An Open-Label Trial of Sildenafil Addition in Risperidone-Treated Male Schizophrenia Patients With Erectile Dysfunction

Alex Aviv, M.D.; Assaf Shelef, M.D.; and Abraham Weizman, M.D.

Background: Sexual dysfunction frequently occurs in treated and untreated patients with schizophrenia. Sildenafil is used for treatment of erectile dysfunction caused by diverse factors. The aim of our study was to evaluate its potential value, safety, and effect on compliance with antipsychotic medications in risperidone-treated male schizophrenia patients suffering from erectile dysfunction.

Method: In a 6-week open-label trial, sildenafil was administered to 12 male schizophrenia (DSM-IV) patients, treated with risperidone and reporting erectile dysfunction. The starting dose was 25 mg with the possibility to increase the dose to 75 mg. Three patients who did not respond stopped sildenafil treatment after 3 weeks. The effect on sexual function was assessed by the International Index of Erectile Function and the Valevski-Weizman Male Sexual Function scale.

Results: Nine (75%) of the 12 patients completed the 6-week trial, and 3 patients (25%) stopped taking sildenafil after 3 weeks due to lack of response. We observed statistically significant improvements in all sexual function domains (desire, erectile function, orgasmic function, intercourse satisfaction, and overall satisfaction) in the 9 patients who completed the trial and in most of the domains for all 12 study participants. More than half (8/12; 67%) of the patients exhibited partial or much improvement.

Conclusion: Sildenafil is a useful agent for the treatment of erectile dysfunction in risperidone-treated male schizophrenia patients.

(J Clin Psychiatry 2004;65:97–103)

Received Jan. 16, 2003; accepted June 9, 2003. *From the Abarbanel Mental Health Center, Bat-Yam (Drs. Aviv and Shelef); the Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv (all authors); and the Research Unit, Geha Mental Health Center, Rabin Medical Center, Beilinson Campus, Petah-Tikva (Dr. Weizman), Israel.*

This study was not supported by external funding, nor do the authors have financial or other relationships to disclose relevant to the subject matter of the article.

Corresponding author and reprints: Alex Aviv, M.D., Director, Department 6B, Abarbanel Mental Health Center, 15 KKL Street, Bat-Yam 59100, Israel (e-mail: drav1@attglobal.net).

Schizophrenia is a severe and disabling psychiatric disorder. Early intervention with antipsychotic medications increases the likelihood of favorable long-term course.[1] However, the pharmacologic management is complicated by a high rate of adverse effects including sexual dysfunction. Neuroleptic-induced sexual dysfunction is manifested in men as loss of libido, erectile dysfunction, impaired ejaculation,[2,3] and priapism.[4] The mechanism underlying the sexual side effects of neuroleptics is mainly related to the central dopamine blockade and the resulting neuroendocrine effects (e.g., hyperprolactinemia).[3,5] Antipsychotic agents also exert autonomic peripheral effects, such as α_1-adrenergic blockade and anticholinergic activity, which might be involved in the impairment of erection and ejaculation.[3] In addition to the iatrogenic sexual dysfunction, it has been demonstrated that schizophrenia, per se, is associated with diminished libido and poor sexual performance.[6]

The main pharmacologic treatment strategies for neuroleptic-induced sexual dysfunction are dose reduction, switching to another neuroleptic, and discontinuation as well as addition of a dopamine agonist, such as bromocriptine or amantadine.[3,7] However, all these strategies except switching to another neuroleptic can increase the risk for reemergence of psychotic symptoms in most remitted patients. Furthermore, most of the add-on strategies have not been shown to be efficacious.

Side effects of neuroleptic treatment are known to interfere with compliance with antipsychotic treatment. This has been demonstrated for extrapyramidal side effects, akathisia, sedation, weight gain, and sexual dysfunction.[8] Prevention and treatment of sexual side effects may improve compliance with antipsychotic treatment, self-esteem, and quality of life of schizophrenia patients.

Sildenafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5, the predominant isoenzyme metabolizing cGMP in the corpus cavernosum. In response to sexual stimuli, cavernous nerves and endothelial cells release nitric oxide, which stimulates the formation of cGMP, which, in turn, relaxes the smooth muscle of the corpora cavernosa and enables penile erection. The sildenafil-induced inhibition of phosphodiesterase type 5 activity leads to pro-erectile effect during sexual engagement. Sildenafil was found to

  © Copyright 2004 Physicians Postgraduate Press, Inc.

Table 1. Demographic and Clinical Characteristics of the Study Population (N = 12)

Characteristic	Mean	SD
Age, y	33.8	7.3
Age at onset, y	22.8	3.7
No. of previous psychotic episodes	3.7	2.1
No. of previous hospitalizations	1.9	1.8
Risperidone dose, mg	2.8	0.9
Duration of risperidone treatment, mo	20.2	9.7
Schizophrenia type, DSM-IV	N	%
Paranoid	6	50
Disorganized	1	8.3
Residual	3	25
Unspecified	1	8.3
Schizoaffective disorder	1	8.3

be effective and well tolerated in men with erectile dysfunction of organic, psychogenic, and mixed causes.[9]

A prospective, randomized, double-blind trial[10] reported on the efficacy of sildenafil in the treatment of antidepressant sexual dysfunction. Improvement was noticed in arousal, orgasm, overall satisfaction, and erectile function.[10] There are only 2 case reports[11,12] regarding the usefulness of sildenafil in schizophrenia spectrum patients indicating a positive effect on erectile function and libido.

The present preliminary open-label study was designed to evaluate the value, safety, and effect on compliance with antipsychotic medication of sildenafil addition to ongoing antipsychotic treatment. To this end, sildenafil was coadministered to 12 risperidone-treated male schizophrenia outpatients who complained of erectile dysfunction. Risperidone-treated patients were chosen for this study, since this drug is a commonly used atypical antipsychotic agent that is associated with hyperprolactinemia and D_2 and α_1 blockade that may lead to sexual dysfunction.

METHOD

Subjects

Twelve risperidone-treated male schizophrenia outpatients (mean age = 33.8 ± 7.3 years; Table 1) who complained of erectile dysfunction were included in the study. The diagnosis of schizophrenia was established on the basis of DSM-IV criteria, following an interview according to the guidelines of the Structured Clinical Interview for Axis I DSM-IV Disorders, Patient Edition (SCID-I/P).[13] All patients had been stable for at least 3 months. The patients reported having sexual dysfunction (including, always, erectile dysfunction, with or without other sexual disturbances) for at least 6 months prior to the study. Erectile dysfunction was defined as a persistent inability to attain or to maintain, until completion of the sexual activity, an adequate erection. The disturbance caused marked distress or interpersonal difficulty.

Inclusion criteria for the study were age 18–50 years, married or living in a stable relationship with a female partner for at least 6 months, stabilized on risperidone treatment, and no diagnosis of alcohol and/or drug abuse or dependence. All patients were physically healthy with no concomitant medications in addition to risperidone except for 1 patient who suffered from hypertension and was maintained on hydrochlorothiazide, 25-mg tablet, once daily. None of the study participants had abnormal findings on routine physical examination and laboratory tests, including electrocardiography.

Procedures

The starting dose of sildenafil in the first week was 25 mg, and the patients were instructed to take it 1 hour before planned sexual intercourse with a partner, but not more than once daily. In case of insufficient improvement in erectile function, the participants were permitted to increase the dose in the second week to 50 mg. In the third week, the sildenafil dose could be elevated to 75 mg according to the erectile response.

Qualitative assessments of the effect of sildenafil were performed weekly using a global-usefulness question: "Did the treatment improve your erections?"[9] The optional responses were not improved, partially improved, and much improved. Participants who experienced no improvement in erectile function were instructed to discontinue sildenafil treatment after 3 weeks. Partial and full responders were included in the second part of the study, aimed to examine the persistence of the beneficial effect of the treatment. This subgroup continued sildenafil treatment for another 3 weeks to a total period of 6 weeks, with fixed dose, according to the third week dosage. We avoided administration of a dose above 75 mg in order to lessen the possible risk of priapism that can be associated with concomitant administration of risperidone and sildenafil.

