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**Add-on mirtazapine improves orgasmic functioning in patients with schizophrenia treated with first-generation antipsychotics**

The short title: **Mirtazapine and sexual functioning**

**Authors:** Viacheslav Terevnikov[a], MD, PhD, Jan-Henry Stenberg[b], PhD, Jari Tiihonen[c,d,e], MD, PhD, Mark Burkin[f], MD, PhD, Grigori Joffe[b,] MD, PhD

[a]Kellokoski Hospital, Kellokoski, Finland

[b]Helsinki University Central Hospital, Helsinki, Finland

[c]Department of Forensic Psychiatry, University of East Finland, Niuvanniemi Hospital, Finland

[d]Department of Mental Health and Alcohol Research, National Institute for Health and Welfare, Helsinki, Finland

[e]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

[f]University of Petrozavodsk, Petrozavodsk, Russia

Correspondence to: Viacheslav Terevnikov, MD, PhD, Kellokoski Hospital, 04500 Kellokoski, Finland. Tel.: +358504273539, e-mail: viacheslav.terevnikov@hus.fi

**Abstract**

**Aim.** Sexual dysfunction, common in schizophrenia, may be further exaggerated by antipsychotics, especially those of First Generation (FGAs), and antidepressants, such as Selective Serotonin Reuptake Inhibitors (SSRs). Mirtazapine, an antidepressant characterised by its different action mechanism compared with that of the majority of other antidepressants, may improve SSRI-induced sexual dysfunction in patients with depression. It is unknown, however, whether mirtazapine improves sexual functioning in schizophrenia.

**Methods.** This study randomly assigned FGA-treated patients with schizophrenia to receive either an add-on mirtazapine (n = 20) or a placebo (n = 19) for six weeks. Sexual functioning was prospectively measured using five relevant items from the UKU side-effect rating scale (UKU-SERS).

**Results.** Orgasmic function significantly improved with statistical significance in the mirtazapine group (p=0.03), with no changes in any other sexual functions in either group.

**Conclusion.** We conclude that mirtazapine does not worsen sexual functioning in FGA-treated patients with schizophrenia and may relieve orgasmic dysfunction.

**Keywords**: mirtazapine, orgasmic dysfunction, sexual dysfunction, RCT, FGA, schizophrenia

The trial was registered with www.controlled-trials.com (no. ISRCTN00721331)

**Background.**

Sexual dysfunction is a common problem in patients with schizophrenia. Estimates for the prevalence of decreased sexual desire reach as high as 54%, while difficulties with achieving orgasm reach 42% (1). Erectile and ejaculatory dysfunction, respectively, may be observed in 48.1% and 64.2% of schizophrenic men (1). Sexual dysfunction may be due to the disease itself, resulting from a number of physiological and endocrine abnormalities (2). Some researchers assume that negative symptoms, especially anhedonia and avolition, may impair an individual's ability to enjoy sexual life (3, 4).

Antipsychotics, the primary psychopharmacological treatment for schizophrenia, may also induce sexual adverse effects, mainly by increasing the plasma prolactin level (4). This is especially true for first-generation antipsychotics (FGAs), which cause sexual dysfunction more often than do second-generation antipsychotics (SGAs) (5, 6). This difference may be due to SGAs' greater affinity for serotonin 5-HT2 receptors than for D2 receptors which results in the reduced incidence of hyperprolactinemia (6).

Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) cause sexual dysfunction in approximately one-third of patients with depression (8). These drugs, especially SSRIs, are widely used to alleviate the negative or depressive symptoms of schizophrenia (9). Combined with antipsychotics, they may further worsen sexual functioning in patients with schizophrenia.

Approaches aiming to diminish sexual dysfunction in schizophrenia include, among others, antipsychotic dose reduction, switching to a prolactin sparing antipsychotic or using adjunctive medication (10). Among adjunctive medications, addition of

aripiprazole (11), or a phosphodiesterase-5 inhibitor (12) has shown positive results, but evidence is currently far from convincing.

Another possible strategy for improving sexual functioning in schizophrenia may be add-on treatment with mirtazapine, an antidepressant that carries a seemingly low risk of sexual dysfunction in patients with depression (13). Hypothetically, mirtazapine, an antidepressant with a serotonin 5HT-2a/c receptor blocking properties added to a pure D2 receptor blocker (i.e., FGA), may emulate the receptor profile of an SGA and, thus, improve sexual functioning (14).

**Aims.**

This study aimed to determine whether an add-on mirtazapine improves the FGA-associated sexual dysfunction in patients with schizophrenia or schizoaffective disorder.

