

ANTIPSYCHOTICS AND SEXUAL DYSFUNCTION:
EPIDEMIOLOGY, MECHANISMS AND MANAGEMENT

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Abstract

Objective: Growing attention has recently been given to the sexual dysfunction (SD) burden related to antipsychotics. The aims of the present work are 1) to review current evidence about SD related to antipsychotics, 2) to explain the need that it is purposely investigated and 3) to summarize available information about the biological underpinnings as well as the main management strategies of antipsychotic-related SD.

Method: Medline, ISI web of science, the Cochrane collaboration database and references of retrieved articles were searched for original studies and review articles focusing on the epidemiology, measurement instruments, biological underpinnings and management strategies of antipsychotic-related SD.

Results: Available evidence suggests that SD has a higher likelihood of occurring in both treated and untreated schizophrenia patients as compared with comparable healthy controls. Clinicians should rely upon specific scales designed to investigate SD, or at least ask directly about SD because otherwise patients tend to scarcely report this side effect. Antipsychotic drugs most commonly associated with SD are olanzapine, risperidone, haloperidol, clozapine, and thioridazine. On the other hand, ziprasidone, perphenazine, quetiapine and aripiprazole are associated with relatively low rates of SD. Biological studies showed that the incidence of sexual dysfunction could be directly related to the ability of an antipsychotic to increase prolactin levels and to bind to cholinergic, α -adrenergic, histaminergic and dopaminergic receptors. Main strategies for the management of antipsychotic-induced SD include dose reduction of current antipsychotic, switching to prolactin-sparing antipsychotics such as quetiapine or using dopamine partial agonists such as aripiprazole.

Conclusions: SD is a relevant issue that should be carefully considered when an antipsychotic is given. Clinicians should purposely investigate this side effect both before and after the prescription of a given antipsychotic and should be aware of strategies to manage antipsychotic-related SD.

Key words: antipsychotics, desire, arousal, orgasm, sexual dysfunction, management

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Introduction

Sexuality is a fundamental aspect of human behavior not only as an act aimed at the reproduction and the pursuit of pleasure, but also as an essential component of social life and relationships. Sexual dysfunction (SD) can disrupt a person's ability to form or sustain intimate relationships. It is relatively common in the general population and it is associated with a significant

reduction of the quality of life. For example, North American adults experience considerably high rates of SD. Indeed, community samples indicate that 10–52% of men and 25–63% of women report some sexual problem in their adulthood (Heiman 2002).

However, current evidence suggests that the prevalence of SD is significantly higher in patients with mental disorders, such as schizophrenia, major depression, anxiety disorders and eating disorders, as

compared with healthy control subjects matched for several socio-demographic features such as age and gender, even when they are untreated (Mathew and Weinman 1982, Segraves 1998, Heiman 2002). In spite of the high prevalence of SD observed in psychiatric patients suffering from these disorders, most sufferers do not seek help either because of a feeling of embarrassment or because they do not view it as a medical problem. Therefore, clinicians should always purposely inquire patients about their sexual function both before and following the initiation of treatment, so as to distinguish among primary sexual functioning disorders, SD associated with the psychiatric condition for which the patient is going to receive treatment, SD related to concurrent physical diseases and treatment-emergent SD (Segraves 1998).

Although significant advancements have been achieved over the last decades in the understanding of illness and drug-related SD in some categories of patients, such as in patients suffering from major depression (Serretti and Chiesa 2009), up to recent years SD in patients with psychotic disorders has been poorly investigated (Kelly and Conley 2004). Indeed, discussing sexual issues with psychotic patients has long been considered inappropriate by clinicians because it was believed that they should not engage in sexual activity. As an example, at the beginning of last century some researchers believed that sexual excesses could actually cause insanity (Von Krafft-Ebing 1905). Furthermore, in the '70s of the past century some psychiatrists still believed that sexual activity could contribute to the development of schizophrenia in most patients with this illness (Pinderhughes et al. 1972).

As a consequence, up to recent years, direct inquire of psychotic patients about their sexual function has received little attention by clinicians and researchers involved with these patients (Kelly and Conley 2004). Likewise, SD related to antipsychotic drugs has been scarcely investigated (Serretti and Chiesa 2011). However, a thorough investigation of sexual function in psychotic patients as well as of antipsychotic-related SD is becoming an issue of paramount importance. First of all, current evidence consistently shows that psychotic patients engage with sexual behaviours, even though their sexuality has been found to differ from that typically observed in non-psychotic subjects (Rozaan et al. 1971). Additionally, antipsychotic-related SD has been found to reduce self-perceived quality of life in psychotic patients. This, in turn, has been found to undermine compliance with treatment (Montejo et al. 2010).

