Comparison of Sexual Dysfunction in Male Schizophrenic Patients Maintained on Treatment With Classical Antipsychotics Versus Clozapine

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Background: Antipsychotic treatment is frequently associated with sexual dysfunction. The objective of the present study was to evaluate and compare sexual function and behavior in male schizophrenic patients who regularly take either classical neuroleptic drugs or the prototypical atypical antipsychotic agent, clozapine.

Method: Participants included 60 schizophrenic male patients (DSM-IV criteria): 30 maintained on treatment with classical antipsychotics and 30 on treatment with clozapine. The patients were evaluated with a detailed 18-item sexual function questionnaire.

Results: Both groups reported sexual dysfunction, although scores were significantly higher, indicating better functioning, in the clozapine-treated group in the domains of orgasmic function (number of orgasms per month, p = .037; frequency of orgasm during sex, p = .046), enjoyment of sex (p = .013), and sexual satisfaction (p = .0004). Equivocal results were obtained for the desire parameters.

Conclusion: Maintenance therapy with the atypical neuroleptic clozapine may be associated with a lesser degree of sexual dysfunction than the classical antipsychotics in male outpatients with chronic schizophrenia.

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Sexual dysfunction is a known side effect of most classes of antipsychotic agents. However, the important clinical problem of neuroleptic-induced sexual dysfunction in schizophrenic patients has so far been a neglected area of research. Although the exact mechanisms are unknown, some authors have suggested an imbalance in biogenic amine activity (notably dopamine blockade) and endocrine effects (e.g., hyperprolactinemia).[1–3] The atypical antipsychotic drug clozapine is used to treat schizophrenic patients who are resistant to the typical neuroleptics.[4] Clozapine, like other atypical antipsychotics, has been reported to have a better effect on negative symptoms than do classical antipsychotics. It is associated with fewer extrapyramidal side effects than the classical agents and is almost devoid of a hyperprolactinemic effect.[5] These advantages are related to clozapine's relatively weak antagonistic activity at the dopamine-2 (D_2) receptors and its potent antagonistic activity at the D_1 and the serotonin-2 (5-HT_2) receptors.[6] Its pharmacologic profile of weak D_2 inhibition, potent antiserotonergic activity, and lack of hyperprolactinemia suggests that clozapine may have a less harmful effect on sexual function than do the classical antipsychotic agents.

The objective of the present study was to compare the sexual function and behavior of male schizophrenic patients maintained on treatment with typical neuroleptics versus the prototypical atypical neuroleptic, clozapine.

METHOD

Sexual function and psychiatric status were evaluated in 60 male patients with chronic schizophrenia being treated at the Shaar-Menashe Mental Health Center (Haifa, Israel). Shaar-Menashe is the largest rehabilitative mental health center in Israel, and its patient population is representative of chronic schizophrenic patients in the country.

The diagnosis of schizophrenia was established according to the DSM-IV criteria, using a psychiatric interview based on the guidelines of the Structured Clinical Interview for DSM-IV Axis I Disorders.[7] Inclusion criteria for the study were age of 20 to 60 years, married or liv-

Table 1. Sexual Function Scores in Clozapine- and Classical Antipsychotic–Treated Schizophrenic Patients

Psychosexual Variable	Clozapine (N = 30)	Classical Antipsychotics (N = 30)	p[a]
Desire, mean ± SD			
1. Frequency of sexual thoughts (1 = never, 4 = daily)	3.73 ± 0.52	3.16 ± 0.95	.006
2. Maximum time comfortable without sex (1 = ≥ 1 year, 4 = < 1 week)	2.90 ± 0.80	2.87 ± 0.78	NS
3. Frequency of desire for sex (1 = never, 4 = daily)	3.27 ± 0.57	3.37 ± 0.76	.025
Arousal			
4. Coital erections (impaired vs unimpaired), N/N	5/25	10/20	NS
5. Sleep erections (impaired vs unimpaired), N/N	4/26	9/21	NS
6. Masturbatory erections (impaired vs unimpaired), N/N	3/27	10/20	.058
7. Ease of arousal (impaired vs unimpaired), N/N	5/25	10/20	NS
8. Frequency of waking erections (1 = none, 4 = daily), mean ± SD	3.77 ± 0.57	3.50 ± 0.90	NS
Sexual activity, mean ± SD			
9. Frequency of coitus (1 = none, 4 = daily)	3.30 ± 0.75	3.30 ± 0.79	NS
10. Frequency of masturbation (1 = none, 4 = daily)	3.85 ± 0.46	3.26 ± 1.05	.013
Orgasmic function, mean ± SD			
11. Number of orgasms per month	10.90 ± 7.22	7.20 ± 6.16	.037
12. Frequency of orgasm during sex (1 = never, 4 = every time)	3.70 ± 0.65	3.23 ± 1.07	.046
Sexual problems, N/N			
13. Erection during sex (impaired vs unimpaired)	4/26	11/20	NS
14. Sexual desire (impaired vs unimpaired)	6/24	17/13	.0073
15. Premature ejaculation (yes vs no)	0/30	1/29	NS
16. Delayed ejaculation (yes vs no)	1/29	5/25	NS
Sexual satisfaction, N/N			
17. Enjoyment of sex with partner (impaired vs unimpaired)	5/25	15/15	.013
18. Satisfaction with own sexual function (impaired vs unimpaired)	4/26	18/12	.0004

