Sexual Dysfunction Related to Psychotropic Drugs: A Critical Review Part II: Antipsychotics

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Key words
- antipsychotic drugs
- sexual dysfunction
- sexual side effects
- treatment-emergent sexual dysfunction

Abstract

Sexual dysfunction is a potential side effect of antipsychotic drugs: this article presents a critical review of the current literature. Although many studies have been published on the subject, only some used a validated sexual function rating scale and most lacked either a baseline or placebo control or both. In addition, many of the studies on sexual dysfunction associated with antipsychotic medication are limited by other methodological flaws. However, there is consistent evidence to suggest that a large number of antipsychotic drugs adversely affect one or more of the 3 phases of sexual response (desire, arousal and orgasm). Among the antipsychotics, the so called "prolactin-raising" are probably most associated with sexual dysfunction, even if further studies to confirm this are needed: the reviewed literature shows no consistent evidence that any one antipsychotic drug has a significantly superior side effect profile over another and current information on this topic is often based on methodologically weak research. Clinicians must be aware of drug-induced sexual dysfunction, since its presence can have important consequences for clinical management and compliance.

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Introduction and Methods

This study was conducted using the paper and electronic resources of the library of the Azienda Provinciale per i Servizi Sanitari (APSS) in Trento, Italy (http://atoz.ebsco.com/Titles/2793). The library has access to a wide range of databases including (DYNAMED, MEDLINE Full Text, CINAHL Plus Full Text), The Cochrane Library, Micromedex healthcare series, BMJ Clinical Evidence. The full list of available journals can be viewed at http://atoz.ebsco.com/Titles/2793, or at the APSS web site (http://www.apss.tn.it).
In completing this review, a literature search was conducted using the key words "antipsychotic drugs", "psychotropic drugs", "sexual dysfunctions", "sexual side effects", "treatment-emergent sexual dysfunction". All resulting listed articles were reviewed.

Sexual Dysfunction Induced by Antipsychotics

Epidemiology

Increasing evidence indicates that sexual dysfunction is common among patients prescribed antipsychotic medication: until a few years ago, this problem was largely neglected by research teams [1–4], and sexual side effects induced by antipsychotic medication received only modest attention [5,6].
The reasons for this are several. Firstly, previous research tended to focus mainly on the effects of the underlying disease on the patient's sexuality, describing sexual disorders and behaviour associated with psychotic symptoms [7–9]. Secondly, patients, especially those suffering from schizophrenia, rarely spontaneously report sexual dysfunction [10]. In addition, similar to patients taking antidepressants, patients with psychosis are more likely to report sexual side effects if directly questioned about them. Studies that relied only on spontaneous reporting of side effects, report low rates of sexual dysfunction, while studies using structured interviews or questionnaires show higher rates of sexual dysfunction [3,11,12]. Despite this finding, in clinical practice psychiatrists often continue to underestimate the importance of formally enquiring about sexual dysfunction among their patients. It should be noted that some researchers [13–18] included iatrogenic endocrine disorders (amenorrhea, galactorrhea and gyne-

Table 1 Classification of sexual dysfunctions in DSM IV TR.

Sexual Desire Disorders	Sexual Arousal Disorders	Orgasmic Disorders	Sexual Pain Disorders	Sexual Dysfunction due to a General Medical Condition	Substance Induced Sexual Dysfunction	Sexual Dysfunction not Otherwise Specified
– hypoactive sexual desire disorder – sexual aversion disorder	– female sexual arousal disorder – male erectile disorder	– female orgasmic disorder – male orgasmic disorder – premature ejaculation	– dyspareunia – vaginismus			

comastia) in their definition of sexual dysfunction which is not in keeping with international classifications (ICD-10, DSM-IV-TR), and which may therefore have affected the data on prevalence rates.

Also, the definition of sexual dysfunction (**Table 1**) used by some investigators [13,14,16,18] included only "decreased libido" and "impotence/sexual dysfunction", without considering other areas of sexual dysfunction. Despite this, psychiatrists frequently do not address issues relating to the sexual health of their patients [9,19–23] and they are uncomfortable [24] or reluctant to discuss this subject [3,22] with the result that the prevalence of sexual dysfunction is underestimated [14,23,25–28]. Sexual side effects however, increase the risk of inadequate compliance or discontinuation of drug therapy: in fact, they are one of the most important factors associated with poor compliance with treatment [29–37].

