that are coordinated by specific centers in the hypothalamus, limbic system, and cortex.¹¹

Dopamine facilitates sexual function in the central nervous system, and this effect is mediated by the mesolimbic system.^{12,13} Serotonin, on the other hand, inhibits sexual desire, ejaculation, and orgasm.¹⁴⁻¹⁷ Peripheral blockade of alpha-adrenergic and cholinergic receptors (genitourinary tract) leads to disorders of sexual function.¹⁸ Antipsychotic agents with a potent anticholinergic and/or alpha-1 receptor-blocking effect have a high capacity to alter the process of sexual arousal.¹⁹ Current data do not show that sildenafil is able to reverse the erectile dysfunction caused by psychotropic drugs, although this could well be possible.

The neuroendocrine abnormalities induced by dopamine inhibition could be particularly relevant in sexual dysfunction experienced by schizophrenic patients taking chronic treatment.²⁰ These abnormalities affect blood levels of prolactin, testosterone, luteinizing hormone, and follicle-stimulating hormone. Hyperprolactinemic syndrome is always accompanied by impotence and reduced semen volume, although the reverse is not always necessarily true.^{21,22} Some authors suggest that sexual dysfunction in patients with schizophrenia is associated with hyperprolactinemia only in men, whereas in women it is usually associated with menstrual disorders.²³

Our research group recently showed that the incidence of sexual dysfunction differs depending on the antipsychotic prescribed,²⁴ and that the percentage of patients affected by adverse effects was greater with risperidone (69.8%) than with haloperidol (14.3%), olanzapine (7.7%), or clozapine (0%), which in no case induced sexual dysfunction. To date, no data have been obtained using specific techniques (eg, questionnaires) to determine the effect of aripiprazole on sexual function. Aripiprazole has a different mechanism of action (partial dopaminergic agonism) and is highly unlikely to produce increased prolactin levels, with the result that, in theory, it cannot affect sexual function. Therefore, we determined whether treatment with aripiprazole induced sexual dysfunction in patients with schizophrenia, by calculating incidence after 3 months of treatment.

METHODS

Patients and methods

We performed a 3-month phase IV post-marketing prospective, observational, noncontrolled open-label multicenter trial under conditions of routine clinical practice. The study population comprised patients with schizophrenia for whom aripiprazole was indicated according to the summary of product characteristics. Aripiprazole was prescribed as a first antipsychotic drug or as a substitute due to adverse effects or lack of clinical efficacy with the previous antipsychotic agent.

A total of 40 patients from at least 9 centers were to be enrolled in the study during a maximum recruitment period of 3 months. The participants were men and women aged 18 to 50 years with diagnosed schizophrenia (DSM-IV criteria), a previously satisfactory and regular sex life (any type of sexual practice with or without a partner during the last 3 months), and normal sexual function before taking the antipsychotic drug. They also had to be sexually active at inclusion.

The exclusion criteria at the baseline visit were as follows: sexual dysfunction before taking an antipsychotic (with the exception of mildly diminished libido secondary to a psychiatric condition), diagnosis of any type of bipolar disorder, need for treatment with another antipsychotic (except for the gradual withdrawal of an antipsychotic drug in patients switching therapy), need for treatment with a selective serotonin reuptake inhibitor, recent hormone therapy or treatment with any medication able to interfere with sexual relations (oral contraceptives, tricyclic antidepressants, venlafaxine, mood stabilizers, antihypertensive drugs, or H₂ receptor antagonists), habitual consumption of substances that might interfere with sexual function (eg, alcohol, drugs), patients with a significant concurrent medical condition that could affect sexual function (eg, diabetes, hypertension, primary hyperprolactinemia, prostate cancer, asthma, chronic obstructive pulmonary disease,

myocardial infarction), and hypersensitivity to aripiprazole or any of its excipients. Table 1 shows how the trial was performed.

The recommended initial dose and maintenance dose of aripiprazole was 15 mg/d, administered once daily without regard to meals. During the study, the summary of product characteristics was modified, and the recommended loading dose was changed to 10-15 mg instead of 15 mg.

