

RELATION BETWEEN ANTIPSYCHOTIC MEDICINES AND SEXUAL DYSFUNCTIONS

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ABSTRACT

The aim of the study was to elucidate the relationship between the use of antipsychotic drugs and the appearance of sexual dysfunctions as an adverse effect. Sexuality is inherent in all human beings, and problems involved in sexuality, such as sexual dysfunctions resulting from the use of medications, become a problem for patient adherence to treatment and quality of life. All antipsychotic drugs (both first generation and second generation) are able to alter levels of prolactin, a hormone that is related to the appearance of various dysfunctions such as infertility, decreased libido and changes in the menstrual cycle. The most commonly encountered symptoms regarding the use of antipsychotics are loss of libido, erectile dysfunction and problems related to ejaculation. It is concluded that these drugs are representative in sexual dysfunctions in men and women, but the dysfunctions may be multicausal, and in clinical practice the treatment may be complex, requiring a combination of pharmacological, psychological and behavioral to obtain a quality of life.

KEYWORDS: Antipsychotics; sexual dysfunction; prolactin; schizophrenia.

1. INTRODUCTION

When talking about psychosis, the literature mainly covers schizophrenia, one of the most common and debilitating forms of mental illness. It presents symptoms such as delusions, hallucinations, abnormal and disorganized behavior, catatonia, social withdrawal, decreased emotional responses and reluctance to perform daily activities¹.

In psychosis there are both positive and negative symptoms. Positive symptoms include hallucinations, disorganized speech, and disorganized behavior, while negative symptoms include a decrease in the range and intensity of expressing emotions. The choice of treatment should be made in an individualized manner, taking into account the profile of adverse effects, dose and preferences of the patient. Patients with mental illness may have a

varied clinical course which may include remission, exacerbation or a more persistent chronic illness².

Sexuality is inherent in all individuals, society, culture and also parents, play a critical role in sex and sexuality education, although they often do not have clear concepts about the issues involved³.

Sexual dysfunctions are problems that involve the intercourse of sex, and can be exemplified as erectile dysfunction, premature and delayed ejaculation, priapism, anorgasmia, decreased libido, presence of pain during intercourse and decreased intimate lubrication^{4,5,6,7,8,9,10,11}. Sexual problems are highly relevant and occur frequently in people with any psychological disturbance^{6,12} and negatively affect patient's quality of life and adherence to treatments¹¹.

Connolly & Taylor (2014)¹³ say that atypical antipsychotics are recommended for the treatment of schizophrenia and other psychotic disorders, because it has a more extensive influence on the symptoms of schizophrenia (deficits, affective, cognitive) than typical antipsychotic drugs. This information is contested by Mcevoy *et al.* (2014)¹⁴, who found no major differences in the efficacy of newer and older antipsychotics. The monitoring of antipsychotics in clinical practice is low¹⁵.

Over the last decades, the side effects of antipsychotics have been more carefully analyzed^{16,17}, and the detection of these effects allows the patients to have the best treatment, improving the quality of life of the patient and adherence to the medication¹⁸, since patients who do not tolerate the adverse effects of antipsychotic drugs may have problems adhering to treatment and consequent reduction of effectiveness^{17,19,20}.

The aim of the study was to verify the sexual dysfunctions in individuals who use antipsychotic drugs and to analyze whether the sexual changes are related to pharmacotherapy.

2. MATERIALS AND METHODS

In order to conduct this study, a bibliographic survey was carried out in the databases of the LILACS

(Latin American Literature in Health Sciences), Google Scholar, SCIELO (Scientific Eletronic Library Online) and PubMed (National Center for Biotechnology Information – NCBI, U.S. National Library of Medicine). After the survey from the keywords “sexual dysfunction”, “erectile dysfunction”, “prolactin” and “antipsychotics”, were discarded those that escape the scope of the research and the selected data were object of reading and development of the discussion of the work.

3. DEVELOPMENT

Psychoses and schizophrenia

Many patients with schizophrenia are no different from controls in terms of sexual behavior⁶. However, most patients with schizophrenia show an interest in sex that differs little from the general population²¹. Compared to men, women with schizophrenia tend to have a better social outcome, demonstrated in longer-lasting relationships and higher frequency of children. Due to social and interpersonal deficiencies, patients with schizophrenia face difficulties in the search for long and stable sexual relations⁶.

The extent to which schizophrenia is linked to problematic sexual behavior has not yet been established, but may include psychotic symptoms of patients or the general loss of initiative and level of activity linked to negative symptoms, in addition to the antipsychotic treatment itself⁶.