The burden of sexual dysfunction is not only relevant to drug compliance: sexual functioning impacts significantly on quality of life. Sexual dysfunction secondary to the use of antipsychotics can adversely affect quality of life and therefore is an important outcome measure of treatment.

The data on antipsychotic-induced sexual dysfunction tend to show high and variable prevalence rates. Baggaley [30] identified that between 30% and 80% of female schizophrenic patients and between 45% and 80% of male schizophrenic patients reported impaired sexual functioning. Other studies have documented much higher rates: for example those of Macdonald et al. [38] (82% of men and 96% of women) and Fan et al. [39] (between 65% and 94% for both sexes, depending on the different scales used). Other studies have reported lower rates: approximately 58% of men and 33% of women in the study by Ghadirian et al. [40], 59.3% of men and 49.1% of women in the study by Fujii et al. [41] while only 10% (for both sexes) in the research by Knegtering et al. [42].

The variation in prevalence rates is related to several factors, but is mainly due to the different methodological approaches adopted by different studies: studies that relied only on spontaneous reporting of side effects, report low rates of sexual dysfunction, while studies using structured interviews or questionnaires show higher rates of sexual dysfunction [3,11,12].

It should be noted that some researchers [13–18] included iatrogenic endocrine disorders (amenorrhea, galactorea and gynecomastia) in their definition of sexual dysfunction which is not in keeping with international classifications (ICD-10, DSM-IV-TR), and which may therefore have affected the data on prevalence rates. Also, the definition of sexual dysfunction used by some investigators [13,14,16,18] only included "decreased libido" and "impotence/sexual dysfunction", without considering other areas of sexual dysfunction.

Table 2 Probable mechanisms of action of antipsychotic-induced sexual dysfunction (from Baggaley [30]; Compton [20]; Haddad and Wieck [44]; Knegtering et al. 2003 [3,45]).

Drug effect	Physiological effect	Sexual function effect
dopamine receptor antagonism	inhibition of motivation and reward	decreased desire
dopamine D2 receptor antagonism (tuberoinfundibular pathway)	hyperprolactinemia	decreased desire, impaired arousal, impaired orgasm
histamine receptor antagonism	sedation	impaired arousal
cholinergic receptor antagonism	reduced peripheral vasodilation	erectile dysfunction
α-adrenergic α receptor antagonism	reduced peripheral vasodilation	priapism, decreased erection/lubrification, abnormal ejaculation

Mechanism of action of antipsychotics on sexual function

Antipsychotic drugs exert numerous different actions on cell receptors in the central nervous system (CNS). They can also cause endocrine disturbances by increasing prolactin.

Different hypotheses have been suggested for the mechanism of action of antipsychotics on sexual function (**Table 2**), including [3,20,23,30,43–47]: (i) dopaminergic antagonist action, (ii) increased prolactin (secondary to dopaminergic antagonist action), (iii) blockage of alpha-adrenergic receptor (antiadrenergic action), (iv) blockage of acetylcholine receptors (anticholinergic action), (v) serotonin antagonist action, (vi) histamine antagonist action.

Binding to dopaminergic, cholinergic, histaminergic and α-adrenergic receptors may directly affect sexual function by inhibiting motivation and reward, increasing sedation and reducing peripheral vasodilation [3,25,30,44,45].

Sthal [48] suggests that the neurotransmitters involved in the 3 stages (desire, arousal and orgasm) of the human sexual response cycle have different mechanisms of action. For example, in stage 1 (desire), dopamine (DA) exerts a positive influence, while serotonin (5HT) has negative effects. In stage 2, several neurotransmitters facilitate sexual arousal, including norepinephrine (NE), acetylcholine (Ach), and dopamine (DA). As with desire, serotonin has a negative effect. Stage 3 (orgasm), is inhibited by serotonin and facilitated by norepinephrine; dopamine may have weak positive influences.