The aims of the present work are, therefore, to review current evidence about SD related to antipsychotics as well as its epidemiology, to explain the need that it is purposely investigated by clinicians and to summarize available information about the biological mechanisms of antipsychotic-related SD as well as the main strategies to manage such side effect.

Methods

Medline, ISI web of science, the Cochrane collaboration database and references of retrieved articles were searched for original studies and review articles focusing on the epidemiology, measurement instruments, biological underpinnings and management strategies of antipsychotic-related SD. Our search strategy included the following terms: "antipsychotics" and the names of each single antipsychotic (e.g. "haloperidol") in combination with "sexual

dysfunction", "sexual side effects", "epidemiology", "biology", "scales" and "management". In order to summarize the growing evidence about this topic as much as possible, when we found a review or a meta-analysis dealing with a specific topic of interest, we mentioned only such review or meta-analysis in order to replace single articles. Otherwise, we gave higher emphasis to larger epidemiological studies and randomized controlled trials, as appropriate to the specific topic of investigation.

Results

Psychotic disorders and sexual dysfunction

The natural history of sexual functioning in people with mental disorders, particularly with psychotic disorders, has received little attention from empirical research so far (Kelly and Conley 2004). The investigation of SD in patients suffering from psychotic disorders is further limited by the notion that their sexual functioning is different both qualitatively and quantitatively from that of non-psychotic subjects (Kelly and Conley 2004). Indeed, psychotic patients engage in less overall sexual activity of any type and are more likely to experience autoerotic behaviors (Rozaan et al. 1971). More recently, however, some studies have been published that showed that SD is highly prevalent in schizophrenia patients, being SD among these patients as high as 30–80% in women and as high as 45–80% in men (Cutler 2003; Kelly and Conley 2004; Bitter et al. 2005; Dossenbach et al. 2005; Baggaley 2008). Of note, some evidence supports the notion that SD is frequently associated with schizophrenia, even when it is untreated, as evidenced by studies showing that even treatment-naive schizophrenia patients commonly exhibit SD (Aizenberg et al. 1995; Bitter et al. 2005). In particular, the frequency of sexual thoughts and the desire for sex seem substantially reduced in the majority of untreated patients with schizophrenia as compared with healthy controls (Aizenberg et al. 1995).

Although the precise nature of the association between SD and schizophrenia remains elusive so far, some authors have hypothesized that it might be a consequence of multiple and somewhat concomitant factors, including disturbed psychomotor performance in schizophrenia patients, social consequences of this condition, such as social stigma and isolation leading to reduced desire, ability or opportunity to form sexual relationships (Smith et al. 2002), comorbid medical conditions such as type 2 diabetes, obesity, cardiovascular, neurologic and urologic disorders (Chiesa and Serretti 2010), non psychiatric drugs used to treat these medical conditions (Smith et al. 2002) as well as antipsychotic treatment itself (Serretti and Chiesa 2011). Pertaining to the latter issue, it has been found that antipsychotic treatment may alleviate some symptoms of schizophrenia that could reduce drive for sexual behaviors, such as anhedonia (Aizenberg et al. 1995). However, antipsychotic drugs have been themselves associated with SD (Dossenbach et al. 2005). This, in turn, has been found to reduce self-perceived quality of life and, consequently, treatment adherence (Heald et al. 2010).

The assessment of SD

Antipsychotic-related SD has long been underestimated. The main reason for such underestimation has been explained by recent works showing that SD rates related to antipsychotics are significantly higher in most recent clinical trials in which clinicians directly question patients about their sexual function or that employ specific sexual questionnaires as compared with older clinical trials relying solely on spontaneous reports (Dossenbach et al. 2005). In a recent study of psychotic patients (71% of which suffered from schizophrenia), Montejo et al. found that SD occurred in 46% of the patients, as measured with the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) (50% of the males and 37% of the females). However, only 37% of patients with SD spontaneously reported such side effect. This finding, along with findings suggesting that a large proportion of patients who develop SD following treatment poorly tolerate this side effect (Montejo et al. 2010) and that SD has been rated as one of the major factors contributing to noncompliance with antipsychotic treatment (Kelly and Conley 2004), points to the importance of a proper investigation and recognition of this unwanted side effect.

