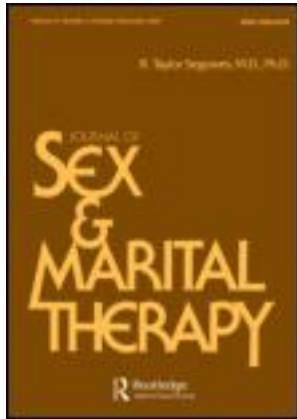


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### Strategies for the Treatment of Antipsychotic-Induced Sexual Dysfunction and/or Hyperprolactinemia Among Patients of the Schizophrenia Spectrum: A Review

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# **Strategies for the Treatment of Antipsychotic-Induced Sexual Dysfunction and/or Hyperprolactinemia Among Patients of the Schizophrenia Spectrum: A Review**

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*There is limited evidence for the management of sexual dysfunction and/or hyperprolactinemia resulting from use of antipsychotics in patients with schizophrenia and spectrum. The aim of this study was to review and describe the strategies for the treatment of antipsychotic-induced sexual dysfunctions and/or hyperprolactinemia. The research was carried out through Medline/PubMed, Cochrane, Lilacs, Embase, and PsycINFO, and it included open labels or randomized clinical trials. The authors found 31 studies: 25 open-label noncontrolled studies and 6 randomized controlled clinical trials. The randomized, double-blind controlled studies that were conducted with adjunctive treatment that showed improvement of sexual dysfunction and/or decrease of prolactin levels were sildenafil and aripiprazole. The medication selegiline and cyproheptadine did not improve sexual function. The switch to quetiapine was demonstrated in 2 randomized controlled studies: 1 showed improvement in the primary outcome and the other did not. This reviewed data have suggested that further well-designed*

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*randomized controlled trials are needed to provide evidence for the effects of different strategies to manage sexual dysfunction and/or hyperprolactinaemia resulting from antipsychotics. These trials are necessary in order to have a better compliance and reduce the distress among patients with schizophrenia.*

Sexual dysfunction due to antipsychotic is not extensively researched, but it is prevalent in 50–60% of patients with schizophrenia who are receiving antipsychotic medication (Haro & Carulla, 2006; Uçok, Incesu, Aker, & Erkoç, 2007, 2008) compared with 31% of men in the general population (Laumann, Paik, & Posen, 1999). The high prevalence of sexual dysfunction in patients with schizophrenia can significantly affect their life expectancy, quality of life, and medication adherence (Heald, 2010). Sexual dysfunction resulting from antipsychotics is not extensively researched (Kelly & Conley, 2004; Rosenberg, Bleiberg, Koscis, & Gross, 2003) and when evaluated by patients, it is rated as significantly more distressing than sedation, extrapyramidal or vegetative side effects of antipsychotics (Lambert et al., 2004).

Antipsychotics can cause sexual dysfunction through multiple mechanisms, including sedation, hyperprolactinemia, and antagonism of  $\alpha$ -adrenergic, dopaminergic, histaminic, and muscarinic receptors (Haddad & Sharma, 2007). Prolactin elevation explained 40% of all sexual dysfunction present in patients with schizophrenia (Knegtering et al., 2008). Moreover, many other factors may cause sexual problems for patients with schizophrenia, including concomitant medications, the effect of the disease itself, and comorbidity with other psychiatric and physical diseases (Olfson, Uttaro, Carson, & Tafesse, 2005). Negative symptoms such as anhedonia, avolition, and blunted affect were related to hypodopaminergic activity in the frontal cortex and can cause severely harm in the ability to enjoy sexual life. These patients face difficulties in establishing relationships as a result of recurrent psychotic episodes, obesity, and low self-esteem (Zemishlany & Weizman, 2008).

Antipsychotic medication is the most common cause of hyperprolactinaemia in patients with severe mental illness; the degree of prolactin elevation varies among agents. The patient should be asked about symptoms possibly related to elevated prolactin (Heald et al., 2010). The short-term effects of prolactin elevation may include menstrual irregularities, galactorrhoea in women, sexual dysfunction, and depression. Long-term risks may include decreased bone mineral density to a greater extent than would be expected with normal aging and it may include osteoporosis (Haddad & Wieck, 2004).