[a]Determined with t test or Fisher exact test.

ing in a stable relationship with a female partner for at least 3 months, physically healthy, and no alcohol or drug abuse.

The patients were divided into 2 groups by type of antipsychotic treatment: classical agents (N = 30) and clozapine (N = 30). The clozapine patients had failed to respond to at least 3 trials with classical neuroleptics. All were evaluated with a modified version of the sexual function questionnaire of Schiavi et al.[8] during a morning visit to the local psychiatric clinic. Although the sexual questionnaire was not validated, we have had previous favorable experience with this questionnaire for evaluating sexual function in schizophrenic patients.[9] For the present study, the range of some of the item scores was decreased, and some items were made dichotomous for purposes of clarity (Table 1). The questionnaire was completed in the presence of the interviewer, who ensured that the patients clearly understood the content of each item and offered assistance as necessary. Patients were also assessed with the Positive and Negative Syndrome Scale (PANSS).[10] Blood samples for the determination of serum prolactin levels were collected in the morning (between 8 and 10 a.m.). Prolactin assay was performed in the same run to avoid interassay variability. Serum prolactin levels were measured by radioimmunoassay using a commercial kit provided by the Diagnostic Products Corporation (Los Angeles, Calif.). The sensitivity of the assay is 2 to 5 ng/mL, and the intra-assay coefficient of variation is 6.5%, as reported previously.[11]

The data were analyzed with 2-tailed Student t test and Fisher exact test, as appropriate. All results are expressed as mean ± SD.

RESULTS

The 2 treatment groups, the typical antipsychotic group and the clozapine group, were similar in mean age (30.0 ± 6.0 years vs. 36.6 ± 4.3 years, respectively; NS) and duration of schizophrenia (9.3 ± 4.8 years vs. 8.7 ± 3.7 years, respectively; NS). Only 5 patients in the clozapine group were married, compared with 20 in the classical antipsychotic group ($p < .001$, Fisher exact test).

The type and doses of the classical agents were as follows: haloperidol decanoate, 100 to 200 mg/4 weeks i.m. (5 patients); fluphenazine decanoate, 12.5 to 50.0 mg/4 weeks i.m. (15 patients); and perphenazine, 24 to 48 mg/day p.o. (10 patients). The mean dose of clozapine was 230.2 ± 102.5 mg/day (range, 100–400 mg/day).

The psychiatric characteristics of the classical antipsychotic and clozapine groups, respectively, as assessed by the PANSS, were as follows: positive symptoms score, 16.2 ± 1.5 versus 9.5 ± 0.2, $p < .0001$; negative symptoms score, 16.5 ± 2.2 versus 24.6 ± 1.0, $p < .001$; general psychopathology, 22.5 ± 0.1 versus 22.4 ± 0.4, NS. As expected, mean prolactin levels were lower in the clozapine group (12.6 ± 11.2 ng/mL) than in the classical antipsychotic group (18.2 ± 16.2 ng/mL, NS). The normal range of serum prolactin in our laboratory is 3 to 16 ng/mL.

