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Review Article

Antipsychotic-Induced Sexual Dysfunction and Its Management

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Sexual dysfunction is a common condition in patients taking antipsychotics, and is the most bothersome symptom and adverse drug effect, resulting in a negative effect on treatment compliance. It is known that hyperprolactinemia is a major cause of sexual dysfunction. Based on the blockade of dopamine D2 receptors, haloperidol, risperidone, and amisulpride are classed as prolactin-elevating antipsychotics, while olanzapine, clozapine, quetiapine, ziprasidone, and aripiprazole are classed as prolactin-sparing drugs. Risperidone and the other typical antipsychotics are associated with a high rate of sexual dysfunction as compared to olanzapine, clozapine, quetiapine, and aripiprazole. With regard to treatment in patients suffering from sexual dysfunction, sildenafil was associated with significantly more erections sufficient for penetration as compared to a placebo. Subsequent studies are needed in order to provide physicians with a better understanding of this problem, thereby leading toward efficacious and safe solutions.

Key Words: Sexual dysfunction, Antipsychotic agents, Management

INTRODUCTION

Sexual dysfunction is a common condition in patients taking antipsychotic medication, with a reported prevalence of 45～80% in males and 30～80% in females. It is the most bothersome symptom and adverse drug effect in men and women with schizophrenia, resulting in a negative effect on treatment compliance.[1-3]

This report will review the current understanding of antipsychotic-induced sexual dysfunction and its management.

PATHOPHYSIOLOGY OF ANTIPSYCHOTIC-INDUCED SEXUAL DYSFUNCTION

The mechanisms by which antipsychotic drugs may cause sexual dysfunction are as follows: histamine receptor antagonism, dopamine receptor antagonism, dopamine D2 receptor antagonism, cholinergic receptor antagonism, and alpha-adrenergic alpha receptor antagonism.[4,5]

Concretely, being bound to histaminergic receptors may impair arousal by directly increasing sedation. Dopaminergic receptor antagonism may decrease the libido by inhibiting motivation and reward. Blockade of dopamine D2 receptors in the tuberoinfundibular pathway by antipsychotics may decrease the libido, impair arousal, and impair orgasm indirectly, by leading to elevated prolactin levels. Cholinergic receptor antagonism may induce erectile dysfunction by reducing peripheral vasodilation. Alpha-adrenergic alpha receptor antagonism can reduce peripheral vasodilation, resulting in erec-

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tile dysfunction in men and decreased lubrication in women. Additionally, abnormal ejaculation is correlated with the anti-adrenergic effects of treatment.

It is well known that hyperprolactinemia is a major cause of sexual dysfunction in men and women taking antipsychotics by the aforementioned mechanisms.[6,7] Depending on the blockade of dopamine D2 receptors, haloperidol, risperidone, and amisulpride are classed as prolactin-elevating antipsychotics, while olanzapine, clozapine, quetiapine, ziprasidone, and aripiprazole are classed as prolactin-sparing drugs.[4]

SEXUAL DYSFUNCTION DEPENDING ON THE TYPE OF ANTIPSYCHOTICS

The large majority of studies concerning antipsychotic-induced sexual dysfunction are small cross sectional studies or small scale observational studies.[8] According to a recent review article, four randomized clinical trials and four large-scale long-term observational studies from three cohorts have reported primary outcomes concerning antipsychotic-induced sexual dysfunction.[9-13] Foremost, we will review these reports as well as other related cross-sectional case control studies and small-scale short-term observational studies (Table 1).