## Methods

*Subjects*

The eligibility criteria for this study have been described elsewhere (11). In brief, the study population comprised patients with schizophrenia or schizoaffective disorder who remained highly symptomatic despite adequate therapy with FGAs in fixed doses for at least six weeks. Patients were recruited from the in- and outpatient psychiatric units in Petrozavodsk, Russian Federation. All patients provided written informed consent, and the study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

*Study design*

This study formed a part of a double-blind, add-on, randomised placebo-controlled trial (RCT). After a one-week placebo run-in period, patients were randomized to receive double-blind treatment with either an add-on 30-mg daily dose of mirtazapine (mirtazapine group) or an add-on placebo (placebo group) for six weeks. The doses of currently prescribed FGAs remained unchanged during the study period.

*Efficacy evaluation*

For this sexual dysfunction branch of the study, the primary measure of efficacy was the change in five items for sexual dysfunction taken from the UKU side effect rating scale (UKU-SERS), clinician rated version (12). These items included Increased Sexual Desire, Diminished Sexual Desire, Erectile Dysfunction, Ejaculatory Dysfunction and Orgasmic Dysfunction. Assessments were made at weeks zero, one, two, four and six.

*Statistical analysis*

Data were analysed using the independent sample t-test for between-group changes or the paired sample t-test for within-group changes (means and standard deviation in both cases). Pearson's correlation analysis was performed to examine correlations between changes in efficacy measures and other clinical parameters, such as the Positive and Negative Syndrome Scale (PANSS) negative, positive, general and total (sub-) scales, as well as the Calgary Depression Scale for Schizophrenia (CDSS). All tests were two-tailed, and a $p < 0.05$ was considered statistically significant. All analyses were performed using SPSS for Windows, version 19.0.

**Results**

*Study population*

A detailed description of the study population appeared elsewhere (11). Among the 41 patients randomised, 40 completed the trial and data of 39 patients were analysed. At baseline, the treatment groups did not differ in terms of demographic or clinical characteristics, with the exception of higher PANSS positive scores in the mirtazapine group (for further details, see Joffe et al. (11).

*UKU-measured sexual side effects of antipsychotics*

At baseline, the treatment groups did not differ statistically significantly on any of the UKU-measured symptoms of sexual dysfunction (Table 1).

After six weeks of double-blind treatment, the mirtazapine group showed a statistically significant improvement on the orgasmic dysfunction item of UKU-SERS ($p=0.03$). No other UKU-SERS parameters changed for either group. Between-group analysis did not reveal any differences between treatment with mirtazapine or the placebo.

*Correlation between changes in clinical parameters and symptoms of sexual dysfunction*

In the mirtazapine group, the improvement in orgasmic dysfunction tended to correlate with an improvement in depressive scores on CDSS ($r=0.48$, $p=0.05$). No other statistically significant correlations were found in either group.

**Discussion**

This trial used a randomised, double-blind, placebo-controlled design to assess the efficacy of adjunctive mirtazapine in alleviating symptoms of sexual dysfunction in a

population of FGA-treated patients with schizophrenia. Mirtazapine was well-tolerated with no drop-outs due to adverse events. The data analysis from the MITT population revealed a favourable effect from mirtazapine on orgasmic dysfunction. This effect tended to correlate with a mirtazapine-induced improvement in depressive symptoms.

To the best of our knowledge, no other published studies on the effects of mirtazapine on sexual dysfunction in schizophrenia exist. According to the findings from studies on Major Depressive Disorder, mirtazapine itself may carry some sexual side effects, although estimates of their prevalence remain lower than for the majority of other antidepressants (13). However, in some studies mirtazapine demonstrated favourable effects on sexual dysfunction in depressed patients (14). Mirtazapine has also repeatedly accompanied improvements in several symptoms of sexual dysfunction caused by SSRIs (15, 16), although these data remain equivocal (17).

Sexual dysfunction in schizophrenia appears as a phenomenon with a complex aetiology. It may result from the negative and depressive symptoms of the disease or emerge as an antipsychotic-induced adverse effect. In previous studies, mirtazapine added to FGAs (11, 18) or SGAs (19) improved the negative symptoms of schizophrenia. Mirtazapine may also carry an antidepressive effect in the treatment of schizophrenia-related depression (20). Thus, the favourable effect of mirtazapine on sexual dysfunction found in this study may be indirect, that is mediated through an improvement of negative or depressive symptoms or both.