Unfortunately, however, data interpretation and evaluation of the effects of antipsychotics on sexual function is not as easy as one would expect. Indeed, although several instruments have been developed for the assessment and measurement of the SD (Kelly and Conley 2004), SD rates measured by different questionnaires are often different from one another (Serretti and Chiesa 2009). This is particularly evident in populations of patients suffering from major depression, for whom several sexual scales are currently available. Five rating scales are most widely used in depressed patients: the Arizona Sexual Experience Scale (ASEX) (McGahuey et al. 2000), the Changes in Sexual Functioning Questionnaire (CSFQ) (Clayton et al. 1997), the Derogatis Interview for Sexual Functioning (DISF) (Derogatis 1997), the PRSexDQ (Montejo et al. 2000) and the Rush Sexual Inventory (RSI) (Zajacka et al. 1997). Because these questionnaires have been already discussed in detail in a previous review of our group, the reader is addressed to such work for a more thorough discussion (Chiesa and Serretti 2010). What is more important to the aim of the present review is that the CSFQ has long been considered as the most appropriate scale to be administered to patients with schizophrenia (Kelly and Conley 2004). In addition, more recently, the PRSexDQ has been specifically validated in a sample of patients treated with antipsychotics, showing good reliability for this target population (Montejo and Rico-Villademoros 2008).

Epidemiology of sexual dysfunction related to antipsychotic drugs

Although hampered by several methodological shortcomings, an increasing number of studies have recently provided strong evidence that both conventional and atypical antipsychotics are associated with a substantial impairment of sexual functioning (Kelly and Conley 2004; Baggaley 2008; Serretti and Chiesa 2011) (**table 1**). In particular, a recent meta-analysis showed increasing rates of total SD in patients treated with quetiapine, ziprasidone, perphenazine, aripiprazole, olanzapine, risperidone, haloperidol, clozapine, and thioridazine, being quetiapine the

antipsychotic associated with the lowest rates of SD and thioridazine the one associated with the highest rates (Serretti and Chiesa 2011). A critical look at the studies included in such meta-analysis showed, however, that the majority of included studies did not allow to distinguish between treatment-emergent SD and pre-existing SD (Serretti and Chiesa 2011). The only study that provided separate data on patients who, at the beginning of treatment, did not complain of SD was the study performed by Dossenbach and colleagues (Serretti and Chiesa 2011). The authors found that 45% of patients treated with haloperidol, 43% of patients treated with olanzapine, 43% of patients treated with risperidone and 34% of patients treated with quetiapine developed SD following the initiation of treatment with these drugs (Dossenbach et al. 2006). Of note, this finding, along with findings suggesting that global SD rates vary as a function of the specific antipsychotic under investigation (Serretti and Chiesa 2011), strongly suggests that the underlying disorder is not the only determinant of SD in psychotic patients. Furthermore, on the contrary of a number of different side effects such as nausea or headache, current evidence suggests that antipsychotic-related SD tend not to disappear with ongoing time (Serretti and Chiesa 2011).

The same meta-analysis showed that the rates of SD in patients taking aripiprazole, olanzapine, and quetiapine are significantly higher in studies allowing concomitant medications that are known to negatively affect sexual function, such as selective serotonin reuptake inhibitors (Serretti and Chiesa 2011), whereas SD rates associated with clozapine, risperidone and haloperidol are not influenced by concomitant intake of drugs affecting sexual function (Serretti and Chiesa 2011). This finding is consistent with the notion that, while the strongest independent predictor of SD for patients treated with the former antipsychotics is the association with a drug that significantly disrupts sexual function, the negative effect on sexual function induced by concomitant treatments could be masked by the higher percentages of SD associated with the latter antipsychotics.

In addition, when studies investigating SD rates by means of the PRSexDQ, the only sexual questionnaire specifically validated in psychotic patients, were separately analyzed, it was found that SD associated with aripiprazole, quetiapine, clozapine, and olanzapine was relatively low, whereas SD rates associated with risperidone were even higher than those observed in the general analysis (Serretti and Chiesa 2011). Further sensitivity analyses showed, however, that the use of different sexual questionnaires had a significant impact on the absolute rates of SD in patients treated with antipsychotics. In particular, the CSFQ and the MdSQ (Multidimensional sexual Questionnaire) were usually associated with higher rates of SD in comparison with SD rates detected by the Udvalg for Kliniske Undersøgelser, the PRSexDQ and direct inquiry (Serretti and Chiesa 2011).