1. Haloperidol

It is known that haloperidol, which is a typical antipsychotic, raises serum prolactin levels to 20～40 ng/ml in therapeutic doses.[5]

From evidence of a large prospective cohort study, 71.1% of men and women taking haloperidol over 12 months complained of sexual dysfunction depending on the modified version of the Udvalg for Kliniske Undersøgelser (Danish for rysfunction Clinical Examinations'; UKU Side Effect Rating Scale) which is composed of 5 items: libido, amenorrhea, gynecomastia, erectile dysfunction/sexual dysfunction, and galactorrhea (Table 1).[14] The prevalence rate of decreased libido is 60.0%, erectile dysfunction/sexual dysfunction is 52.3%, and amenorrhea is 53.8%. The odds ratio, compared to patients treated with olanzapine, for decreased libido, erectile dysfunction/sexual dysfunction, and amenorrhea are 3.25 (2.14～4.92), 3.04 (1.94～4.74), and 4.06 (2.20～7.51), respectively.

In a cross sectional study (n=131), 30.8% of male patients complained of decreased libido, 30.8% complained of erectile dysfunction, and 27.7% complained of ejaculatory disorder. In female patients, 23.8% complained of decreased libido, 9.4% complained of arousal disorder, and 8.1% complained of vaginal dryness.[15]

2. Risperidone

Risperidone is a representative atypical antipsychotic drug with a high probability of prolactin elevation. According to clinical trials and cross sectional studies, risperidone elevates the serum prolactin in a dose dependent manner and up to a level of 30～60 ng/ml when used at therapeutic doses.[9,16] A prospective 5 year observational study evaluating 128 men and 90 women reported that risperidone induces a higher prolactin elevation than other atypical antipsychotics (Table 1).[17]

Evidence from a large prospective observational study showed that 67.8% of men and women receiving risperidone for over 1 year experienced sexual dysfunction.[14] Reduced libido is the most commonly reported disturbance (described by 60.0% of patients), while 46.0% of patients report erectile dysfunction/sexual dysfunction and 42.1% of patients report amenorrhea. The rate of sexual dysfunction is significantly high as compared with patients receiving olanzapine (odds ratio: 2.02; 95% confidence interval: 1.63～2.49).

According to a cross-sectional study studying males and females separately (n=131), 37.8% of males reported decreased libido, 32.1% reported erectile dysfunction, and 32.6% reported ejaculatory disorder. In female patients, 40.5% reported decreased libido, 19.0% reported arousal disorder, and 15% reported vaginal dryness.[15]

A small scale study reported gynecomastia, galactorrhea, and priapism in male patients. Further, female patients were reported to experience amenorrhea and galactorrhea.[6]

3. Clozapine

A cross-sectional study including 60 schizophrenic male patients who showed atypical neuroleptic clozapine was associated with low prolactin serum level as compared to classical antipsychotics (mean=12.6 ng/ml, standard deviation [SD]=11.2 vs. mean 18.2 ng/ml,

Table 1. Randomized clinical trials and large-scale long-term observational studies concerning antipsychotic-induced sexual dysfunction

Author (date)	Sample size	Drug	Mean dosage (SD)*	Method of inquiry	Diagnosis	Study design	Duration of the study
Knegtering et al (2004)[10]	25 24	Quetiapine Risperidone	580 (224) 3.2 (1.3)	Sexual questionnaire based on UKU	Schizophrenia and other psychotic disorders	Open-label RCT	6 weeks
Knegtering et al (2006)[9]	25 21	Olanzapine Risperidone	9.4 (not given) 3.4 (not given)	Sexual questionnaire based on UKU	Schizophrenia and other psychotic disorders	Open-label RCT	6 weeks
Kinon et al (2006)[12]	27 27	Olanzapine Risperidone	12.8 (4.8) 4.8 (2.1)	Global impressions of sexual function	Schizophrenia and other psychotic disorders	Open-label RCT	16 weeks
Kelly and Conley (2006)[13]	12 6 9	Risperidone Quetiapine Fluphenazine	4 (0) 400 (0) 12.5 (0)	Changes in Sexual Functioning Scale	Schizophrenia	Double-blinded RCT	12 weeks
Dossenbach et al (2004)[44]	3222 1116 189 256	Olanzapine Risperidone Quetiapine Haloperidol	9.7 (4.0) 3.4 (1.7) 241 (165) 12.0 (9.3)	Modified UKU (sexual side effects)	Schizophrenia	Observational study	6 months
Dossenbach et al (2006)[14]	2638 860 142 188	Olanzapine Risperidone Quetiapine Haloperidol	10.8 (4.8) 4.0 (2.2) 334.1 (199) 11.8 (8.8)	Modified UKU (sexual side effects)	Schizophrenia	Observational study	12 months
Eberhard et al (2007)[17]	218	Risperidone	Physician's discretion	Sexual questionnaire based on UKU	Schizophrenia and other psychotic disorders	Observational study	5 years
Bitter et al (2005)[24]	362 140 68	Olanzapine Risperidone Typical	Physician's discretion Physician's discretion Physician's discretion	Structured interview	Schizophrenia	Observational study	6 months