As shown in Table 1, a substantial proportion of patients from both groups reported an impairment in sexual function on the sexual function questionnaire. Nevertheless, the scores of the patients maintained on clozapine were significantly higher than those of the classical drug group in several domains: frequency of sexual thoughts, masturbation, orgasm during sex, and number of orgasms per month. In addition, the proportion of patients with unimpaired sexual desire (item 14), capability to enjoy sex with a partner (item 17), and preserved satisfaction with own sexual function (item 18) was significantly higher in the clozapine-treated group. The only item on which the clozapine patients scored significantly lower was frequency of desire for sex (item 3).

DISCUSSION

To the best of our knowledge, this is the first comparative study of sexual function in chronic schizophrenic patients maintained on treatment with classical antipsychotic agents or clozapine. According to the regulations of the Israel Ministry of Health, clozapine is to be administered only to schizophrenic patients who fail to respond to at least 3 conventional neuroleptics. Thus, it is noteworthy that, prior to clozapine treatment, this group of patients exhibited a lower therapeutic response to classical neuroleptics than did the classical drug group, who were not switched to clozapine. In terms of psychopathology, as assessed by the PANSS, the clozapine-treated patients scored higher in negative symptoms and lower in positive symptoms than did the classical antipsychotic group. (No difference was noted for general psychopathology.) Yet, our results show that the patients maintained on treatment with clozapine displayed better sexual function in several domains, specifically, orgasmic function (items 11, 12) and sexual satisfaction (items 17, 18). Both groups had similar scores for erectile capacity (arousal items 4–8). The results obtained in the area of desire were equivocal; the clozapine patients fared better on item 1 (frequency of sexual thoughts), but scored lower than the classical drug patients on item 3 (frequency of desire for sex). In addition, a higher proportion of clozapine patients noted unimpaired sexual desire (item 14).

Five of the 30 classical drug–treated patients reported delayed ejaculation compared with only 1 clozapine-treated patient; however, the difference did not reach statistical significance. These results are consistent with the impression that ejaculatory dysfunction is rarely reported in patients treated with atypical antipsychotics, including clozapine.[12] The antagonistic effect of clozapine at the 5-HT_2 receptor[6] might be relevant to our observation that few patients on clozapine treatment reported ejaculation dysfunction. In addition, the clozapine patients scored significantly lower on frequency of desire for sex, a phenomenon that may be a serotonin-mediated effect combined with blockade of dopamine receptor subtypes.

A recent prospective drug monitoring program using the UKU Side Effect Rating Scale[13] to assess neuroleptic-induced side effects demonstrated comparable rates of sexual dysfunction in patients taking clozapine and haloperidol.[14] The inconsistency of these findings with our own may be ascribed to differences in the patient samples (chronic outpatients vs. acute inpatients) and in duration of drug administration (maintenance vs. 6 weeks' treatment). Furthermore, we included only patients with a steady sexual partner, whereas these data were unavailable in the monitoring study.[14] Finally, we assessed sexual function with a detailed questionnaire that was specifically designed for the evaluation of phases of the sexual response cycle and the detection of sexual dysfunctions, including such areas as satisfaction and masturbatory activity.

The better sexual function noted here in the clozapine-treated patients cannot be explained by the better effect of clozapine than classical drugs on negative symptoms,[4,6] since the clozapine group exhibited higher scores than the typical neuroleptic group for negative symptoms (but lower scores for positive symptoms), as assessed with the PANSS. Thus, it seems that the impact of the antipsychotics on sexual function may not correlate with the severity of the psychotic symptoms, at least in patients on chronic maintenance treatment. Moreover, since the clozapine patients had failed to respond to 3 or more classic antipsychotics, they were expected to have greater psychopathology and as a result more sexual dysfunction.

The mechanism responsible for the surprisingly lesser degree of sexual dysfunction associated with clozapine is unclear, but it may involve clozapine's lack of a hyperprolactinemic effect. The role of prolactin in neuroleptic-induced sexual dysfunction is not fully understood.[1] Furthermore, although prolactin levels were lower in the clozapine-treated patients, the difference from the classical drug patients was not statistically significant.

In summary, chronic maintenance clozapine treatment seems to be associated with a lesser degree of sexual dysfunction than does classical antipsychotic treatment in schizophrenic outpatients. Clinician awareness of neuroleptic-induced sexual dysfunction can improve the quality of life among this group of patients, whose sexual function might already be compromised by the underlying mental disorder, and may increase patient compliance with treatment.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), perphenazine (Trilafon and others).

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