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# EJACULATORY DYSFUNCTION IN PATIENT WITH SCHIZOPHRENIA ON SERTINDOLE

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***SUMMARY***

*The antipsychotic drugs can be of great benefit for the wide range of psychotic disorders, but all are associated with various adverse effects. Patients with psychotic disorder consider the sexual dysfunction to be among the most important side effects. Although, it is not uncommon for the patients with schizophrenia to report the sexual dysfunction, patients with untreated schizophrenia have fewer dysfunctions compared to those on antipsychotic medication. The decision whether the current treatment with a prolactin-increasing antipsychotic or sexual dysfunction inducing drug should be continued or switched to another antipsychotic drug, has to be made on the basis of the patient's risk-benefit estimation. It has to be kept on mind that adverse effects are usually dose dependent. In this case report, sertindole treated patient with chronic schizophrenia developed sexual side effect manifested as ejaculatory dysfunction that was significantly ameliorated by drug-dose reduction.*

***Key words:*** *sexual dysfunction – schizophrenia – antipsychotics - sertindole*

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## INTRODUCTION

There is no doubt that sexual dysfunction occurs in schizophrenia. The illness itself as well as the side effects of antipsychotic medication influences seriously the sexual functioning. The investigators made different study designs to measure the rates of sexual dysfunction in people with schizophrenia - mainly lacking the control group. One study compare the prevalence of sexual dysfunction in people with schizophrenia (N=135) and general population (N=114). The sexual dysfunction was common in patients, with 82% men and 96% of women reporting at least one sexual dysfunction. Erectile dysfunction was present in the majority of male patients. However, it has to be bared on mind that few of the patients and most of the members of control group in the study had a partner (MacDonald et al. 2003). Although, it is not uncommon for the patients with schizophrenia to report the sexual dysfunction, patients with untreated schizophrenia have fewer dysfunctions compared to those on antipsychotic medication (Baldwin & Birtwistle 1997).

However, two thirds of psychiatrists do not routinely ask the patients about sexual dysfunction - in spite that 88% of them agree that good sexual functioning is important for the patients. The results of this research point out that the sexual dysfunction is under-recognized and therefore untreated (Nnaji & Friedman 2008).

## SEXUAL SIDE EFFECTS OF ANTIPSYCHOTICS

Antipsychotic therapy may be followed by wide range of serious sexual adverse effects (Folnegović-Šmalc et al. 2000, Folnegović-Šmalc et al. 2003, Uzun et al. 2005). Sexual dysfunction includes low sexual desire, difficulty maintaining an erection and difficulty in achieving orgasm. The main sexual side effects in men are decreased libido, erectile dysfunction, azoospermia, gynaecomastia, and occasionally galactorrhoea. Women mostly report galactorrhoea and the disturbances in menstrual cycle. The sexual dysfunction symptoms occur rather often and are recorded during the therapy of almost any antipsychotic agent. For example, impotence is reported during therapy by chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, thiothixene and sulpiride. The treatment with chlorpromazine, thioridazine, thiothixene, fluphenazine and molidone may be followed by pain during intercourse and priapism. Priapisam has been also recorded during therapy with clozapine (Folnegović-Šmalc et al. 2003). In patients treated with risperidone may occur priapisam, erectile or ejaculatory dysfunction and anorgasmia (Mimica & Folnegović-Šmalc 2002). Nowadays we are aware that the antipsychotic-induced sexual adverse effects are mediated by the effects of the drugs on alpha-1 and alpha-2 adrenergic, $H_1$ histamine and dopaminergic receptors. For example, the antipsychotics causing

erectile dysfunction mainly act as alpha-1 antagonists such as thioridazine, mesoridazine, chlorpromazine, chlorprothixene, and perphenazine (Mimica et al. 2005). The particularly important is blockade of $D_2$ receptors in pituitary lactotrophic cells. Dopamine itself is a powerful inhibitor of prolactine secretion and the blockade of D2 receptors by antipsychotics leads to an excess of prolactin secretion and hyperprolactinemia. Hyperprolactinemia cause galactorrhea, anemorrhoea, disturbance in menstrual cycle and anovulatory cycling in women. In men may occur impotence and azoospermia with or without gynaecomastia, and galactorrhoea. Conventional antipsychotics, with exception of risperidone and amisulpride, cause hyperprolactinemia more often then novel antipsychotics (Mimica et al. 2005). Novel antipsychotics have number advantages over the standard agents with regard to sexual functioning (Meltzer et al. 1979, Aizenberg et al. 2001, Knegtering et al. 2003). Clinical reports indicate that novel antipsychotics are associated with less sexual adverse effects with significant differences of effects on serum prolactine level (Table 1). For example, the dose related increases of prolactine may be recorded during risperidone treatment. Olanzapine is associated with mild and transient increases of prolactine during long-term treatment regiment. Treatment with clozapine is not followed by increases of prolactine level while ziprasidone therapy is followed by mild, transient increase. Quetiapine has not got any effect to level of prolactine than placebo in any compared dose (Cutler 2003). There is tendency to differ the antipsychotics as prolactine-raising and prolactine-sparing. Also, the reduction of sexual side effects may be recorded with prolactine-raising antipsychotics due to the reduction of serum prolactine (Knegtering et al. 2008).