Sexual behavior and dysfunctions

Sexual behavior is composed of autonomous, cognitive and emotional components that are related to the socio-cultural role²². Sexual functioning is not routinely discussed, this may lead to an underestimation of the frequency and impact of sexual problems^{6,23}.

The etiology of sexual dysfunction may be multicausal because it usually involves more than one factor of sexual functioning^{12,24}. A correct diagnosis of the dysfunction allows to increase the possibility of cure of the condition¹¹. Patients with symptoms of depression and anxiety are more likely to have some sexual dysfunction^{25,26}.

By obtaining prolactin and testosterone levels, one can in many cases elucidate a sexual dysfunction caused by testosterone (hormonal) decline or by mental causes, functional stress, adverse drug effects, or other etiologies such as diabetes, hypertension or neurological causes²⁷.

Sexual dysfunction in men

The erection describes the non-flaccid state of the penis and is in most cases the physiological expression of sexual arousal, the result of complex neurovascular mechanisms^{6,28}. Several central and peripheral neurological factors in addition to molecular, vascular and psychological factors are involved. The sexual functionality of the penis is

determined by the balance between these factors²⁸. Erectile dysfunction should be investigated and diagnosed initially for vascular, neurological, endocrine and drug causes, so that the cause may be considered to be psychogenic by exclusion^{11,23}.

There are few clinical studies performed to represent the regulation of ejaculation, which is a complex process involving various anatomical structures and extensive neurochemical and hormonal regulation. Many neurotransmitters are involved in the ejaculatory process, and defining the exact role of these neurotransmitters is difficult because of the variety of sexual parameters affected, different sites of action, and the presence of multiple types of receptors²⁸. With the elucidation of these parameters, it is easier to control and treat dysfunctions that affect ejaculation.

Premature ejaculation is one of the most common sexual dysfunctions, it is defined as the inability to control or delay ejaculation, which results in patient dissatisfaction or distress^{5,29}. Psychological components often contribute to premature ejaculation, and a complex interaction between neurophysiological factors is likely to predominantly influence premature ejaculation^{5,26}. Treatment options available for premature ejaculation include oral pharmacotherapy (including antipsychotics) and topical anesthetics²⁹. The causes of delayed ejaculation are mostly caused by medications or by psychological causes, with less incidence of hormonal causes⁴.

Sexual dysfunction in women

Female sexual dysfunction is a heterogeneous condition that causes significant stress for the woman. It's dysfunction should not be attributed solely to psychological causes but also to possible organic causes or a combination of the two factors. This multifactorial etiology makes the clinical challenge complex⁹. The most common dysfunctions in women are loss of libido and lack of vaginal lubrication⁷.

Studies of populations with female sexual dysfunction have increased in number and different cultural configurations³⁰. Research on the identification of neurobiological, physiological, and cognitive processes underlying affective experiences and female sexual functioning is important because the female sexual response is closely linked to mood³¹. Cultural beliefs are significant in the sexuality and relevance of sexual function in society, complicating the classification and determination of female sexual dysfunction³². This suggests that female sexuality is less approached, so that identification or treatment of dysfunction does not occur.

Andreucci *et al.* (2015)³³ reports that women who suffered a perineal injury at child-birth may have dyspareunial sexual dysfunction, and the greater the injury, the worse the dysfunction and the lower the

sexual frequency, which can result in problems in the quality of life of the woman and her partner.

Antipsychotics

Antipsychotics may be exemplified by: chlorpromazine, fluphenazine, pericyazine, pituitazine, thioridazine, trifluoperazine, clozapine, quetiapine, olanzapine, droperidol, haloperidol, penfluridol, pimozide, amisulpride, sulpiride, thiapride, veralipride, risperidone, ziprasidone, aripiprazole, among others³⁴.

There are few differences in the tolerability of long-acting injectable antipsychotics and oral antipsychotics. While those for oral use can be stopped promptly, long-acting injectables would not lead to discontinuation of treatment³⁵. This possibility facilitates the search for an adequate medication according to the patient's need and individuality.

The use of more than one antipsychotic drug, called antipsychotic polypharmacy, is associated with higher doses and in chronic and severe individuals. Monotherapy is the choice for younger patients, because they have fewer episodes of the disease and greater sensitivity to adverse effects¹³.

Antipsychotics x sexual dysfunctions

People receiving psychiatric treatment, the possibility of other factors affecting sexual functions should be evaluated, such as metabolic problems or other medications³⁶, because they can influence the neural and vascular structures, resulting in alterations of the sexual function¹¹.