In order to avoid withdrawal symptoms or recurrence of clinical symptoms, antipsychotics were discontinued gradually and the dose was reduced to half for 1 week; in cases where the presentation of the drug did not allow the dose to be divided, the complete dose was taken on alternate days. Furthermore, aripiprazole was introduced in such a way that it overlapped with the discontinuation of the other antipsychotic drug; the initial dose was 15 mg for 1 or 2 weeks increasing, if necessary, to a maximum of 30 mg/d, depending on the clinical response.

Benzodiazepines were only permitted in new cases. If a patient used another benzodiazepine with an antipsychotic agent on entering the trial, that same benzodiazepine had to be maintained, if possible.

The main efficacy endpoint was the incidence of sexual dysfunction after 3 months of treatment. The primary efficacy analysis was performed in patients treated with aripiprazole for at least 40 days.

The criteria for evaluating efficacy were an increase in any of the items on the Psychotropic-Related Sexual Dysfunction Questionnaire (SALSEX²⁵, modified 1998) with respect to baseline, mean change since inclusion in the total SALSEX score, and change since inclusion in the Global Clinical Impression-Severity Scale (CGI-S) and the change or improvement in the Clinical Global Impression-Improvement Scale (CGI-I) for sexual dysfunction. The CGI-S for psychotic disorder and the CGI-I for change or improvement in psychosis were also completed, and the Brief Psychiatric Rating Scale (BPRS) was administered.^{26,27} Sexual dysfunction was considered to exist if any of the items on the SALSEX scale had increased with respect to baseline.

Safety was evaluated by taking into account the adverse events reported spontaneously by the patient or observed by the physician between the baseline visit and the last visit. Information on the severity of the event, causal relationship with the study drug, and action taken was also recorded.

Statistical analysis

The safety analysis was performed in those patients who took at least 1 dose of aripiprazole, and the efficacy analysis on those who also fulfilled the most relevant inclu-

Table 1	Study development		
	V1 Baseline	V2	V3 Month 3
	Day 0	Day 40 (± 5 days)	Day 90 End*
Informed consent	X		
Inclusion-Exclusion criteria	X		
Sociodemographic data	X		
Psychiatric clinical history	X		
Clinical characteristics	X		
Toxic habits (smoking, alcohol)	X		
Physical examination (blood pressure/pulse)	X	X	X
Sexual habits	X		
CGI-S for sexual dysfunction	X	X	X
CGI-I for sexual dysfunction		X	X
SALSEX questionnaire	X	X	X
BPRS	X	X	X
CGI-S Psychotic disorder	X	X	X
CGI-I Psychotic disorder		X	X
Study treatment	X	X	X
Concomitant treatment	X	X	X
Adverse events	X	X	X
Adherence to study treatment			X
Overall satisfaction with treatment			X

CGI-S: clinical global impression-severity; CGI-I: clinical global impression-improvement; BPRS: Brief Psychiatric Rating Scale.
* Assessments performed in the case of a premature interruption.

sion criteria.

We planned to include a minimum of 40 patients from at least 9 centers. Our minimum sample size was 30 patients, since the sensitivity of the SALSEX scale was 0.93 (greater than 90%). However, a potential dropout rate of 20% meant that it was prudent to aim for 40 patients. The final sample comprised 42 patients, who were enrolled between June 2006 and May 3, 2007.

The total for the safety analysis was 42 patients, since they all received at least 1 dose of aripiprazole. This was the total number of patients recruited, since all the patients were treated with the study drug and all the patients (including the 4 patients who withdrew from the trial early) were evaluated at least once after starting therapy.

The 5 subpopulations analyzed were as follows: intention-to-treat population (ITT, patients who were prescribed aripiprazole and who had valid assessments with the SALSEX questionnaire at all 3 visits or, at least, at visit 1 and at

1 of the 2 follow-up visits [visits 2 and 3]); the per-protocol group (PP, patients from the ITT group who also fulfilled the selection criteria), the TOL group (patients who received at least 1 dose of the study drug and who were assessed at least once after the start of treatment); the AFAD group (patients who received aripiprazole as their first antipsychotic drug); and the SDSDB group (patients who presented some degree of sexual dysfunction with their regular treatment at baseline). Table 2 shows the different subgroups of patients analyzed.