However, the exact nature of involvement of the various neurotransmitters in antipsychotic induced sexual dysfunction remains unclear.

Differences in receptor-affinity profiles of antipsychotics may help explain the differences in their sexual side-effect profiles [49]. For example, antipsychotics with α-adrenergic antagonis-

tic properties are associated with priapism [50]. Although antipsychotics can induce relatively isolated effects on the neurotransmitters involved in the response cycle, the mechanism of action leading to sexual dysfunction is more complex. Sexual side effects often occur in combination, and pharmacological effects on one component may have an indirect effect on another area of sexual functioning. Furthermore, the etiology of sexual dysfunction may in many cases be multifactorial [2].

Hyperprolactinemia is caused by blockage of dopamine D2 receptors in the hypothalamic infundibular system [51–55]. Dopamine (DA) has an antagonistic effect on the production of prolactin (one of the hormones most implicated in sexual response). Hence, the use of antipsychotics can lead to a decrease in dopamine and a consequent rise in prolactin, which can inhibit sexual function.

Sexual dysfunction is most prevalent in patients with hyperprolactinemia; a correlation between antipsychotic-induced hyperprolactinemia and sexual dysfunction rates has also been documented [2,3,5,20,26,30,44,51,56–61]. This correlation, however, is neither confirmed [15,62–67] nor clear [68,69] in other studies. There have also been reported cases of sexual dysfunction with normal prolactin levels [70,71]: in these cases, the sexual dysfunction was probably associated with other physical (e.g., diabetes) or psychological (e.g., quality of partner relationship) factors.

It is unclear whether sexual dysfunction correlates to a direct effect and/or an indirect effect of hyperprolactinemia. Increased prolactin levels, inhibit the hypothalamic release of GnRH (gonadotropin releasing hormone), a hormone that releases gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (FSH) from the anterior pituitary gland. The end result of an increase in prolactin, may therefore consist of a reduction in levels of gonadal hormones (e.g., decreased levels of estrogen in women and testosterone in men) [9,44,72]. During long-term treatment with typical antipsychotics, it is reported that women have significantly more elevated prolactin levels than men [73]. Increased prolactin levels are also more common among women [3,74]. Smith et al. [75], for example, found that after 2 years on antipsychotics medication, 75% of women and 34% of men had high levels of prolactin.

An increase in prolactin is very common among psychotic patients treated with a first generation antipsychotic, but also with risperidone and amisulpride [3,23,59,76,77].

Based on these observations, some authors make the distinction between antipsychotics that elevate prolactin levels (so-called "prolactin-raising") and those that have minimal and/or transient effects on prolactin levels ("prolactin-sparing") (**Table 3**) [59,72,78,79].

It is worth highlighting that hyperprolactinemia is not always accompanied by clinical symptoms (such as amenorrhea, or gynecomastia) [73].

In addition to direct pharmacological effects (such as, for example, the antagonistic action on dopamine receptors) and endocrine dysfunction, other pharmacological side effects including sedation (mainly related to antihistaminergic action), extrapyramidal effects and weight gain, can indirectly reduce sexual desire [85].

It is difficult to evaluate the effects of antipsychotic drugs on sexual function in patients with schizophrenia because they are often superimposed on sexual impairment caused by the disease itself [25]. In a comparison group study comparing schizophrenic patients on antipsychotic medication with schizophrenic patients taking no medication and healthy individuals with no schizophrenia, there was a high rate of sexual dysfunction in both patient groups [86].

Table 3 Prolactin and antipsychotics (from Baggaley [30], Maguire [54]; Montejo [59]; Montgomery et al. [84]).

	Prolactin-raising	prolactin-sparing
amisulpride	☻	
aripiprazole		☺
asenapine	?	?
clozapine		☺
haloperidol	☻	
iloperidone	?	?
lurasidone	?	?
olanzapine		☺
paliperidone	☻	
quetiapine		☺
risperidone	☻	
ziprasidone		☺
other typical antipsychotics	☻	

? = limited data available, although some evidence to indicate minimal effect on prolactin levels for asenapine [80,81], iloperidone [82], and lurasidone [83]

Antipsychotics and sexual dysfunction

Antipsychotic-induced side effects on sexual function are usually inhibitory in nature and may affect all phases of the sexual response cycle.