Studies have documented that atypical antipsychotics cause less sexual dysfunction and/or hyperprolactinemia than do conventional antipsychotics or atypical risperidone (Aizenberg, Modai, Landa, Gil-Ad, & Weizman, 2005;

Bobes et al., 2003; Cutler, 2003; Gonzalez, Villademoros, & Tafalla, 2005; Kelly & Conley, 2006; Lambert et al., 2005; Peuskens, Sienaert, & De Hert, 1998; Van Bruggen et al., 2009; Volavka et al., 2004). Quetiapine was associated with less severe sexual dysfunction than was olanzapine and risperidone (Byerly et al., 2006). Other studies have found no differences between first- and second-generation antipsychotics (Costa et al., 2007; Lambert et al., 2004; MacDonald et al., 2003).

No universal guidelines exist for management of sexual dysfunction and/or hyperprolactinemia resulting from antipsychotics in patients with schizophrenia and spectrum. Different strategies to treat psychotropic-induced sexual dysfunction have been developed, including taking drug holidays, reducing dosage, switching to another psychotropic drug that is meant to be less likely to cause sexual dysfunction, and the use of adjunctive treatment (Berner et al., 2007).

The purpose of the present study was to review all the studies that included the strategies for the treatment of antipsychotic-induced sexual dysfunction among patients of the schizophrenia spectrum.

## METHOD

We established a protocol to review strategies for the management of antipsychotic-induced sexual dysfunction in patients of the schizophrenia spectrum.

### Types of Studies

We performed our review by seeking and selecting any studies related to this topic, from open labels to randomized clinical trials. We excluded studies with possible sexual dysfunction and/or hyperprolactinemia caused by chronic disease, studies that did not include patients of the schizophrenia spectrum, studies that included children and animals and studies of case report. We included the articles that were available in English, Spanish, Portuguese, and French. We decided to consider only published studies because they have been subjected to peer review and provide more information than meeting abstracts.

### Types of Participants

The studies' participants included men and women who were older than 18 years of age and who were suffering from sexual dysfunction (libido, sexual arousal, penile erection/lubrication, orgasm, satisfaction with orgasm, overall sexual satisfaction, menstrual dysfunction, and hyperprolactinemia

and related symptoms), as measured by criteria defined by the primary authors of the trials. The sexual dysfunction also had to be attributed to the antipsychotic drug therapy, and the patient had to be in use of antipsychotic therapy for at least 4 weeks.

### Types of Intervention

The types of interventions included the following: (a) dose reduction of the agent causing the sexual dysfunction; (b) symptomatic therapy, such as use of adjunctive therapy, such as sildenafil; (c) switching to other antipsychotic drug meant to be less likely to cause sexual dysfunction; and (d) placebo or no intervention in the untreated control groups.

### Search Strategies for Identification of Studies

Medical literature using data from treatment of antipsychotic-induced sexual dysfunction and/or hyperprolactinemia among patients of the schizophrenia spectrum was identified using electronic database MEDLINE/PubMed, COCHRANE, LILACS, EMBASE, and PsycINFO. Search terms included *schizophrenia, disorders with psychotic features, antipsychotic agents, neuroleptics, sexual dysfunctions, hyperprolactinemia, clinical trial, and randomized controlled trial*. For the generic names of the antipsychotic drugs as potential causes of sexual dysfunction, we performed a search also on the following terms: *aripiprazole, amisulpride, benperidol, bromperidol, chlorpromazine, chlorprothixene, clopenthixol, clozapine, dixyrazine, flupenthixol, fluphenazine, fluspirilene, haloperidol, levomepromazine, molidone, olanzapine, penfluridol, perazine, pericyazine, pimozide, pipamperone, promazine, prothipendyl, quetiapine, reserpine, risperidone, sulpiride, thioridazine, trifluoperazine, trifluoperidol, triflupromazine, ziprasidone, zotepine*. In addition, we searched articles using the following terms for sexual dysfunction and hyperprolactinemia: *sexual dysfunction, physiological, dyspareunia, erectile dysfunction, ejaculation, libido/drug effects, libido/drug therapy, inhibited sexual desire, premature ejaculation, ejaculation disorder, impotence, priapism, vaginismus, anorgasmia, orgasm, sexual arousal, amenorrhea/blood, amenorrhea/chemically induced, galactorrhea/blood, galactorrhea/chemically induced, oligomenorrhea/blood, oligomenorrhea/chemically induced, prolactin/blood, hyperprolactinemia, sexual behavior/drug effects, menstruation disturbances/chemically induced, sildenafil, vardenafil, tadalafil, bromocriptine, amantadine, selegiline, carbegoline, ciproheptadine, and shakuyaku kanzo*.