Assessment

Sexual function. Sexual function was assessed at baseline (1 day prior to sildenafil administration) and at weeks 1, 2, 3, and 6 of treatment. Evaluation was performed using:

1. International Index of Erectile Function (IIEF), a 15-question validated, multidimensional self-administered rating scale used for clinical assessment of male sexual function.[14] Usefulness of treatment was determined on the basis of the scores for 5 separate response domains. Erectile function (question 1 through 5 and 15; possible total score 1–30), orgasmic function (questions 9 and 10; possible total score 0–10), sexual desire (questions 11 and 12; possible total score 2–10), intercourse satisfaction (questions 6, 7, and 8; possible total score 0–15), and overall satisfaction (questions 13 and 14; possible total score 2–10).

The changes in the IIEF scores quantified the magnitude of the response.

2. In order to support the findings obtained in the IIEF, we also used the Valevski-Weizman Male Sexual Function (VWMSF) scale.[7] This easy-to-administer scale was found to detect alterations in sexual function following amantadine addition in a similar population of schizophrenia patients maintained on antipsychotic therapy. VWMSF includes assessment of 4 sexual function domains: desire, erection, ejaculation, and satisfaction from sexual performance. Each item was rated in comparison with pretreatment function on a scale of 1 to 5 (1 = markedly decreased, 2 = moderately/mildly decreased, 3 = unchanged, 4 = mildly increased, 5 = markedly increased).

Psychiatric assessment. The severity of symptoms of schizophrenia was assessed with both the Positive and Negative Syndrome Scale (PANSS)[15] and the Clinical Global Impressions-Severity of Illness scale (CGI-S)[16] at baseline and at the endpoint (endpoint was 3 weeks for nonresponders and 6 weeks for partial and full responders).

Drug attitude, compliance, and side effects. Subjective attitude toward the ongoing antipsychotic treatment was evaluated with the Drug Attitude Inventory (DAI-30),[17] a self-rating instrument made up of 30 true/false questions. This instrument contains 15 items that are scored as true and 15 that are scored as false with regard to whether there is totally satisfactory attitude toward the medication. Each positive response to these items is scored as +1 and each negative as –1. The total score is the sum of the positive and negative scores. DAI-30 was completed at baseline, at the end of the third week for nonresponders, and after the sixth week for responders.

In addition, compliance with antipsychotic medications was assessed by direct questioning of the patients: the patients were asked whether they took the medications every day as prescribed (yes or no response) and how many days during the last week they did not take the medications as prescribed. The reason for noncompliance was noted, with options of side effects, stigmatization of the medication, thinking they are not helping, forgetting, worry of long-term damage, or another reason. All observed and spontaneously reported side effects were recorded at weeks 0, 1, 2, 3, and 6.

The study was approved by the Abarbanel Mental Health Center Review Board and written informed consent was obtained from all participants after the nature of the study was fully explained to them.

Statistical Analysis

Analysis of variance (ANOVA) with repeated measurements was used to evaluate the alterations in sexual functioning parameters. Paired Student t test was used for comparisons of PANSS, CGI, and DAI-30 before and at the end of sildenafil treatment.

For evaluation of compliance with respect to whether the medications were taken every day (yes or no response), McNemar test was used; for the other compliance question, we used Wilcoxon signed rank test. All results are expressed as mean ± SD.

RESULTS

The mean age at onset of the first psychotic episode was 22.8 ± 3.7 years. The mean number of previous psychotic episodes was 3.7 ± 2.1, with a mean of 1.9 ± 1.8 hospitalizations (Table 1). All the patients were treated with risperidone for at least 3 months (mean ± SD length = 20.2 ± 9.7 months), with a mean dose of 2.8 ± 0.9 mg.