The favourable effect of mirtazapine on orgasmic dysfunction may be explained by its receptor profile. Some evidence suggests that both the inhibition of 5-HT2 receptors and the stimulation of the 5-HT1A receptor facilitate sexual functioning (22). This evidence mainly derives from clinical trials where a 5-HT2 inhibitor cyproheptadine (23) and a

partial 5-HT1A receptor agonist buspirone (24) reduced SSRI-induced sexual dysfunction. As a 5-HT2 antagonist and 5-HT1a indirect agonist, mirtazapine may mitigate orgasmic dysfunction relying on these mechanisms. Mirtazapine can also diminish the antipsychotics-induced hyperprolactinemia *via* the increase of dopamine release resulting from the 5-HT2a/c receptor blockade. As an alpha-2 receptor antagonist, mirtazapine shares this feature with yohimbine, a drug with an established efficacy in treating erectile and orgasmic dysfunction in men (25).

The limitation of this study is that, as a secondary branch of an RCT, it was not designed specifically to investigate the effects of mirtazapine on sexual dysfunction. That is, we did not select patients for the presence of sexual dysfunction and the UKU-measured sexual dysfunction served as a secondary outcome. Furthermore, we didn't measure the development of the mirtazapine's effect on sexual dysfunction, i.e. measurements were only made on baseline and endpoint, without any measures on intermediate time-points. The authors assume that the possible beneficial effect of mirtazapine on sexual dysfunction has emerged only partially due to the short duration of the study. Presumably, long term treatment would provide better insights in the potential effects of mirtazapine on sexual dysfunction. Another limitation of this study lies in its relatively small sample size. The scale used to measure sexual dysfunction was clinician-rated, although patients' rating may differ from those of clinicians', especially for sexual dysfunction. Future studies should comprise larger populations, should be of longer duration and focus on patients with schizophrenia experiencing sexual dysfunction.

**Conclusion.**

We conclude that mirtazapine added to FGAs does not worsen sexual functioning and may serve as an alternative to SSRIs (and, possibly, to SNRIs) when a clinician considers antidepressant treatment for a patient with schizophrenia. Mirtazapine may improve orgasmic dysfunction, presumably through both direct pharmacodynamic (the noradrenergic and specific serotoninergic receptor affiliation) and indirect (those mediated by improved negative and depressive symptoms) mechanisms. Studies with a larger sample size and specifically designed to investigate the influence of adjunctive mirtazapine on sexual dysfunction in patients with schizophrenia are warranted.

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**Disclosure statement**

The authors declare no conflict of interest.

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Table 1. UKU-SERS[1]-measured sexual dysfunction in FGA[2]-treated patients with schizophrenia during a six-week double-blind treatment period with an add-on mirtazapine or placebo

| Parameter | Baseline | | | Change from week zero to week six[3] | | |
|---|---|---|---|---|---|---|
| | Mirtazapine group (n = 20) | Placebo group (n = 19) | Mirtazapine vs placebo group | Mirtazapine group | Placebo group | Mirtazapine vs placebo group |
| **Increased sexual desire** | 0.24 (0.44)[4] | 0.25 (0.58) | t = 0.38 p=0.71 | 0.19 t = 1.00 p=0.32 | 0.06 t = 0.43 p=0.67 | t = -1.09 p=0.29 |
| **Diminished sexual desire** | 2.05 (1.03) | 1.5 (0.93) | t = 1.48 p=0.15 | -0.05 t = -0.37 p=0.72 | 0.06 t = -0.56 p=0.58 | t = 1.8 p=0.08 |
| **Erectile dysfunction** | 2.29 (0.76) | 1.56 (0.73) | t = 1.01 p=0.33 | 0.14 t = 1.00 p=0.36 | -0.22 t = -1.50 p=0.17 | t=1.25 p=0.23 |
| **Ejaculatory dysfunction** | 2.50 (0.70) | 1.40 (0.55) | t = 0.57 p=0.59 | 0.50 t = 1.00 p=0.5 | 0.20 t = 1.00 p=0.37 | t = 1.28 p=0.26 |
| **Orgasmic dysfunction** | 1.24 (0.97) | 1.28 (0.75) | t = -0.15 p=0.88 | 0.47 t = 2.42 ***p=0.03*** | 0.11 t = 0.69 p=0.49 | t = -1.81 p=0.08 |
| **UKU sexual dysfunction module, total score** | 8.32 (2.83) | 5.99 (1.79) | t = 1.65 p=0.14 | 1.25 t = -1.46 p=0.5 | 0.21 t = -2.45 p=0.07 | t = 0.80 p=0.43 |

[1] UKU-SERS, UKU side effects rating scale
[2] FGA, first-generation antipsychotic
[3] A positive value indicates an improvement.
[4] Data displayed as mean (standard deviation).