In addition, we scrutinized the reference lists of the obtained articles for studies not indexed in the electronic databases.

## RESULTS

### Selection of Studies

MEDLINE/PubMed searches yielded 659 articles, COCHRANE yielded 204 articles, *LILACS* yielded 42 articles, *EMBASE* yielded 2,785 articles, and PsycINFO yielded 837 articles.

Although most of the studies examined the sexual dysfunction in patients with schizophrenia on antipsychotic medication, we only selected data from studies that we identified the following outcomes of interest: (a) improvement of sexual dysfunction, (b) decrease of prolactin levels, (c) all outcomes for the short term (2–12 weeks), medium term (13–26 weeks), and long term (>26 weeks).

### Data Extraction and Management

Studies that met the inclusion criteria were obtained for data extraction by two reviewers (the first and the second authors) using a standard extraction form. Reviewers were not blinded to the names of the authors, institutions, or journal of publication.

### Randomized, Double-Blind Controlled Trials and Open-Label Studies

We selected 6 studies from 4,527 articles that were randomized, double-blind, controlled trials for the treatment of antipsychotic-induced sexual dysfunction and/or hyperprolactinemia, and these studies are summarized in Table 1. We selected 25 open-label studies for the treatment of antipsychotic-induced sexual dysfunction and/or hyperprolactinemia, which are presented in Table 2.

### Management with Adjunctive Treatment

There were few randomized, double-blind controlled studies found for treatment as an additional medication to antipsychotic-induced sexual dysfunction: a sildenafil study (Gopalakrishnan, Jacob, Kuruvilla, Vasantharaj, & John, 2006), a selegiline study (Kodesh et al., 2003), and a cyproheptadine study (Lee et al., 1995). Only one adjunctive treatment with aripiprazole to decrease of prolactin levels (Shim et al., 2007).

There was one randomized, double-blind study that had positive result in improving sexual functioning and it involved the use of sildenafil. The trials conducted with the drugs selegiline and cyproheptadine were not effective in improving any domain of sexual functioning or prolactin levels, respectively.

Gopalakrishnan et al. (2006) studied the efficacy and tolerability of sildenafil in patients with antipsychotic-induced erectile dysfunction, in a

**TABLE 1.** Randomized, Double-Blind Controlled Clinical Trials Studies for the Treatment of Antipsychotic-Induced Sexual Dysfunction and Hyperprolactinemia

Author and year	Scale used	Prolactin levels	Induced by	Study design	Duration (weeks)	Participants		Intervention	Participants who completed the study	Primary outcome
						N	Mean age (years)			
Byerly et al. (2008)	ASEX scale (sexual drive, arousal, penis erection/vaginal lubrication, ability to reach orgasm, and satisfaction with orgasm)		Risperidone	Randomized double-blind, pilot trial	6	42 (22 men, 20 women)	42.3	Schizophrenia or schizoaffective disorder <sup>1</sup>	100%	Sexual functioning measured by ASEX scale did not differ significantly between quetiapine switch versus risperidone continuation
Nakonezny et al. (2007)	ASEX scale (sexual drive, arousal, penis erection/vaginal lubrication, ability to reach orgasm, and satisfaction with orgasm)		Risperidone	Randomized double-blind, pilot trial	6	22 men	40.8	Schizophrenia or schizoaffective disorder <sup>1</sup>	100%	Higher serum prolactin level was related to greater impairment of sexual functioning in male outpatients who were treated with risperidone but not with quetiapine
Shim et al. (2007)	Prolactin-Related Adverse Event Questionnaire (menstrual disturbances and galactorrhea)	Hyperprolactinemia prolactin levels	Haloperidol	Randomized, double-blind, placebo controlled trial at Inje University	8	54 (22 men, 32 women)	39.5	Schizophrenia <sup>1</sup>	96.2%	Adjunctive aripiprazole led to prolactin level normalization in 84.6% of patients, resulting in reinstatement of menstruation in women