SD: standard deviation, UKU: the 'Udvalg for Kliniske Undersøgelser' (Danish for 'Choice of Clinical Examinations') – UKU side effect scale, RCT: randomized controlled study.
*Values are expressed in mg/day.

SD=16.2).[18] Also, another cross sectional study (n=18 schizophrenic male patients) showed clozapine was associated with a low prolactin serum level as compared to risperidone (mean=27 ng/ml, SD=14 vs. mean=27 ng/ml, SD=14).[19] It is generally believed that clozapine produces a low incidence of hyperprolactinemia-related adverse sexual events including decreased libido and impaired arousal relative to classical antipsychotics.[18]

A retrospective study investigated by review of medical records reported a significantly lower proportion of patients with sexual dysfunctions in the clozapine group as compared to the haloperidol and risperidone groups.[20] However, sexual dysfunction related to anti-adrenergic and anticholinergic effects (erectile and ejaculatory problems as well as priapism) does occur with clozapine.[6,21]

4. Olanzapine

Olanzapine temporarily increases the prolactin level. Moreover, in most cases, the elevated prolactin level returns to a normal level. In a double blind clinical trial, prolactin elevation caused by olanzapine normalized after six weeks as compared to the control group in both male and female patients.[22]

According to a 28-week double-blind clinical trial conducted with 339 patients and aimed at the efficacy of olanzapine, olanzapine produces a low incidence of adverse sexual events in men as compared to risperidone-treated men. Further, delayed ejaculation was significantly lower (2.8% vs. 11.5% of male patients, respectively; $p<0.05$).[23]

An open-label, prospective 4-month study in hyper-

prolactinemic patients with schizophrenia explored whether prolactin levels decrease after switching from antipsychotic therapy to olanzapine therapy. This study reported that patients who switched to olanzapine experienced significant reductions in mean serum prolactin levels in both males and females; furthermore, galactorrhea, gynecomastia, and sexual functioning were significantly improved in both genders (Table 1).[12]

A 6-month observational study examining sexual functioning among first-time treated schizophrenia patients showed that the loss of libido was significantly less common in the olanzapine group (17.8% at 6 months) as compared to the risperidone (35.5% at 6 months) and haloperidole groups (38.7% at 6 months).[24]

In a randomized open-label comparison of the impact of olanzapine versus risperidone on sexual functioning, less sexual dysfunction occurred in the group treated with olanzapine (n=20) than the risperidone group (n=19), with a major significant difference in erectile dysfunction (erectile dysfunction: 0% in the olanzapine group vs. 31.6% in the risperidone group).[9]

5. Quetiapine

In a large population study, quetiapine was not associated with the increase in prolactin levels when a therapeutic dose was used.[6,25-28]

In an open-label study, including patients with schizophrenia or a related psychotic illness who were randomized to quetiapine (200~1200 mg/day) or risperidone (1~6 mg/day) for 6 weeks, sexual dysfunction was lower in patients treated with quetiapine (n=25) compared to those treated with risperidone (n=26). Specifically, there was a significant difference in decreased libido and impaired arousal.[10]

There has been just one double-blind clinical trial to evaluate sexual dysfunction as a primary outcome measure.[27] People with treatment-resistant schizophrenia participated in a randomized double-blind 12-week trial of risperidone (4 mg/day), quetiapine (400 mg/day), or fluphenazine (12.5 mg/day). Overall, only quetiapine was associated with the normalization of prolactin levels and had the greatest benefits among these drugs regarding sexual functioning; in particular, there was a significant difference in orgasmic function.[13] Thus, it appears that quetiapine is associated with a lower sexual dysfunction rate than risperidone and haloperidol.