In conclusion, consistent evidence suggests that antipsychotics as a class are significantly associated with SD. However, significant differences exist between different antipsychotics, such that a number of antipsychotics mainly including aripiprazole, quetiapine and ziprasidone is associated with relatively low rates of SD, particularly when these drugs are used as mono-therapy, whereas other antipsychotics such as olanzapine, risperidone, clozapine, haloperidole and thioridazine are associated with high rates of treatment-dependent SD.

| Molecule | Percentage of patients with total sexual dysfunction | Percentage of patients with desire dysfunction | Percentage of patients with arousal dysfunction | Percentage of patients with orgasm dysfunction |
|--------------|--|--|---|--|
| Aripiprazole | 0-71% | 26% | 15% | 11% |
| Clozapine | 14-55% | 14-50% | 14-40% | 7-40% |
| Haloperidole | 38-51% | 12-57% | 21-30% | 15-21% |
| Olanzapine | 13-61% | 14-77% | 9-50% | 3-61% |
| Perphenazine | 25% | - | - | - |
| Quetiapine | 1-53% | 4-72% | 5-36% | 5-32% |
| Risperidone | 19-82% | 8-82% | 16-93% | 13-86% |
| Thioridazine | - | - | - | - |
| Ziprasidone | 14-19% | 7-20% | 7-22% | 7-24% |

Table 1. Total and phase-specific sexual dysfunction among patients treated with antipsychotics

Phase-specific antipsychotic-related SD

According to the current classification established by the American Psychiatric Association, disorders of sexual function are divided into 4 categories: 1) disorders of sexual desire, 2) disorders of arousal, 3) disorders of orgasm and 4) sexual pain disorders (American Psychiatric Association 1994). Antipsychotic use has been mainly associated with dysfunctions of sexual desire (libido), arousal (including vaginal lubrication in women and erectile dysfunction in men), and orgasm (Kelly and Conley 2004, Baggaley 2008). According to a recent meta-analysis, antipsychotics linked with lower levels of total SD were the same as those associated with lower levels of phase-specific SD and vice versa (Serretti and Chiesa 2011). Notable exceptions included clozapine, that was associated with relatively low rates of arousal and orgasm dysfunction, aripiprazole, associated with the lowest SD rates on each phase of sexual function, and haloperidol, that was related to relatively low rates of orgasm dysfunction (Serretti and Chiesa 2011) (**table 1**). Finally, it is worth mentioning that males treated with haloperidol and risperidone show higher arousal and orgasm dysfunction as compared with females, whereas no different sex-specific SD rates have been observed for olanzapine and quetiapine (Serretti and Chiesa 2011).

Biology of SD antipsychotic related

Antipsychotic treatment can cause SD by means of both direct and indirect mechanisms (Haddad and Wieck 2004, Baggaley 2008). All antipsychotics act on a variety of neurotransmitter systems including cholinergic, adrenergic, histaminergic and dopaminergic systems, although the extent to which these different neurotransmitter systems are involved depends on the specific antipsychotic (Haddad and Wieck 2004, Baggaley 2008). Pertaining to direct effects, the cholinergic receptor antagonism reduces peripheral vasodilation and causes erectile dysfunction. Furthermore, α -adrenergic receptor antagonism results in reduced peripheral vasodilation as well which, in turn, leads to decreased erection/lubrication and abnormal ejaculation (Cutler 2003, Haddad and Wieck 2004, Baggaley 2008). Moreover, an antagonist action on the histaminergic receptors can lead to sedation and, indirectly, to impaired desire and arousal. Likewise,

dopamine receptor antagonism has been linked to the inhibition of motivation and reward that, in turn, is indirectly associated with decreased libido (Cutler 2003, Haddad and Wieck 2004, Baggaley 2008).

Note also that dopamine 2 (D2) receptor antagonism can lead to hyperprolactinaemia. Hyperprolactinaemia has been consistently associated with decreased libido, impaired arousal and impaired orgasm (Cutler 2003, Haddad and Wieck 2004, Baggaley 2008). Indeed, blockade of dopamine receptors on lactotrophs cells leads to a tonic inhibition of these cells resulting in increased circulating prolactin levels that, in turn, have been associated with several side effects such as gynaecomastia, amenorrhoea, and galactorrhea (Gitlin 1997).

