

Sexual Side Effects of Antipsychotic Drugs

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The use of antipsychotic drugs carries a difficult balance between the benefit of relieving psychotic symptoms and the risk of suffering from some of troubling adverse effect. Sexual dysfunction is very common among the patients taking antipsychotic drugs, but this area has been relatively neglected to date. This review article will summarize our current understanding of sexual dysfunction caused by the use of antipsychotic drugs. Sexual dysfunction is considered by many schizophrenia patients to be more troublesome than most other symptoms and adverse drug effects [1,2] and is a major cause of poor quality of life [3], negative attitude to therapy and treatment non-compliance [2].

The First Generation Antipsychotics (FGAs) or typical ones are thought to act through dopaminergic D2 neuroreceptor blockade and are further divided into “low potency” and “high potency”, not to indicate their clinical effectiveness but rather to indicate their potency in binding to this dopamine D2 neuroreceptor. There is more variability among specific antipsychotic medications than there is between first and second generation antipsychotic classes [4]. High potency older first generation antipsychotics are more likely to be associated with extra pyramidal side effects, but this is basically true of medications that bind tightly to dopaminergic receptors and less for those that bind lightly with dopaminergic receptors such as chlorpromazine or thioridazine. All types of antipsychotic medications are associated with few common adverse effects like sedation, weight gain, postural hypotension, cardiac arrhythmias and sexual dysfunction. Human sexual function is complex and is affected in many ways by schizophrenia, comorbid mental disorders such as depression, DM, substance use, smoking as well as by drugs like antipsychotics, beta blockers and anti depressants. It has been reported that patients with schizophrenia are more commonly affected by sexual dysfunction than those with affective disorders, and that untreated schizophrenia patients have fewer dysfunctions compared to those on antipsychotic medications [5]. In addition, despite its influence on treatment outcomes, few studies have evaluated the relationship between antipsychotic induced sexual dysfunction and treatment adherence [6], these studies suggest that sexual dysfunction may have a negative impact on treatment adherence.

Mechanisms Underlying Sexual Dysfunction in Patients Taking Antipsychotic Drugs

A recent study evaluated that for men, increasing age, higher levels of depression, higher doses of medication or worse anticholinergic or antiadrenergic side-effects were all associated with higher levels of reported sexual dysfunction. These relationships ceased to exist when men were hyperprolactinaemic [7]. This indicates that treatment emergent sexual dysfunction is most commonly associated with the autonomic side-effects of antipsychotic drugs, but, if a man becomes hyperprolactinaemic following antipsychotic treatment, this raised prolactin is likely to be the main cause of any sexual dysfunction seen. But for females when depression and dose of medication were controlled, the relationship between prolactin and sexual dysfunction strengthened implying that hyperprolactinaemia is the main cause of sexual dysfunction in females taking antipsychotic treatment [7].

All antipsychotic medications have the potential to cause hyperprolactinaemia, as the inhibition of dopamine release effectively removes the negative feedback loop for prolactin secretion from the anterior pituitary gland [8]. Elevated serum prolactin levels have been shown to have profound effects on reproductive health and sexual function, including hypogonadism, decreased libido in sexes, amenorrhea and infertility in women and low sperm count and reduced muscle mass in men [9]. In patients with schizophrenia taking antipsychotics reduced sexual activity may also be related to the underlying multiple pathological processes of schizophrenia itself, including disturbed psychomotor performance, as well as to social consequences of the condition like reduced sexual desire or inability to perform sexual activity and it has been suggested that there are some gender-specific differences in the mechanisms which underlie sexual dysfunction [7]. The implications of sexual dysfunction for treatment compliance and the prevention of relapse, together with the potential link between primary and secondary prolactinaemia and breast cancer and/or decreased bone mineral density [9] makes serum prolactin an important endpoint in the assessment of antipsychotic therapy [10].

Action on different receptors as well as binding to dopaminergic, cholinergic, histaminergic and the adrenergic receptors may affect sexual function directly by inhibiting motivation and reward, increasing sedation and reducing peripheral vasodilation [11,12]. Sexual dysfunction being a very common problem in general population has provoked many researchers to work on it and iatrogenic sexual dysfunction by antipsychotic treatment is one of the most frequent iatrogenic cause of sexual dysfunction. In fact, previous clinical studies, which involved males with schizophrenia, have found a relationship between higher prolactin levels and greater impairment in sexual functioning [13-17]. One of the pilot studies showed that, among male outpatients with schizophrenia or schizoaffective disorder who had sexual dysfunction associated with a prolactin elevating antipsychotic (e.g. risperidone), a prolactin threshold may exist that is sensitive and specific in identifying male patients who are likely to experience improvement in sexual functioning when switched to a prolactin neutral antipsychotic (e.g. quetiapine) [18] (Table 1).

Conventional antipsychotic medications cause significant levels of sexual dysfunction at different phases of sexual cycle. Table 2 depicts the sexual side effects of both typical and atypical antipsychotic drugs. Risperidone seems to be the antipsychotic associated with a greater risk of sexual dysfunction; the increased risk of sexual dysfunction with conventional depots (and also with the second-generation depot antipsychotics) and their impact on sexual functioning should be

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Drug Effect	Physiological effect	Sexual function effect
Histamine receptor antagonism	Sedation	Impaired arousal
Dopamine receptor antagonism	Inhibition of motivation and reward	Decreased libido
Dopamine D2 receptor antagonism (tuberoinfundibular pathway)	Hyperprolactinaemia	Decreased libido, impaired arousal, impaired orgasm
Cholinergic receptor antagonism	Reduced peripheral vasodilation	Erectile dysfunction
α-Adrenergic α receptor antagonism	Reduced peripheral vasodilation	Decreased erection/lubrication, abnormal ejaculation

Table 1: Mechanisms by which antipsychotics may cause sexual dysfunction (Haddad and Wieck. [12], Knegtering et al. [15]).