These effects include decreased sexual desire ("libido"), difficulties with erection, achieving orgasm and sexual satisfaction, as well as ejaculation disorders (delayed or inhibited ejaculation, retrograde ejaculation, spontaneous ejaculation in the absence of sexual stimulation, decreased ejaculatory volume) [20,72,85,87,88].

Data from the early literature generally showed that (i) all antipsychotics are associated with decreased sexual desire [89]. (ii) Most antipsychotics are associated with erectile dysfunction. Those most frequently cited in the literature include: chlorpromazine, pimozide, thioridazine, thiotixene and sulpiride [90]. (iii) Thioridazine was probably one of the first antipsychotic drugs identified as having the ability to cause delayed ejaculation [90]. (iv) There are many case reports on antipsychotic-induced anorgasmia: among these, the most frequently cited antipsychotic is thioridazine [89], followed by trifluoperazine [91]. (v) Priapism is a possible side effect of all antipsychotic drugs [92], particularly for phenothiazines (chlorpromazine, fluphenazine and thioridazine), although more recently isolated cases have been reported with aripiprazole [93], clozapine, flupenthixol [89], olanzapine, quetiapine [94,95], risperidone [25] and ziprasidone [95–97].

To date, most of the studies conducted have been observational comparison studies of various typical and atypical antipsychotic drugs. The number of randomized controlled trials that specifically focus on antipsychotic induced sexual dysfunction is small [4].

The interpretation of data relating to the assessment of sexual functioning is complex because of the different assessment tools and study methods adopted in the various studies, making it difficult to compare findings. The conclusions reached by the various researchers as summarized below, are not definitive and they are difficult to interpret and need to be confirmed by further studies [98–100].

In this review we have provided a summary of the main conclusions reached by studies in the current literature, as well as summarizing the most salient information on individual drugs.

Serretti et al. [11], in a recent meta-analysis (which included data on studies investigating sexual dysfunction related to treatment with antipsychotics) showed that quetiapine, ziprasidone, perphenazine and aripiprazole were associated with relatively low rates of sexual dysfunction (16–27%), whereas olanzapine, risperidone, haloperidol, clozapine and thioridazine were associated with higher rates of sexual dysfunction (40–60%).

In the randomized double-blind study by Kelly et al. [101] (with a sample size of only 27 patients) the side effects of fluphenazine, quetiapine and risperidone were compared. Patients experienced high rates of sexual dysfunction with each of these drugs (78% with fluphenazine, 50% with quetiapine, and 42% with risperidone). Symptom improvement, mainly with regards to arousal/erection, was observed during the trial only in those patients treated with quetiapine. The authors concluded that quetiapine has a better side effect profile than the other two drugs.

In a randomized open label comparison study by Knegtering et al. [102] (comparing the atypical antipsychotics, risperidone and olanzapine), 46 patients initially taking a typical antipsychotic, were switched to risperidone or olanzapine. Olanzepine was found to cause less sexual dysfunction.

In a study on 199 patients using combined data from an open and combined study, Knegtering et al. [3] concluded that typical antipsychotics and risperidone (considered to be prolactin-raising) are associated with higher rates of sexual dysfunction (decreased libido, problems with orgasm) compared to prolactin-sparing antipsychotics (clozapine, olanzapine, quetiapine and sertindole).

In an observational study by Bobes et al. [103] conducted in Spain on 636 patients, lower rates of sexual dysfunction were found with quetiapine (18%) compared to olanzapine (35%), haloperidol (38%) and risperidone (43%).

In another observational study by Uçok et al. [104] conducted on 827 stable patients, it was reported that over 50% of patients experienced sexual dysfunction. Patients receiving poly-pharmacy experienced more severe side effects than those taking a single second-generation antipsychotic.