6. Aripiprazole

According to double-blind clinical trial studies, aripiprazole did not increase the prolactin level or normalize prolactin levels in patients with elevated baseline levels caused by typical antipsychotics.[29-37]

In an open-label randomized clinical trial, patients for whom a change of antipsychotic medication was indicated due to a lack of tolerability and/or symptom control, switched to aripiprazole and were treated for 26 weeks, showing a significant reduction in overall sexual dysfunction as measured on the total score of the Arizona Sexual Experience Scale (composed of following five domains: sex drive, arousal, vaginal lubrication or penile erection, and ability to reach orgasm).[38] Also, in another open label study, switching to aripiprazole was associated with a significant improvement in sexual desire, erectile dysfunction, and ejaculatory disorder.[39]

MANAGEMENT OF ANTIPSYCHOTIC-INDUCED SEXUAL DYSFUNCTION

Dopamine agonist (bromocriptine, cabergoline) and dopamine releasing agent (amantadine) were tried in a patient suffering from sexual dysfunction secondary to antipsychotics, however most of the studies are open label, uncontrolled studies, or case reports.

According to a Cochrane Database Systematic Review, only two well-designed randomized controlled trials can be relied on for determining the effects for treatment of sexual dysfunction due to antipsychotic therapy.[40]

In the first of these two studies, a randomized, double-blind, placebo controlled, flexible-dose, two-way crossover trial was carried out. Thirty-two married male outpatients with schizophrenia or delusional disorder and antipsychotic-induced erectile dysfunction were recruited for the trial. The patients reported significant improvement while taking sildenafil in the number of adequate erections (number of erections hard enough for penetration: 6.52 vs. 3.32; $p<0.001$), satisfaction with sexual intercourse, and ability to undergo erections for over 2 weeks. The odds ratios for adequate erections and for satisfactory

sexual intercourse with sildenafil were 4.07 and 3.77, respectively. There were no major side effects or adverse drug interactions, specifically nasal congestion (12.5% vs. 0%) or headaches (9.4% vs. 3.1%).[41]

Another double-blind, placebo-controlled crossover study was undertaken in 10 neuroleptic-treated male schizophrenic outpatients in order to assess the effect of co-administration of 15 mg/day of selegiline (selective monoamine oxidase inhibitor, inducing dopamine secretion) for 3 weeks on their sexual dysfunction. Selegiline was not found to be effective in improving any domain of sexual functioning despite a significant decrease in prolactin levels.[42]

On the basis of the scarce data available, Costa et al[43] attempted to design a preliminary stepwise algorithm for the clinical management of antipsychotic-induced sexual dysfunction, as follows: 1. Gradually reduce dosage of the antipsychotic 2. If there is no symptoms improvement, switch to other antipsycotics with better sexual profile; 3. If the symptoms still persist, prescribe drug association already mentioned in the article.

CONCLUSION

While the literature clarifying the influence of antipsychotic on sexual funtion is limited, these studies suggest that the relative impact of antipsychotics on sexual dysfunction can be summarized as risperidone, and typical antipsychotics are associated with a high rate of sexual dysfunction as compared to olanzapine, clozapine, quetiapine, and aripiprazole. Thus, it is possible for psychiatrists to minimize the risk of sexual dysfunction through the appropriate choice of antipsychotics.

With regard to treatment in patients suffering from sexual dysfunction, sildenafil was associated with significantly more erections sufficient for penetration as compared to a placebo. Subsequent studies are needed in order to provide physicians with a better understanding of this problem, thereby leading toward efficacious and safe solutions.

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