Antipsychotics	Sexual Disturbances in men	Sexual Disturbances in women
Aripiprazole	The available naturalistic data consistently show that this drug reduces sexual dysfunction in patients previously treated with other antipsychotics like risperidone, olanzapine and quetiapine [20].	
Risperidone: Atypical antipsychotic whose prolactin elevating effect is dose dependent.	Reduced libido, erectile dysfunction, ejaculatory difficulty, impaired orgasm [21].	Amenorrhea, reduced libido, impaired orgasm, decreased vaginal lubrication [21].
Haloperidol: Highly potent typical neuroleptic.	Erectile dysfunction [22].	Reduced libido [22].
Olanzapine		Olanzapine reversed hyperprolactinemia in risperidone-treated female schizophrenic patients. This was associated with a decrease in amenorrhea, improved cycle regularity, and a decrease in sexual side effects that the women attributed to antipsychotic medication [23].
Quetiapine	Severity of sexual dysfunction seems to be lower among the patients receiving quetiapine than among patients receiving risperidone, haloperidol or olanzapine [24, 25].	

Table 2: Sexual side effects of both typical and atypical Antipsychotic drugs.

further investigated because this impact might limit its usefulness in improving treatment adherence [19].

Antipsychotics and Associated Sexual Dysfunction Symptoms

In symptomatic cases of schizophrenia with prominent negative symptoms, the frequency of sexual activity is reduced to masturbation [26]. Loss of libido was the most frequently reported sexual dysfunction with both haloperidol (58%) and clozapine (50%) in one of the studies [27]. Another study also reported that impaired desire was the most common sexual dysfunction due to risperidone [28]. Talking about erectile dysfunction, one of the studies reported that Olanzapine was most commonly associated with erectile dysfunction as compared to risperidone and Quetiapine [29]. In a study conducted by Wirshing et al. orgasmic and ejaculatory difficulties were found in 86% of patients on risperidone as compared to 20% on clozapine. Nevertheless, the sample size was too small (n=14 for risperidone and n=5 for clozapine) and a type 2 error was clearly evident [30]. However, in another study the orgasmic capacity was equally impaired both with risperidone and quetiapine groups [29]. In former study, the patients received drugs only for 12 weeks, whereas in a later one, duration of treatment was beyond 6 months. This could explain the difference in impairment of orgasm between 2 studies [29].

Possible Ways to Manage Sexual Dysfunction in Patients with Schizophrenia Taking Antipsychotics

It is very important to maintain compliance on patients taking antipsychotics as they may stop taking a prescribed medication if they find that they are unable to have a natural sex life because of it. So proper follow up regarding sexual dysfunction should be done for these patients, if any kind of sexual dysfunction is identified, proper management strategies should be planned like decreasing the dose of antipsychotic, switching to other antipsychotic with prolactin sparing effect or prescribing other drugs like phosphodiesterase type 5 inhibitors [31, 32] or appropriate hormone replacement therapy like estrogen/progesterone in women and testosterone in men [12]. Sexual dysfunction is usually

considered an under reported side effect. Results show that only 37% of patients spontaneously reported their impairment of sexual functioning [19]. Therefore, there is a need for a greater awareness among psychiatrists about sexual dysfunction, including the need for a systematic assessment of this side effect as well as prolactin levels in patients receiving antipsychotic therapy [33]. Pharmacological interventions that may reduce antipsychotic-induced sexual dysfunction include gradually reducing the dose or changing the type of medication and administering other medications such as bethanechol, neostigmine, cyproheptadine, and bromocriptine that are known to improve sexual dysfunction [9]. Also, short-term clinical studies with aripiprazole have shown comparable serum prolactin levels to placebo [34], the effects of aripiprazole on serum prolactin and sexual function over a longer period of time have yet to be investigated. But the results of one study showed that treatment with aripiprazole has the potential to improve not only the clinical effectiveness, but also to reduce the potential for sexual dysfunction, which is increasingly held to be one of the most distressing side effects associated with antipsychotic treatment, as well as the risk of severe side effects associated with hyperprolactinaemia such as loss of bone mineral density and osteoporosis [35].

Conclusion

It is very important to maintain compliance on patients taking antipsychotics as they may stop taking a prescribed medication if they find that they are unable to have a natural sex life because of it. So proper follow up regarding sexual dysfunction should be done for these patients, if any kind of sexual dysfunction is identified, proper management strategies should be planned like decreasing the dose of antipsychotic, switching to other antipsychotic with prolactin sparing effect or prescribing other drugs like phosphodiesterase type 5 inhibitors [31, 32] or appropriate hormone replacement therapy like estrogen/progesterone in women and testosterone in men [12]. Sexual dysfunction is usually considered an under reported side effect. Results show that only 37% of patients spontaneously reported their impairment of sexual functioning [19]. Therefore, there is a need for a greater awareness among

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