In the study by Nakonezny et al. [105] (conducted on a sample of 22 men) a switch from risperidone to quetiapine was not associated with any improvement in sexual function, assessed using a 5 item questionnaire.

Byerly et al. [106] using adjusted average ASEX (Arizona Sexual Experience Scale) rating scale scores, reported less severe sexual dysfunction with quetiapine compared to olanzapine and risperidone: however, these differences, were not clinically significant. Nagaraj et al. [107] also found no statistically significant differences in sexual dysfunction induced by risperidone, olanzapine and quetiapine: in this study, sexual function was measured using the SFQ (Sexual Functioning Questionnaire), which revealed a reduction in overall sexual functioning in 96% of cases for risperidone, 90% for olanzapine and 88% for quetiapine.

Another study by Byerly et al. [108] did not show any statistically significant difference in sexual functioning (as assessed by ASEX) after switching from risperidone to quetiapine.

Dossenbach et al. [31] conducted an observational study on 3838 patients. Sexual problems were common among all patients taking antipsychotic drugs, although there were no statistically significant differences in prevalence: haloperidol (71%), risperidone (68%), quetiapine (60%), olanzapine (56%).

In an observational study by Strouse et al. [109], conducted over only 12 weeks, comparing risperidone, olanzapine and clozapine, a worsening of sexual performance was reported in men only for each of these 3 drugs.

A study by Bitter et al. [110] showed a mild improvement in sexual function with olanzapine (compared to risperidone), which however was limited to libido.

In a study by Mahmoud et al. [111], it was reported that sexual functioning (as measured by the SR-DISF: Derogatis Interview for Sexual Function) of 42 schizophrenics improved after a switch from typical to atypical antipsychotics (amisulpride, olanzapine, quetiapine and risperidone) in spite of the fact that two of the atypical antipsychotic drugs prescribed (amisulpride and risperidone) are noted for their capacity to induce sexual dysfunction.

Montejo et al. [112] conducted an observational cross-sectional study on a sample of 243 patients with a diagnosis of psychotic disorder and found (using the PRSexDQ-SalSex) that 46% of patients experienced sexual dysfunction, among whom those treated with risperidone and typical antipsychotics had a significantly increased risk of sexual dysfunction. In the **Table 4** we have summarized the effect of individual antipsychotic drugs on sexual dysfunction (SD).

Treatment of sexual dysfunction induced by antipsychotics

Some recommended treatment approaches for the management of sexual dysfunction induced by antipsychotic drugs include the following: (i) A thorough clinical evaluation, to exclude comorbid conditions (physical and psychiatric) or sexual dysfunction secondary to alcohol or illicit drug use or other prescribed medication. The assessment should include measurement of serum prolactin in patients presenting with side effects suggestive of hyperprolactinemia [2, 74]. (ii) Modification of risk factors (where possible, avoid use of other drugs associated with sexual dysfunction, smoking cessation, abstinence from alcohol and illicit drugs, maintaining normal blood sugar levels in diabetic patients, treatment of hypertension and hypercholesterolemia). (iii) In the early phase of treatment, if possible, consider waiting for a spontaneous improvement in side effects [63]. (iv) Reduction in dose of antipsychotic drug responsible for side effects. (v) Switch to another antipsychotic drug with a more tolerable side effect profile (ideally to a "prolactin-sparing" antipsychotic) [59]. (vi) Addition of symptom targeted therapy – using dopaminergic drugs (amantadine, bromocriptine, cabergoline) or drugs with specific effects on sexual functioning (such as phosphodiesterase inhibitors or yohimbine) [1, 2, 5, 23, 72, 140, 141]. In a study by Inder et al., selegiline was not found to alleviate symptoms of antipsychotic-induced sexual dysfunction [142]. Sildenafil may be a useful option in the treatment of antipsychotic-induced sexual dysfunction in men [141]. In general, the evidence supporting the addition of symptomatic therapies is weak [1, 2, 143].