Men and women were compared using nonparametric tests (Wilcoxon rank sum test, equivalent to the Mann-Whitney test).

RESULTS

Efficacy results

The incidence of sexual dysfunction in patients with schizophrenia after 3 months of treatment with aripiprazole was zero in all the subpopulations studied. As the study period progressed, the SALSEX score fell, with the result that the (mean [SD]) overall reduction was -5 (3.6) points. The greatest reduction was observed in the subgroup of patients who presented sexual dysfunction at baseline (-6 [3.1]) (Figure 1). All the symptoms on the questionnaire improved, and the symptom with the most marked mean improvement was delayed ejaculation/orgasm (Figure 2).

Changes in sexual function were not statistically significant ($P=.5000$) in patients prescribed aripiprazole as their first antipsychotic drug, indicating that aripiprazole does not affect sexual function in this small group of patients.

An adjusted model of the results suggested that there was a statistically significant linear relationship between total SALSEX score and dose: the SALSEX score decreased by

an average of 0.35 points for each additional unit (mg) of the dose (in the dosing interval studied) at visit 2 ($P=.0003$; 95% CI, 0.17-0.53) and at visit 3 ($P=.0010$; 95% CI, 0.15-0.54). These results indicate that improved sexual function depends on the dose of aripiprazole at the visits (40 days [visit 2] and 90 days [visit 3]). The analysis by gender showed that men with sexual dysfunction at baseline achieved a more marked improvement than women after 40 days on treatment ($P=.0447$), although both groups experienced a similar recovery of their sexual function after 90 days (Figure 3).

According to the physician's clinical impression at the end of the treatment period, most patients were considered not ill or slightly ill; high severity levels were recorded in only 4 cases (11.2%). As for the clinical impression of im-

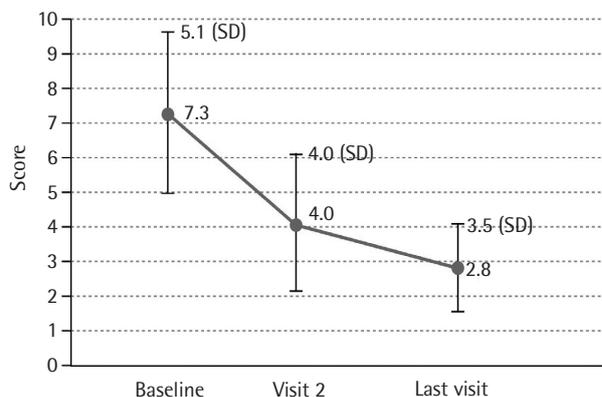


Figure 1 Total mean score on the SALSEX scale in the subgroup of patients with sexual dysfunction at baseline.

Table 2 Patient subgroups		
Population	Patients	Percentage
Patients included*	42	100%
Safety (TOL)	42	100%
Intention-to-treat (ITT)	41	97.6%
Per protocol (PP)	36	85.5%
SDSDB	32	76.2
AFAD	9	21.4

AFAD: aripiprazole as first antipsychotic drug; SDSDB: some degree of sexual dysfunction at baseline.
*CRFs entered into the database.

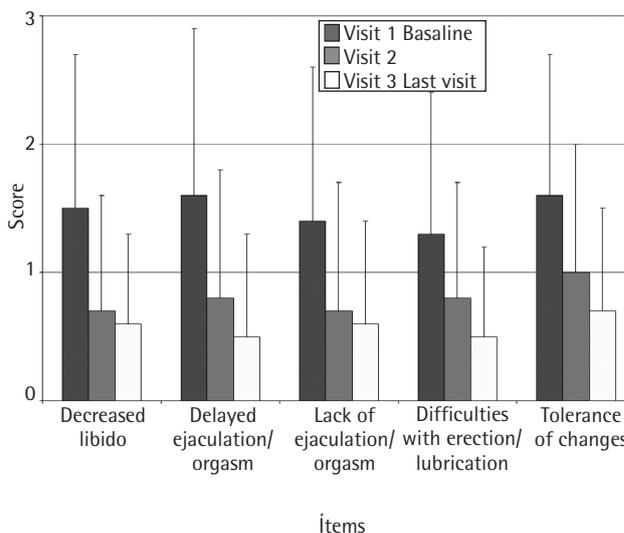


Figure 2 Outcome for items on the SALSEX scale.

provement, no patients were considered by the investigator to have impaired sexual function at 40 days or at 90 days of treatment (Figure 4). Only 2 patients were evaluated as «no change», and 1 patient was evaluated as «moderately worse».