Antipsychotic medications may induce sexual dysfunction, but research on the treatment of sexual dysfunction induced by these drugs is remarkably small and often inconsistent. However, treatment of sexual adverse effects in patients with psychotic disorders is extremely important, because sexual dysfunction may contribute to difficulties with social functioning and non-compliance with treatment. Sexual dysfunction should be evaluated so that, if necessary, clinical management²³.

Patients taking antipsychotics generally report being less sexually susceptible. It is suggested that this decrease can also be associated with the general reduction of the initiative, called negative symptoms. Still, pharmacotherapy may be the most prominent cause, underscoring the importance of considering with patients which factors are important in their individual situation⁶.

As antipsychotics may increase prolactin secretion, Peuskens *et al.* (2014)³⁷ suggest that hyperprolactinemia may cause such dysfunctions, while the anti-serotonergic properties of atypical antipsychotics may to some extent prevent sexual dysfunction¹⁹ and are better tolerated, since the impact of adverse effects is significant when compared to the impact of treatment on symptoms¹⁷.

Peuskens *et al.* (2014)³⁷ claim that all antipsychotics have the propensity, especially during

the first hours, to raise prolactin levels through dopaminergic blockade, but Ames *et al.* (2016)¹⁶ reported that there are drugs in which such elevation is low, as in the case of clozapine, aripiprazole and quetiapine. Considering the first generation antipsychotics, the increase caused by sulpiride is noteworthy, while in the second generation, amisulpride, risperidone and paliperidone are more associated with an increase in prolactin^{37,38}. The literature presents several different methodologies when analyzing the relation between antipsychotics and prolactin, which include analysis time, patient's gender, drug use and how prolactin is analyzed, making the results not completely homogeneous³⁹.

High frequencies of sexual dysfunction have been found for risperidone and classical antipsychotics and lower frequencies for clozapine, olanzapine, quetiapine and aripiprazole. The causes that may be the most relevant factors in the pathogenesis are postsynaptic antagonism of dopamine, elevation of prolactin, and blockade of D_1 receptors⁶. Antipsychotics with a low potential to increase prolactin, such as clozapine, are also associated with sexual dysfunction, where the cause may be related to anticholinergic mechanisms¹⁶. These results reiterate the fact that sexual dysfunctions are multicausal.

The anterior pituitary gland secretes prolactin - whose function is to prepare the mammary gland for lactation. Dopamine negatively regulates prolactin. When prolactin is at high levels, it inhibits the hypothalamic secretion of the gonadotropin releasing hormone, which decreases the secretion of luteinizing hormone and pituitary gland follicle stimulating hormone, resulting in low gonadal steroids such as estrogen and testosterone. High levels of prolactin are termed hyperprolactinemia and are dependent on many factors, such as the moment of measurement. They can cause infertility, decreased libido, erectile dysfunction, menstrual irregularity or amenorrhea^{16,27,37}.

Treatment strategies for antipsychotic-induced sexual dysfunction are similar to strategies for antidepressant-induced sexual dysfunction. Dose reduction requires close monitoring of relapse of psychotic symptoms, and discontinuation of treatment is not recommended. The strategies of choice are to switch to an antipsychotic that brings less incidence of sexual dysfunctions or adding a medication that treats unwanted sexual symptoms²³.

Prolactin dosages should be obtained prior to initiation of psychotropic drug treatment, but in many cases this is not possible, especially when the medication is to be used urgently²⁷. Can also decrease prolactin levels with a dopamine agonist or switch to an antipsychotic with less influence on prolactin⁶.

Due to the few studies on recently approved antipsychotics, there are no firm conclusions about the prolactin profile. Showing the need for additional controlled trials to assess the degree of safety and which of these agents are potentially less problematic

with respect to prolactin³⁷. More studies or surveys should be performed to analyze different cultural groups of individuals or the effect of antipsychotic medications on a particular sexual dysfunction.

4. DISCUSSION

Adverse effects of antipsychotics

Millier *et al.* (2014)¹⁷ found most common side effects extrapyramidal symptoms (in almost 60% of patients), followed by sedation and weight gain (mean of 50% for each symptom) and sexual dysfunctions (30%). According to Green *et al.* (2015)⁴⁰, a change in lifestyle in patients taking antipsychotics may reverse some of the symptoms. Connolly & Taylor (2014)¹³ and McEvoy *et al.* (2014)⁴¹ also cite weight gain as a common effect in the use of antipsychotics, but specifically in atypical antipsychotics. Hocaoglu *et al.* (2014)⁴² affirm that other studies are necessary to distinguish cultural norms, schizophrenia and the use of antipsychotic medication in the etiology and development of sexual dysfunction.