**Table 1.** Effects of antipsychotics on the serum prolactin level

| | |
|---|---|
| amilsulpride, fluphenazine, haloperidol, chlorpromazine, risperidone, sulpiride, zuclopenthixol | +++ |
| promazine, thioridazine | ++ |
| olanzapine | + |
| ziprasidone | +/- |
| aripiprazole, clozapine, quetiapine, sertindole | - |

+++ strong; ++ moderate; + weak; +/- moderate weak; - very weak

Some investigators did not find significant difference causing sexual dysfunction between those taking conventional or novel antipsychotics (MacDonald et al. 2003, Hummer et al. 1999). It may be explained that schizophrenia itself may take a great impact in sexual functioning and the dopamine and hyperprolactinemia may be just a part of complex interactions between illness, medications and sexual functioning.

## SERTINDOLE

Sertindole is a non-sedating atypical antipsychotic agent recently reintroduced in the market with high selectivity for dopaminergic neurons in the mesolimbic system with affinity for 5-$HT_{2C}$, 5-$HT_{2A}$, $D_2$, $alpha_1$, and $alpha_2$ receptors. Sertindole is associated with a low rate of extrapyramidal side effects, lacks sedative properties, and may induce a moderate weight gain. Sertindole has beneficial effects on cognitive function (Gallhofer et al. 2007). No clinically relevant elevations in serum prolactin (Knegtering et al. 2003, Knegtering et al. 2008), glucose or lipid levels have been so far reported. The tratment with sertindole may result in a prolongation of the QTc interval but there is a controversy over that issue and some studies have recently indicated that sertindole is not associated with a higher rate of cardiovascular mortality than other antipsychotic agents (Attmaca et al. 2008). Sertindole is also associated with orthostatic hypotension, particularly during the initial titration period. It must be used with caution in patients with renal and hepatic impairments. Other common side effect of sertindole was ejaculatory dysfuntion in men. This side effect is usually not associated with erectile disturbances or decreases in libido. Nevertheless, this is very important for the patient's adherence because most of men with schizophrenia are very young and sexuall life changes could interfere with the succesfull treatment. Men should be told about tendency of sertindole to decrease ejaculatory volume and reassured that this is a manageable side effect (Uzun et al. 2005). In summary, sertindole is an effective antipsychotic that has minimal to no extrapyramidal symptoms (EPS) when prescribed in recommended doses. Optimal dosage range is between 12 and 20 mg per day administrated in single dose. Because of possible initial orthostatic hypotension, sertindole should be given during initial titration period. The most serious concern for clinicians is its tendency to prolong QT interval on ECG.

## CASE REPORT

Fifty-two years old man, single, has been in treatment since experienced the first psychotic episode of paranoid schizophrenia 1987. The first twenty years of illness he has been treated by fluphenazine without long-term period of remission. In 2007, for the first time, he has been treated with novel antipsychotics – olanzapine and afterwards risperidone but the stabile remission has not been achieved. The patient considered being resistant to antipsychotic treatment. So, the therapy with clozapine began during hospitalization from January 2008. The increase of clozapine dosage needed to control psychotic symptoms was followed by serious disturbing adverse effects (hypersalivation, sedation). So, the sertindole was introduced gradually into the treatment since July 2008 until the dosage of 16 mg was achieved. On the follow-up examination in September 2008 the increase of dosage to control psychotic symptoms was indicated. The sertindole was prescribed in dosage of 20 mg. Four month later patient reported a complete reduction of ejaculatory volume while masturbating. At that point of treatment his psychotic symptoms were well controlled. The decision whether the current treatment with sertindole should be continued or switched to another antipsychotic drug has to be made on the basis of the patient's risk-benefit estimation. After the long period of time the patient was satisfied with the course of his illness and rather stable remission without prominent psychotic symptoms. We decided to reduce the dosage of sertindole to 16 mg. During the next few weeks the patient reported that ejaculatory dysfunction subsides. In summary, the patient with chronic schizophrenia on sertindole has developed sexual side effects manifested as ejaculatory dysfunction that completely ameliorated by drug-dose reduction.

## INSTEAD OF RESUME

Non-adherence to antipsychotic medication is the most important cause of relapse in patients with psychotic disease. The side-effects of antipsychotics are mostly cited as reason for non-adherence. The rather disturbing, but neglected (even by professionals), sexual dysfunction as a side-effect of treatment seems to worry more seriously patients than EPS (Finn et al. 1990). In this paper we would like to emphasize the importance of carrying in mind that sexual dysfunction appear during the treatment with novel generation of antipsychotics as well as commonly accompanies the other psychotropic drugs (e.g. antidepressants). The professionals must be more sensitive on this issue and always need to ask about patient sexual functioning.

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