Psychotic symptoms, measured using the BPRS, also diminished as the treatment period advanced. The most marked reduction with respect to baseline was observed at 90 days (-10.0 [9.6] points; 95% CI, -13.1 to -6.9). The greatest antipsychotic effect was observed after 40 days of treatment, with a mean reduction of -7.3 (6.6) points (Figure 5).

At the end of the study, 22 patients (53.7%) were considered responders, either because their BPRS score fell ≤30% or because the investigator considered their clinical status as «much improved» with respect to baseline. The physician considered the clinical status to be «much improved» in 15 cases (38.7%).

Safety results

Sixteen patients (38.1%) reported adverse events that were not present or recorded at the baseline visit. These patients presented a total of 25 adverse events (Table 3), the most common of which was insomnia, recorded in almost half the cases with treatment-emergent events (7 cases). The incidence of insomnia was 17% of all the cases treated. The causal relationship of almost all the events (23) recorded during treatment was «possible»; the investigator considered the relationship to be «certain» in 1 case of akathisia and «unrelated» in 1 case of pregnancy.

Only 2 adverse events (akathisia and sleepiness) at the second visit led to a dose reduction. At the third visit, only sleepiness led to a dose reduction. The investigator took no

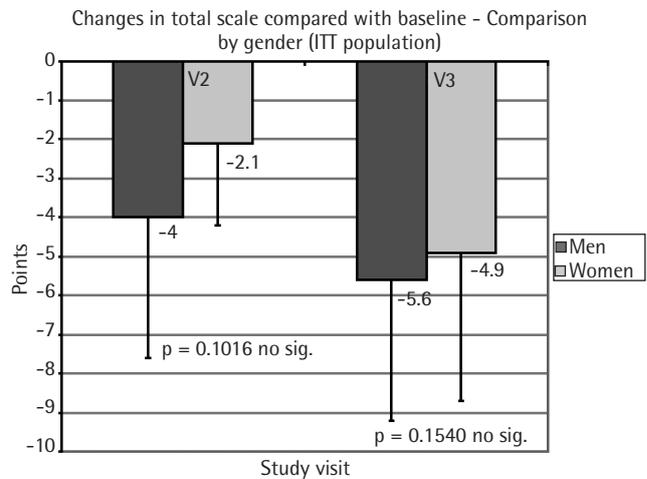


Figure 3 Outcome of sexual dysfunction by gender (ITT population).

action with regard to the remaining adverse events at the second and third visits.

The adverse events reported at visits 2 and 3, in order of frequency were insomnia (most frequent), sexual dysfunction, sleepiness, akathisia, headache, abnormal dreams, anxiety, dyspepsia, hiccuph, nasal congestion, restlessness, hypertension, impaired memory, hyperprolactinemia, weight gain, and vomiting.

DISCUSSION

Our objectives were to determine whether aripiprazole was associated with sexual dysfunction and whether it re-