Gopalakrishnan et al. (2006)	International Index of Erectile Function	Erectile dysfunction	Risperidone, olanzapine, clozapine, fluphenazine decanoate	Randomized, double blind, placebo-controlled, flexible dose, crossover trial	2	32 men	35.1	Schizophrenia or delusional disorder <sup>2</sup>	1. Adjunctive sildenafil, 25–50 mg 2. Placebo	96.9%	Improvement in number and mean duration of erections and in combined number of satisfactory times of intercourse
Kodesh et al. (2003)	Sexual Functioning Scale (sexual drive, arousal, penis erection/vaginal lubrication, ability to reach orgasm, and satisfaction with orgasm)	Prolactin serum levels	Perphenazine or haloperidol	Randomized double-blind, placebo-controlled crossover study	3	10 men	44.8	Schizophrenia <sup>1</sup>	1. Selegiline, 15 mg/day as adjunctive treatment 2. Placebo	100%	It was not found to be effective in improving any domain of sexual functioning, despite a significant decrease in prolactin levels
Lee et al. (1995)		Prolactin levels	Haloperidol	Double-blind placebo controlled trial	6	40 (20 men, 20 women) <sup>3</sup>	34	Schizophrenia	1. Cyproheptadine, 24 mg/day 2. Placebo	87%	Cyproheptadine augmentation did not reduce the plasma prolactin level but did induce a decrease in the plasma cortisol level

Note. ASEX = Arizona Sexual Experiences Scale.

<sup>1</sup>Determined by the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.).

<sup>2</sup>Determined by the International Classification of Diseases-10.

<sup>3</sup>Original number of participants was 46; however, 6 dropped out, yielding 40 participants.



**TABLE 2.** Open-Labels Studies for the Treatment of Antipsychotic-Induced Sexual Dysfunction and Hyperprolactinemia

Sexual dysfunction	Induced by	Number of patients and gender	Therapy, dose, and duration	Study design	Number of participants who completed the study (%)	Primary outcome	Author and year
1. Hyperprolactinemia	Risperidone	16 women	Adjunctive treatment with aripiprazole, 3–12 mg/day	Open-label study	12 (100%)	Aripiprazole reduces the prolactin levels	Yasui-Funukori et al. (2010)
2. Hyperprolactinemia	Risperidone	21 men	Adjunctive aripiprazole, 10 mg	Open-label study	19 (90.4%)	Aripiprazole reduces the prolactin levels	Chen et al. (2009)
3. Hyperprolactinemia	Risperidone, olanzapine	269 men and women	Switch from risperidone or olanzapine to aripiprazol (10–30 mg/day), 8 weeks	Randomized open-label study	199 (74%)	Mean prolactin levels decreased significantly	Byerly et al. (2009)
4. Libido, erectile, ejaculatory, menstrual dysfunction, satisfaction in overall sexual functioning, and hyperprolactinemia	Antipsychotic (not aripiprazole)	27 (14 men, 13 women)	Switch to aripiprazole or the addition of aripiprazole (15–30 mg/day) to another antipsychotic regime, 26 weeks	Open-label study	22 (81%)	Improvement in sexual performance and reduction in prolactin	Mir et al. (2008)
5. Hyperprolactinemia	Risperidone, sulpiride	23 women	Switch from risperidone or sulpiride to aripiprazol (10–30 mg/day), 4 weeks	Open-label noncontrolled drug study	20 (87%)	Reduced serum prolactin levels and restoring menstruation	Lu et al. (2008)
6. Hyperprolactinemia, oligomenorrhea, or amenorrhea	Risperidone	20 women	Peony-glycyrrhiza decoction with bromocriptine for 4 weeks each, with an interval of 4-week washout period	Randomized crossover study	2 (90%)	Peony-glycyrrhiza decoction treatment produced a significant decrease in serum Prolactin levels	Yuan et al. (2008)