Global-Usefulness Question

At the end of the first week (sildenafil, 25 mg), 10 (83%) of 12 patients reported partial improvement in erectile function, as assessed by the global-usefulness question; 1 patient reported lack of response and 1 patient had an equivocal response. During week 2, sildenafil dose was increased in all participants to 50 mg, and, at the end of this week, 4 patients (33%) reported much improvement in erectile function (and continued on the same dose until the end of the trial), 4 (33%) experienced partial improvement, and 4 (33%) had no improvement.

For the 8 patients with partial or no improvement in erectile function, sildenafil dose was further increased to a maximal dose of 75 mg. At the end of the third week, 5 (42%) of the 12 patients reported much improvement and 3 (25%) reported partial improvement for a total of 8 improved patients (67%) among the 12. One patient (8%) had an equivocal response, and 3 (25%) continued to report no improvement. Sildenafil treatment was discontinued at the end of week 3 in the 3 nonresponders. It is of note that all the responders (8/12) achieved an IIEF erectile function domain score > 20 by the end of both 3 and 6 weeks.

Briefly, 8 (67%) of the 12 patients completed the 6-week trial and had at least partial improvement in erectile dysfunction, while 4 patients (33%), including the one with equivocal response, did not achieve even partial response. It is of note that these 4 patients did not respond at the end of the second week to a dose of 50 mg of sildenafil. The 1 remitted schizoaffective patient responded with much improvement to sildenafil treatment.

Sexual Function

A statistically significant increase in the mean scores of all sexual function domains ($p < .01$ for all domains) according to both the IIEF and VWMSF scales was found among the 9 participants who completed the 6-week trial.

Table 2. Mean (SD) Scores on the International Index of Erectile Function for 12 Risperidone-Treated Patients During the First 3 Weeks of the Sildenafil Trial[a]

Sexual Function Domain	Baseline	Week 1	Week 2	Week 3	F (df = 3,33)	p Value
Erectile function	13.8 (3.9)	17.8 (4.3)	22.1 (5.5)	21.1 (7.4)	18.4	.001
Orgasmic function	5.8 (2.1)	5.5 (1.1)	6.5 (1.7)	7.0 (1.7)	2.8	.053
Sexual desire	6.3 (1.5)	6.8 (1.4)	7.1 (1.5)	7.3 (1.9)	3.0	.044[b]
Intercourse satisfaction	6.3 (2.1)	5.8 (1.4)	7.1 (1.8)	7.5 (2.5)	5.7	.003
Overall satisfaction	5.1 (0.83)	5.6 (1.0)	6.8 (1.4)	6.7 (1.8)	8.5	.001

[a]Analysis of variance with repeated measures.
[b]Not significant following Bonferroni post hoc test.

Table 3. Mean (SD) Scores on the Valevski-Weizman Male Sexual Function Scale in 12 Risperidone-Treated Patients During the First 3 Weeks of the Sildenafil Trial

Sexual Function Domain	Baseline	Week 1	Week 2	Week 3	F (df = 3,33)	p Value
Desire	2.5 (1.0)	2.8 (0.9)	3.2 (0.9)	3.2 (1.4)	2.8	.054
Erection	1.8 (0.5)	2.8 (0.8)	3.5 (0.9)	3.6 (1.4)	20.2	.001
Ejaculation	1.7 (0.5)	2.2 (0.6)	2.5 (1.2)	2.6 (1.3)	3.2	.037[a]
Satisfaction	1.7 (0.5)	2.3 (0.8)	2.9 (1.2)	3.3 (1.4)	9.0	.001

[a]Not significant following Bonferroni post hoc test.

Since maximal improvement had already been achieved after 3 weeks in the 9 patients who completed the 6-week trial, with no further improvement or deterioration, we analyzed the first 3 weeks of data regarding all 12 participants (including the 3 patients that stopped sildenafil treatment after 3 weeks). In this analysis, we found in the IIEF a statistically significant increase in the scores of 3 of 5 sexual domains, i.e., erectile function, intercourse satisfaction, and overall satisfaction; however, the increase in the orgasmic function domain did not reach a significant level and the score in the sexual desire domain became nonsignificant following Bonferroni post hoc test (Table 2). According to the VWMSF, a statistically significant increase was found after 3 weeks in the 12 participants in 2 of 4 sexual function domains: erection and satisfaction, but not in desire and ejaculation ($p > .05$ after Bonferroni post hoc test) (Table 3).