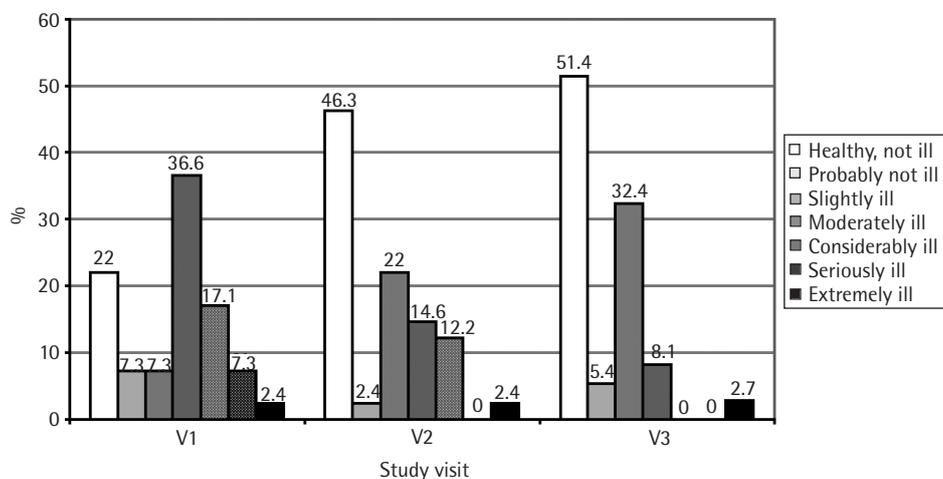


Figure 4 Clinical global impression-severity of sexual dysfunction during the treatment period.

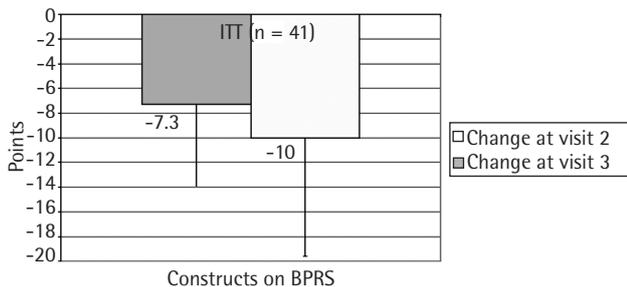


Figure 5 Change in BPRS score compared with baseline.

duced, either partially or totally, the dysfunction produced by other habitually prescribed antipsychotic drugs. The frequency of iatrogenic sexual dysfunction has been reported to be as high as 60% and 96%²⁸⁻³² in many patients with schizophrenia, and is clearly associated with antipsychotic treatment rather than with the disease. Nevertheless, there are differences between antipsychotic drugs, and some (ziprasidone, quetiapine, olanzapine, and clozapine) do not have significant sexual side effects.³³ With some antipsychotic agents (risperidone, amisulpride, and typical antipsychotic drugs), the pathogenesis of sexual dysfunction seems to be related to increased prolactin levels,³⁴⁻⁴⁰ both in men and women,⁴¹ although hyperprolactinemia may not be the only mechanism involved.

The sexual adverse effects observed in patients with schizophrenia and other psychotic disorders often go un-

noticed if specific questionnaires are not administered to detect dysfunction.²⁸⁻³⁰ The results of the present study showed the incidence of sexual dysfunction after a 3-month course of aripiprazole to be zero in all the patients analyzed. We observed a significant improvement in all the symptoms evaluated using the SALSEX questionnaire, which examines sexual desire and problems of arousal and orgasm. The most marked mean improvement was in delay in ejaculation/orgasm. The score for item 5, which explores acceptance of sexual dysfunction and the subsequent risk of discontinuing treatment, fell significantly in patients taking aripiprazole; therefore, adherence improved considerably in this group when the previous sexual dysfunction disappeared. Another important observation was that sexual function improved as the treatment period advanced, both in patients taking aripiprazole as their first antipsychotic and patients who switched to aripiprazole due to sexual dysfunction at baseline. The strongest effect was seen in the latter group. These data suggest that aripiprazole could help improve sex life; there has even been an anecdotal report of aripiprazole-related hypersexuality in a female patient with schizoaffective disorder.⁴² This positive effect could improve relationships with others and minimize the negative symptoms of the disease. Further studies are warranted to investigate this aspect.

Our study showed that men with sexual dysfunction at baseline improve more quickly than women, although the recovery in sexual function is equivalent after 90 days of treatment.

In a similar study,⁴³ women showed a somewhat more discreet improvement than men, suggesting that changes are more marked in men, and that men benefit most from the return to normality. Furthermore, an association was documented between a greater decrease in prolactin levels in men and a more noticeable improvement in sexual dysfunction.

Our data are consistent with those of other authors who have analyzed the frequency of antipsychotic-induced sexual dysfunction^{31,43} and with the results of a recent similarly designed study on the switch to aripiprazole,⁴⁴ which concludes that combining aripiprazole with another antipsychotic substantially improved sexual dysfunction induced by the other drug.