This information is consistent with findings from studies suggesting that long-term treatment with conventional antipsychotics, risperidone and paliperidone (which are associated with a strong D2 receptor antagonism) are associated with dose-related hyperprolactinaemia, whereas other antipsychotics such as olanzapine (that has a lower effect upon the D2 receptor) has been associated with lower and transient increases in prolactin concentrations (Cutler 2003, Cookson et al. 2012). Similarly, only transient increases in prolactin levels occur with ziprasidone (Cutler 2003). Quetiapine has been associated with low rates of reproductive or hormonal side effects, and its effects on prolactinaemia are comparable to those observed with placebo across its full dose range (Cutler 2003). Of note, aripiprazole, which is characterized by a partial agonist activity at D2 receptors in the mesocortical pathway and by an agonistic activity at the serotonin 1a receptors (Goodnick and Jerry 2002), has been found not to increase prolactin levels as compared with placebo (Kane et al. 2002; Haddad and Wieck 2004). Moreover aripiprazole displays low affinity for α 1-adrenergic H1-histaminergic and M1-muscarinic receptors (Goodnick and Jerry 2002). The specific receptor profile of aripiprazole explains the low rates of SD and endocrinologic side effects associated with this drug (Goodnick and Jerry 2002).

Importantly, the degree of prolactin elevation has been found to be related not only to the specific antipsychotic employed, but also to other factors such as dose and duration of treatment, genetic factors (particularly polymorphisms within the dopamine-2 receptor gene), age and sex of the patient and previous history of exposure to antipsychotics (Cookson et al. 2012).

However, on account of the dearth of findings dealing with this topic, further research is needed before more definitive conclusions can be drawn.

Strategies for treatment of sexual dysfunction during antipsychotic treatment

Although SD is a critical issue and one of the major factors contributing to noncompliance with antipsychotic treatments in schizophrenic patients (Kelly and Conley 2004), only a small number of open-label studies and a few small, randomized, placebo-controlled studies have been published so far that were specifically concerned with strategies aimed at managing SD during antipsychotic treatment (Nunes et al. 2012). In sum, different strategies can be employed, partially depending on the specific side effects one wishes to treat. Most commonly investigated interventions include the reduction of current antipsychotic dosage, switching to prolactin-sparing antipsychotics, such as quetiapine, or using dopamine partial agonists such as aripiprazole, that can decrease hyperprolactinaemia induced by other antipsychotics (Nunes et al. 2012). Switching to olanzapine may improve sexual functioning in men and women, but the only controlled trial available on this drug so far is limited by a small sample size (Schmidt et al. 2012). In male patients with erectile dysfunction, or in case of patients presenting with other factors associated with SD (including smokers, diabetic patients and so forth), phosphodiesterase-5 inhibitors, such as sildenafil and vardenafil, but also amantadine and cabergoline, can be employed (Nunes et al. 2012). However, findings about phosphodiesterase-5 inhibitors rely on studies with a small sample size and available findings should therefore be considered with caution (Schmidt et al. 2012). Accordingly, further well designed randomized controlled trials, that are blinded and well conducted and reported, aimed at investigating the effects of dose reduction, drug holidays, symptomatic therapy and switching antipsychotic on sexual function in people with antipsychotic-induced SD are needed before more definitive conclusions can be drawn (Schmidt et al. 2012).

Conclusion

SD related to antipsychotics is a critical issue that can reduce quality of life and undermine compliance with treatment. As a consequence, it represents an important clinical issue that should be always discussed with the patient before a specific antipsychotic is given. Reviewed data provide strong evidence that both conventional and atypical antipsychotics are often associated with a substantial impairment of sexual functioning. In addition, they suggest that different antipsychotic agents lead to different SD rates, probably by means of both direct and indirect mechanisms. In particular, whereas some antipsychotics, including aripiprazole, ziprasidone and quetiapine have been associated with relatively low SD rates, several other antipsychotics, including clozapine, risperidone and some conventional antipsychotics, have been associated with high rates of SD, suggesting that the underlying disorder is not the only determinant of SD in psychotic patients. In case of treatment emergent SD, different strategies, such as dose reduction of current antipsychotic, symptomatic adjunctive therapy, switching to prolactin-sparing antipsychotics or using dopamine agonists such as aripiprazole can be employed in order to dampen SD.

However, more research is needed in order to better distinguish between antipsychotic related SD and pre-existing SD in patients suffering from psychotic disorders and to better investigate strategies for the management of SD by means of properly powered placebo-controlled randomized controlled trials.

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