Psychiatric Assessment

No differences were found between baseline and final (3 weeks for nonresponders; 6 weeks for partial and full responders) assessments in the total PANSS, the 3 subscales of the PANSS (positive symptoms, negative symptoms, general psychopathology), and CGI-S scores (Table 4).

Drug Attitude and Compliance

No difference was found in DAI-30 scores at baseline and in the final assessment. One of the 12 patients did not complete the last compliance questionnaire; thus, only 11 patients were included in the compliance analysis. This result remains insignificant following last-observation-carried-forward analysis. The proportion of patients reporting not taking the antipsychotic medications as prescribed was similar before and after sildenafil treatment. No difference was found in the number of days (per week) patients reported not taking risperidone as prescribed (Table 4). Reasons for not taking the medication as prescribed at the baseline assessment were forgetfulness (N = 5), adverse effects (N = 3; sexual dysfunction, drowsiness, fatigue), worry of long-term damages (N = 2), patient's feeling that medications are not helpful (N = 1), and falling asleep before taking the drug (N = 1). At the final assessment (3 weeks for nonresponders; 6 weeks for partial and full responders), 7 patients reported that they forgot to take the medications, 2 reported adverse effects (drowsiness, fatigue), and 1 patient fell asleep before taking the drug.

Adverse Events

Table 5 shows treatment-emergent adverse events. Sildenafil-treated patients reported nasal congestion, headache, constipation, diarrhea, dyspepsia, orthostatic hypotension (based on symptomatic complaint), and abnormal vision. Two patients reported recurrent prolonged erections. The first one was a 48-year-old patient who had been maintained on risperidone therapy at a dose of 4 mg/day for the last 3 years. He had hypertension that was under control with a 25-mg tablet of hydrochlorothiazide once daily. After using sildenafil, 75 mg, he reported prolonged erections that lasted 30 minutes to 1 hour subsequent to sexual intercourse and ejaculation. The second patient was 34 years old and had been treated with risperidone, 1 mg/day, for the last 1.5 years. He reported prolonged erections following a sildenafil dose of 50 mg/day that lasted about 30 minutes after sexual intercourse and ejaculation. The prolonged erections were nonpainful and did not meet the criteria for priapism.

DISCUSSION

High frequency of sexual dysfunction in treated and untreated male schizophrenia patients has long been recog-

Table 4. PANSS, CGI-S, DAI-30, and Compliance With Antipsychotic Medications Questionnaire for 12 Patients at Baseline and at the Final Assessment

Assessment	Baseline	Final Assessment[a]	p Value	t Value
PANSS, mean ± SD score				
Total	56.4 ± 10.5	56.0 ± 9.6	.80, NS[b]	0.26
Positive symptoms	11.4 ± 3.5	11.2 ± 3.2	.46, NS[b]	0.76
Negative symptoms	14.8 ± 5.4	14.6 ± 5	.59, NS[b]	0.56
General psychopathology	30.2 ± 5.1	30.2 ± 5.1	.94, NS[b]	0.08
CGI-S, mean ± SD score	3.2 ± 0.7	3.2 ± 0.7	.34, NS[b]	1.00
DAI-30, mean ± SD score	7.2 ± 9.5	10.2 ± 5.7	.22, NS[b,e]	–1.31
Compliance Questionnaire				
Do you take risperidone every day as prescribed? (yes/no, N)	Yes, 7 No, 4	Yes, 8 No, 3	1.00, NS[c,e]	
How many days during the last week did you not take risperidone as prescribed? (mean ± SD, d)	1.0 ± 0.8	0.7 ± 0.6	.20, NS[d,e]	

[a]Final assessment = 3 weeks for nonresponders; 6 weeks for partial and full responders.
[b]According to paired t test (df = 11).
[c]According to McNemar test.
[d]According to Wilcoxon signed rank test.
[e]Nonsignificant following last-observation-carried-forward analysis.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness, DAI-30 = Drug Attitude Inventory, PANSS = Positive and Negative Syndrome Scale.