Aripiprazole is generally well tolerated and is unlikely to induce hyperprolactinemia as an adverse effect. A systematic review of short-term studies has shown results similar to those obtained with placebo and significantly lower than those obtained with risperidone in a Cochrane review from 2006.⁴⁵ Another comparative open-label study between aripiprazole and standard treatment (olanzapine, quetiapine, and risperidone), with serial prolactin determinations taken over 6 months, revealed that the switch to aripiprazole normalized the high prolactin levels observed in patients taking

Diagnosis	Frequency	
	n	%
Insomnia	10	40
Sleepiness	3	12
Akathisia	2	8
Restlessness	2	8
Pressure headache	2	8
Nightmares	1	4
Hiccough	1	4
Anxiety	1	4
Dyspepsia	1	4
Hypertension	1	4
Pregnancy	1	4
Total	25	100

Percentages related to emergent adverse events that were not present at baseline.

other antipsychotics.⁴³ In the same study, aripiprazole did not induce sexual dysfunction, which was evaluated using a specific questionnaire (ASEX), and sexual dysfunction clearly improved in those patients who switched to aripiprazole. The favorable tolerability profile of aripiprazole has led psychiatrists in the United Kingdom to agree to recommend this drug as first choice on the basis of its beneficial profile in sexual and physical health, and the improvement in cognitive and affective function.⁴⁶

Given that sexual dysfunction usually goes unnoticed if it is not targeted, we used a widely applied and validated questionnaire to detect antidepressant-induced sexual dysfunction. The questionnaire used in our study (SALSEX) has been validated for schizophrenia. It can detect whether there has been spontaneous reporting of sexual problems and risk of discontinuation (item 5 on the scale), thus demonstrating that many patients would voluntarily discontinue treatment if the dysfunction extended into the medium or long term.

The importance of this adverse effect is consistent with the results of recent studies showing that sexual dysfunction is one of the worst tolerated side effects because of the decrease in quality of life,⁴⁷ especially if the patient is a man.⁴⁸ The results of previous studies by our group in Spain showed that 40% of men and 20% of women with sexual dysfunction had considered discontinuing treatment for this reason. The social, health-care, financial, and familial consequences are usually dramatic when treatment is discontinued; therefore, early detection is essential, particularly considering that there are alternative treatments, for example, switching the antipsychotic to another such as quetiapine, ziprasidone, or olanzapine.^{28-30,49}

The present study is limited by its small sample size and the fact that it is observational and noncontrolled. Controlled studies would help to avoid the biases of the current one. Nevertheless, the effectiveness of the switch and the coherence and conclusive nature of the results, which reveal a considerable improvement in the whole sample, suggest that the same findings could be repeated with larger samples. Furthermore, the procedure for switching antipsychotics could be a risk factor for the reappearance of psychotic symptoms if the switch is made very quickly; therefore, every precaution should be taken. In our study, we made a gradual change during the first month, although more time may be necessary in other patients. The onset of insomnia, akathisia, and restlessness in a large subgroup in our sample seems to advise prudence when switching and combination with benzodiazepines or other drugs when necessary.

CONCLUSIONS

We showed that aripiprazole does not induce sexual dysfunction in patients diagnosed with schizophrenia and

that it is an effective substitute for the previous antipsychotic in the case of poor tolerability of sexual dysfunction and risk of discontinuation. Determination of possible sexual dysfunction using specific validated instruments that can be applied in daily practice due to their brevity and simplicity, such as the SALSEX questionnaire, could prove very helpful for clinicians in the overall approach to schizophrenia.

When deciding on the initial treatment, we should take into account the frequent onset of sexual dysfunction in young patients during the first episodes of the disease. Aripiprazole seems to be an excellent immediate alternative in patients with an active sex life, thus avoiding the onset of a poorly tolerated adverse effect that lasts throughout treatment and seriously compromises adherence.

The improvement in quality of life and adherence would provide added value of incalculable clinical and pharmacoeconomic interest in patients with schizophrenia.

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