7. Sexual dysfunction of any type	Antipsychotics (the most frequent were risperidone and olanzapine)	41 patients	Switch to ziprasidone, mean dose of 140 mg/day, 3 months	Multicenter, non-comparative, observational, and naturalistic study	41 (100%)	Normalization on sexual function. 50% of patients had much or very much improvement on sexual function and 24% a slight improvement	Montejo and Rico-Villademoros (2008)
8. Erectile dysfunction	Clozapine, risperidone, amisulpride, olanzapine, haloperidol, aripiprazole	25 men	Vardenafil 5–20 mg/day, 12 weeks	Flexible-dose open-label study	21 (84%)	Improvement in sexual function and in quality of life	Mitsonis et al. (2008)
9. Hyperprolactinemia	Risperidone, amisulpride	7 women	Switch to aripiprazole (10–20 mg/day), 8 weeks	Noncontrolled open-label trial	5 (71%)	Serum prolactin levels were normalized and hyperprolactinemia symptoms were resolved in all patients	Lee et al. (2006)
10. Prolactin levels	Risperidone or olanzapine	8 women, 9 men	Switch risperidone to olanzapine or olanzapine to risperidone, 3 months	Observational, noncontrolled, and crossover study	17 (100%)	When patients switched from risperidone to olanzapine, serum prolactin level decreased significantly	Lin et al. (2006)
11. Hyperprolactinemia and comorbid symptoms	Conventional antipsychotics or risperidone	26 men, 28 women	Switch from conventional antipsychotics or risperidone to olanzapine (5–20 mg/day), 4 months	Open-label, prospective, and randomized study	41 (76%)	Reduction in serum prolactin and improvement in sexual and reproductive comorbid symptoms	Kinon et al. (2006)
12. Hyperprolactinemia	Conventional antipsychotics	25 women	Switch from conventional antipsychotics to quetiapine, 8 weeks	Open-label study	17 (68%)	Serum prolactin levels were significantly decreased without any	Nakagima et al. (2005)

(Continued on next page)

**TABLE 2.** Open-Labels Studies for the Treatment of Antipsychotic-Induced Sexual Dysfunction and Hyperprolactinemia (*Continued*)

Sexual dysfunction	Induced by	Number of patients and gender	Therapy, dose, and duration	Study design	Number of participants who completed the study (%)	Primary outcome	Author and year
13. Hyperprolactinemia	Risperidone	19 patients	Cabergoline, 0.125–0.250 mg/week, 8 weeks	Open-label pilot study	19 (100%)	Decrease in plasma prolactin levels and 11 patients showed remission of clinical signs with prolactin values within the normal range	Cavallaro et al. (2004)
14. Sexual drive, arousal, penis erection/vaginal lubrication, ability to reach orgasm, and satisfaction with orgasm, prolactin serum levels	Risperidone, haloperidol	8 men	Switch outpatients with schizophrenia and antipsychotic-induced sexual dysfunction to open-label quetiapine treatment (300–800 mg/day), 6 weeks	Open-label trial	6 (75%)	Clinically and statistically significant improvement in ASEX total scores; Plasma prolactin levels tended to decrease.	Byerly et al. (2004)
15. Prolactin levels	First generation antipsychotics (bromperidol, chlorpromazine, fluphenazine, haloperidol, levomepromazine, moshapramine, pipamperone, sulpiride, timiperone, zotepine)	30 men	Switch to olanzapine, perospirone, or quetiapine, 6 weeks	Prospective open-label study	30 (100%)	Reduced elevated prolactin without affecting the gonadal hormones and in improving quality of life	Kaneda et al. (2004)
16. Erectile dysfunction	Risperidone	12 men	Sildenafil 25–75 mg, 6 weeks	Open-label noncontrolled drug study	9 (75%)	Improvements in all sexual Function domains	Aviv et al. (2004)