Table 5. Treatment-Emergent Adverse Events in Risperidone-Treated Patients During a 6-Week Trial of Sildenafil

	Week 1 (N = 12)		Week 2 (N = 12)		Week 3 (N = 12)		Week 6 (N = 9)	
Adverse Event	N	%	N	%	N	%	N	%
Headache	1	8.3	4	33.3	4	33.3	3	33.3
Nasal congestion	3	25.0	0	0	1	8.3	0	0
Orthostatic hypotension[a]	1	8.3	2	16.7	2	16.7	1	11.1
Abnormal vision	1	8.3	1	8.3	3	25.0	0	0
Constipation	1	8.3	2	16.7	2	16.7	1	11.1
Diarrhea	0	0	2	16.7	3	25.0	1	11.1
Dyspepsia	0	0	2	16.7	1	8.3	1	11.1
Flushing	0	0	1	8.3	1	8.3	1	11.1
Prolonged erection	0	0	1	8.3	2	16.7	2	22.2

[a]Based on symptomatic complaint.

nized.[6] The impaired sexual activity may have a negative impact on quality of life, social interactions, and self-esteem.[12] The neuroleptic-induced sexual dysfunction may be related, at least partially, to iatrogenic hyperprolactinemia. Clozapine, the prototype of atypical antipsychotics, has minimal or no effect on prolactin levels.[18] It is of note that, despite its lack of hyperprolactinemic effect, clozapine was found by 1 study[19] to have rates of sexual side effects comparable to those of haloperidol among acute psychotic inpatients. However, a later study[20] found that maintenance therapy with clozapine might be associated with a lesser degree of sexual dysfunction as compared with typical antipsychotics.

Risperidone is an atypical antipsychotic agent that induces pronounced hyperprolactinemia.[21] Among men, the incidence of prolactin-related adverse events (decreased libido, erectile dysfunction, ejaculatory dysfunction, and gynecomastia) was positively correlated with risperidone dose.[22] In a recent retrospective chart review of the frequency of sexual dysfunction,[23] a significantly higher proportion of risperidone-treated patients suffered from sexual dysfunction (males, 66%; females, 86%) compared with patients on haloperidol (males, 29%; females, 30%) and clozapine (males, 60%; females, 58%).

To the best of our knowledge, this is the first report to examine sildenafil use in a prospective fashion in a population of schizophrenia patients with erectile dysfunction. Because the literature is sparse on matters relating to treatment of sexual dysfunction in this population, this report may help bring awareness to the fact that sexual dysfunction is a real issue in this population and can be addressed and treated.

Our open-label trial suggests that sildenafil is a useful and safe treatment for erectile dysfunction, at least in male schizophrenia outpatients treated with risperidone. Based on the global-usefulness question, 75% of the patients (9 of 12) were instructed to complete the entire 6-week trial (completers), and 67% of the patients (8 of 12) exhibited a favorable response to sildenafil. Among the patients that responded to sildenafil, a mild improvement of sexual function was already noticed after a 25-mg dose. The response to sildenafil was dose-dependent, with a better effect obtained with 50 mg and 75 mg compared to 25 mg. Since the 4 patients who did not respond to sildenafil at a dose of 50 mg never responded despite dosing up to 75 mg of sildenafil, it may be that lack of response to 50 mg predicts inefficacy of sildenafil in patients with erectile dysfunction on risperidone treatment. In the present study, the sildenafil dose was not increased to 100 mg, and further dose-response studies are needed to determine the safe and optimal range for treating erectile dysfunction in schizophrenia patients, as was described in various other conditions.[9] It is possible that a higher rate of success could be obtained with a maximal dose of 100 mg.