Conclusions

All antipsychotics drugs can cause sexual dysfunction, although it is extremely difficult to accurately determine the true prevalence. This review confirms that antipsychotic-induced sexual

Table 4 Sexual dysfunction (SD) and antipsychotics.

amisulpride	High rates of SD similar to paliperidone, risperidone, quetiapine, clozapine and typical antipsychotics. Amisulpride tends to elevate prolactin levels [113–115].
aripiprazole	Lower SD for aripiprazole as compared with other antipsychotics. Aripiprazole seems to reduce rates of SD in patients previously treated with other antipsychotics [116–118]. Switch from other antipsychotics or add aripiprazole seems to normalize prolactin levels [55, 78, 119–121].
clozapine	High rates of SD but significantly lower as compared with olanzapine, risperidone, and typical antipsychotics [12, 23, 25, 63, 122–125].
haloperidol	High rates of SD, more than 70%. No significant difference in SD compared to risperidone. Haloperidol tends to elevate prolactin levels [14, 31, 63, 103].
olanzapine	Contrasting evidence exists. High SD rates (>50%) similar to haloperidol or other typical antipsychotics reported in some studies [126], but other studies report significantly lower rates [102]. Some studies suggest that olanzapine may be associated with a lower incidence of SD than risperidone, amisulpride, clozapine and quetiapine. [3, 13, 16, 106, 110, 127]. Switching from typical antipsychotics or risperidone to olanzapine may improve sexual functioning in men and women [128]. Olanzapine causes a transient increase in prolactin, which returns to normal after a few weeks in most but not all patients [22, 25].
quetiapine	Prevalence of sexual dysfunction induced by quetiapine varies between 50% and 60%, and is therefore similar or lower to that of risperidone [101, 129] and similar to that of olanzapine [31]. Severity of sexual dysfunction seems to be lower compared to patients taking risperidone, haloperidol or olanzapine [101, 106, 108, 130, 131, 133]. A case of increased libido is reported [132]. Quetiapine is not associated with increased prolactin [25].
risperidone and paliperidone.	Risperidone: high rates (60–70%) of SD similar to those for haloperidol, other typical antipsychotics and clozapine [14, 58, 64, 134]. Significantly higher levels of SD compared to quetiapine and olanzapine [14]. Commonly reported SD included decreased libido, erectile dysfunction, ejaculatory problems, impaired orgasm, menstrual irregularities and decreased vaginal lubrication [3, 14, 22, 101, 103, 135]. Risperidone tends to elevate prolactin levels: some authors have proposed that it is a dose-dependent effect [3, 64, 79, 136], although this is disputed by Konarzewska et al. [65]. These authors also reported markedly higher prolactin levels in patients treated with risperidone compared to those treated with olanzapine. In contrast, in the study by Eberhard et al. [15], the authors argue that high levels of prolactin induced by risperidone, tend to decline over a period of years and that prolactin levels did not correlate significantly with sexual dysfunction. Paliperidone: causes elevated prolactin levels similar to risperidone [137].
ziprasidone	No significant differences in rates of sexual side effects between ziprasidone and olanzapine [126]. Switching from typical and atypical antipsychotics to ziprasidone was related to a significant reduction of SD [138, 139].

dysfunction is common among patients taking antipsychotic medication.

The conclusions reached by the different researchers are not definitive and are difficult to interpret mainly because of the significant differences in methods used for assessing sexual function: further studies are needed on the underlying causes and types of sexual dysfunction, and on the factors linking antipsychotic use and sexual dysfunction, in particular with regard to the specific mechanisms of action including alterations in prolactin levels and binding to dopaminergic, histaminergic, cholinergic, serotoninergic and α-adrenergic receptors.

Some evidence suggests that second-generation antipsychotics (with some exceptions, for example, risperidone) seem to have a better sexual side effect profile compared to traditional first generation antipsychotics.

The impact of antipsychotic-induced sexual dysfunction negatively affects quality of life; it has potential implications for patient adherence to medication and the success of antipsychotic treatment. Antipsychotic-induced sexual dysfunction adversely affects compliance, and is one of the factors that must be taken into account when selecting treatment. Further well designed randomized control trials, investigating the effectiveness of different strategies of managing antipsychotic-induced sexual dysfunction are needed [144–146].

Conflict of Interest

The authors declare no conflicts of interest.

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