In the review conducted by Just (2015)¹⁹, it is concluded that patients who do not tolerate the adverse effects of atypical antipsychotic drugs may abandon treatment. To aid in the reduction or resolution of sexual dysfunctions caused by antipsychotics, other medicinal products may be used. Gur & Sikka (2015)²⁹ report that dapoxetine, for example, is a selective short acting serotonin reuptake inhibitor that is safe and effective in the treatment of premature ejaculation.

Boer *et al.* (2015)⁶ concludes that most schizophrenic patients have an interest in sex, differing little from the healthy population, although psychiatric symptoms and antipsychotic medication may cause various sexual dysfunctions.

Despite Morrison *et al.* (2014)²⁰ emphasize that other studies are necessary, affirm that cognitive therapy can significantly reduce psychiatric symptoms, establishing itself as an acceptable choice even when antipsychotic medications are not used. Psychotherapy can be used to help patients deal with the social difficulties of the disease and the adverse effects resulting from the treatment, as well as to help when sexual dysfunction is a psychogenic cause.

Pharmaceutical care in the use of antipsychotics

Wallerstedt & Lindh (2015)¹⁵ analyzed the prevalence of therapeutic monitoring of antidepressant and antipsychotic drugs, concluding that monitoring is low, but more common for antipsychotic drugs and when the patient is male. Hynes *et al.* (2015)¹⁸ have developed a scale of the side effects of clozapine, such a study demonstrates how these strategies can be used in clinical practice, reiterating the importance of new studies.

Connolly & Taylor (2014)¹³ cite that polypharmacy is highly utilized, leading to high doses of antipsychotic medications and high rates of side

effects. Clayton *et al.* (2014)²³ claim different information about the use of more than one drug in patients with major depressive disorder who use aripiprazole, where he cites that adverse effects are few and the sexual function can modestly improve. This data suggest how complex sexuality is. Park *et al.* (2016)³⁸ report that antipsychotic medication increases prolactin levels, often related to sexual dysfunction, but treatment with risperidone and paliperidone may help to regulate these levels.

Gender, sexual dysfunctions and schizophrenia

Rubin *et al.* (2015)²¹ report that during the menstrual cycle the levels of oxytocin do not change. Physiological levels of oxytocin may therefore be more beneficial in some cognitive domains than estrogens in patients with schizophrenia. Better understanding of how sexual dysfunction affects women in different age groups and ethnic groups may help in the clinical care of these patients⁷.

González-Rodríguez *et al.* (2014)⁴³ evaluated the gender-related differences in the pathophysiology of schizophrenia, but found similar results, suggesting that the gender does not show great variation in the analyzed variables. In the last decade, female sexuality, especially sexual dysfunction related to women, has increased the number of studies based on populations from different cultural contexts³⁰. Boer *et al.* (2015)⁶ report that women with schizophrenia, with or without sexual dysfunction, have a better quality of life than men. In addition to antipsychotics, other factors affect female sexuality, such as maternity³³. Sharma & Kalra (2016)⁹ grouped the information referring to everything that encompasses female sexual dysfunctions, such as definition, etiology and diagnosis.

Antipsychotics and prolactin

Many studies do not detail how prolactin was measured³⁷. All antipsychotics (first or second generation) has the ability to alter prolactin, and this effect is more pronounced for amisulpride, risperidone and paliperidone, whereas aripiprazole and quetiapine have less effect on prolactin^{16,23,37,43,44}. The relation between prolactin increase and schizophrenia is very complex and can not be confined only to antipsychotic medication³⁹. In addition to this information, Ajmal *et al.* (2014)²⁷ cites that it is important to exclude diseases of the pituitary and hypothalamic glands, which is also related to the increase of prolactin.

5. CONCLUSION

It is concluded that antipsychotic drugs are representative for their adverse effects as causes of sexual dysfunction in men and women, but the dysfunctions may be multicausal. The health monitoring is necessary to use the best pharmacological method for the treatment of psychoses, being performed with dose adjustment and

change or addition of medication so that it is not cause of sexual problems. In clinical practice, the treatment is complex and may require a combination of pharmacological, psychological and behavioral treatments so that the patient can have a good quality of life.

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