Among the completers (N = 9), a significant improvement was found in sexual function domains according to both the IIEF and VWMSF scales. Similar improvement in most sexual function domains, as assessed by the IIEF or Arizona Sexual Experience Scale, was also noticed previously in male patients with ischemic heart disease (a retrospective subanalysis of 11 studies)[24] and in male patients with antidepressant-induced sexual dysfunction.[10]

The magnitude of improvement achieved after 3 weeks was similar to that observed after 6 weeks of sildenafil treatment, indicating persistence of the beneficial effect. These results demonstrate that, in a dose-escalating approach, improvement in sexual function in neuroleptic-treated schizophrenia patients is detectable within the first 3 weeks of sildenafil treatment. A similar time-course was

reported also in nonschizophrenic patients with erectile dysfunction.[9]

From the data concerning all 12 patients that received sildenafil for 3 weeks, a measurable improvement was reflected only in the erectile function and satisfaction domains as assessed by both scales (IIEF and VWMSF). According to the IIEF, a significant improvement was noticed in 3 of the 5 sexual function domains: erectile function, intercourse satisfaction, and overall satisfaction but not in sexual desire and orgasmic function. Similar results were obtained using the VWMSF scale, namely, significant improvement in 2 of the 4 sexual function domains: erection and satisfaction, but not desire and ejaculation domains. Lack of effect of sildenafil on sexual desire was reported previously in a heterogeneous nonschizophrenic population.[9] The inefficacy of sildenafil in the domains of sexual desire and orgasm is consistent with the mechanism of action of the drug, namely, cGMP-mediated restoration of the natural erectile response to sexual stimulation.

The rate of response to sildenafil (67%) in our open-label trial is similar to the rate found among male patients suffering from erectile dysfunction due to broad-spectrum etiologies (organic, psychogenic, or mixed) (69%)[9] and ischemic heart disease male patients (70%),[24] as well as in a double-blind study of sexual dysfunction due to antidepressants in males (54.5%).[10]

Sildenafil treatment was well tolerated. Its main adverse effects were headache and prolonged erection (< 1 hour). The observed side effects are related to the pharmacologic activity of sildenafil as a phosphodiesterase type 5 inhibitor. None of the patients discontinued treatment because of side effects, suggesting a relatively high level of drug tolerability and acceptance. Although we did not encounter any case of priapism in our sample, concomitant administration of sildenafil with antipsychotics that exhibit α_1-adrenergic antagonism, such as risperidone, should be used with caution considering the rare, but not negligible, risk of priapism.[25] Patients with sildenafil-induced prolonged erection should be monitored frequently since they may be at a higher risk for priapism.

Sildenafil addition did not affect the psychiatric status of our patients as measured by the PANSS and CGI-S. Neither did the treatment change compliance with the antipsychotic treatment, as measured by DAI-30 and our own compliance behavior questionnaire. It is possible that a longer follow-up period is required to detect a possible improvement in compliance with antipsychotic treatment due to restoration of sexual function.

The main limitations of our study are the small sample size (N = 12), short follow-up period (6 weeks), narrow range of sildenafil dose (25–75 mg), the open-label nature of the study, and the lack of a placebo-control arm. Thus, a nonspecific, placebo effect cannot be ruled out. However, this is the first prospective investigation of sildenafil effect in schizophrenia patients.

In summary, our prospective, 6-week, small-scale, open-label trial suggests that sildenafil might be efficacious in the treatment of erectile dysfunction in remitted schizophrenia patients maintained on risperidone therapy. The improvement was achieved in most of the domains of sexual dysfunction, with no impact on the schizophrenia symptoms. It is not known whether improvement in sexual function will persist over a longer period of time and whether it will affect the quality of life of this population. Our preliminary findings should be replicated in randomized, long-term, large-scale, double-blind, placebo-controlled studies with higher dose of sildenafil (up to 100 mg) in patients treated with typical and atypical neuroleptics.

Drug names: amantadine (Symmetrel and others), bromocriptine (Parlodel and others), clozapine (Clozaril and others), haloperidol (Haldol and others), hydrochlorothiazide (Microzide, Oretic, and others), risperidone (Risperdal), sildenafil (Viagra).

REFERENCES

1. Hegarty JD, Baldessarini RJ, Tohen M, et al. One hundred years of schizophrenia: a meta-analysis of the outcome literature. Am J Psychiatry 1994;151:1409–1416
2. Segraves RT. Effects of psychotropic drugs on human erection and ejaculation. Arch Gen Psychiatry 1989;46:275–284
3. Gitlin MJ. Psychotropic medications and their effects on sexual function: diagnosis, biology, and treatment approaches. J Clin Psychiatry 1994;55: 406–413
4. Thompson JW Jr, Ware MR, Blashfield RK. Psychotropic medications and priapism: a comprehensive review. J Clin Psychiatry 1990;51: 430–433
5. Meston CM, Frohlich PF. The neurobiology of sexual function. Arch Gen Psychiatry 2000; 57:1012–1030
6. Aizenberg D, Zemishlany Z, Dorfman-Etrog P, et al. Sexual dysfunction in male schizophrenic patients. J Clin Psychiatry 1995;56:137–141
7. Valevski A, Modai I, Zbarski E, et al. Effect of amantadine on sexual dysfunction in neuroleptic treated male schizophrenic patients. Clin Neuropharmacol 1998;21:355–357
8. Fleischhacker WW, Meise U, Gunther V, et al. Compliance with antipsychotic drug treatment: influence of side effects. Acta Psychiatr Scand 1994;89(suppl 382):11–15
9. Goldstein I, Lue TF, Padma-Nathan H, et al. Oral sildenafil in the treatment of erectile dysfunction. N Engl J Med 1998;338:1397–1404
10. Nurnberg HG, Hensley PL, Gelenberg AJ, et al. Treatment of antidepressant-associated sexual dysfunction with sildenafil. JAMA 2003;289:56–64
11. Lare SB, Labbate LA. Sildenafil and erectile dysfunction [letter]. Am J Psychiatry 2000;157:2055–2056
12. Benatov R, Reznik I, Zemishlany Z. Sildenafil citrate (Viagra) treatment of sexual dysfunction in a schizophrenic patient [letter]. Eur Psychiatry 1999;14:353–355
13. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P, Version 2.0). New York, NY: Biometric Research Department, New York State Psychiatric Institute; 1995
14. Rosen RC, Riley A, Wagner G, et al. The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997;49:822–830
15. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
16. Guy W. ECDEU Assessment Manual for Psychopharmacology, Revised Edition. US Department of Health, Education and Welfare publication (ADM) 76-338. Bethesda, Md: 1976:534–537
17. Hogan TP, Awad AG, Eastwood R. A self report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity.

Psychol Med 1983;13:177–183
18. Meltzer HY, Goode DJ, Schyve PM, et al. Effect of clozapine on human serum prolactin levels. Am J Psychiatry 1979;136:1550–1555
19. Hummer M, Kemmler G, Kurtz M, et al. Sexual disturbances during clozapine and haloperidol treatment for schizophrenia. Am J Psychiatry 1999;156:631–633
20. Aizenberg D, Modai I, Landa A, et al. Comparison of sexual dysfunction in male schizophrenic patients maintained on classical antipsychotics versus clozapine. J Clin Psychiatry 2001;62:541–544
21. David SR, Taylor CC, Kinon BJ, et al. The effects of olanzapine, risperidone, and haloperidol on plasma prolactin levels in patients with schizophrenia. Clin Ther 2000;22:1085–1096
22. Kleinberg DS, Davis JM, de Coster R, et al. Prolactin levels and adverse events in patients treated with risperidone. J Clin Psychopharmacol 1999; 19:57–61
23. Mullen B, Brar JS, Vagnucci AH, et al. Frequency of sexual dysfunction in patients with schizophrenia on haloperidol, clozapine or risperidone [letter]. Schizophr Res 2001;48:155–158
24. Conti CR, Pepine CJ, Sweeney M. Efficacy and safety of sildenafil in the treatment of erectile dysfunction in patients with ischemic heart disease. Am J Cardiol 1999;83:29C–34C
25. Compton MT, Miller AH. Priapism associated with conventional and atypical antipsychotic medications: a review. J Clin Psychiatry 2001;62: 362–366