17. Prolactin levels	Olanzapine, risperidone, and conventional antipsychotic	270 (177 men, 93 women)	Switch to ziprasidone (40–160 mg/day), 6 weeks	Open label	205 (76%)	Prolactin levels decreased among those switched from risperidone or conventional, but not for patients switched from olanzapine	Weiden et al. (2003)
18. Erectile dysfunction	Olanzapine	10 men	Sildenafil 50–100 mg, 4 weeks	Noncontrolled open-label study	10 (100%)	Sildenafil use is effective and well-tolerated in patients with olanzapine-induced ED	Amaca et al. (2002)
19. Menstrual disturbances, galactorrhea, and/or sexual dysfunction	Risperidone	20 women	Switch from risperidone to olanzapine (5–20 mg/day), 10 weeks	Noncontrolled open-label study	20 (100%)	Reversed hyperprolactinemia, decrease in amenorrhea, improved cycle regularity, and a decrease in sexual side effects.	Kim et al. (2002)
20. Sexual drive, erection, ejaculation, and satisfaction with sexual performance	First-generation antipsychotics (haloperidol, thioridazine, fluphenazine, propericiazine)	12 men	Amantadine 100 mg/day, 6 weeks	Open-label noncontrolled drug study	12 (100%)	Improvement in all events evaluated except ejaculation. Decreased serum prolactin.	Valevski et al. (1998)
21. Hyperprolactinemia and sexual dysfunction	Neuroleptic	20 men	Shakuyaku-kanzo-to (TJ-68) 7.5 g, 8 weeks	Noncontrolled open-label study	20 (100%)	Decreased prolactin levels in 5 patients, improvement in sexual desire	Yamada et al. (1997)
22. Orgasmic	Thioridazine	8 men	Imipramine 25–50 mg/day, 2 weeks	Open-label noncontrolled drug study	8 (100%)	50% returned to previous ejaculatory function	Aizenberg et al. (1996)

(Continued on next page)

**TABLE 2.** Open-Labels Studies for the Treatment of Antipsychotic-Induced Sexual Dysfunction and Hyperprolactinemia (*Continued*)

Sexual dysfunction	Induced by	Number of patients and gender	Therapy, dose, and duration	Study design	Number of participants who completed the study (%)	Primary outcome	Author and year
23. Hyperprolactinemia	Neuroleptic	10 (4 women, 6 men)	Amantadine 200–300 mg/day, 7 weeks	Open-label reversal drug study	10 (100%)	Improvement on parameters: serum prolactin levels, body weight, gynecomas-tia/galactorrhea, breast tenderness, decreased libido, and amenorrhea	Correa et al. (1987)
24. Amenorrhea, galactorrhea, and impotence	First-generation antipsychotics, on the basis of the date of the study	35 (24 women, 11 men)	Bromocriptine 5.0–7.5 mg/day	Open-label noncontrolled drug study		Return of menstrual cycle in 70%, relief of galactorrhea in 80% and improvement of impotence in 66%	Matsuoka et al. (1986)
25. Erection, ejaculation, libido, amenorrhea, galactorrhea, and weight change	Fluphenazine, pipotiazine, levomepromazine, cyamemazine, sulphiride	30 (20 women, 10 men)	Bromocriptine 5–10 mg/day	Open-label noncontrolled drug study	30 (100%)	Decreased serum prolactin, weight loss, normalization of menstrual cycle, relief in galactorrhea, and little improvement of erectile and ejaculatory dysfunction	Beau and Guillard (1980)

*Note.* ASEX = Arizona Sexual Experiences Scale.

randomized, double-blind, placebo-controlled, flexible-dose, two-way crossover trial. Thirty-one patients reported significant improvement while taking sildenafil in the number of adequate erections, satisfaction with sexual intercourse, and the duration of erections over 2 weeks.

Kodesh et al. (2003) conducted a double-blind, placebo-controlled crossover study in Israel with selegiline. It was undertaken in 10 neuroleptic-treated male schizophrenic outpatients to assess the effect of coadministration of selegiline 15 mg/day 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.

Lee et al. (1995) conducted a 6-week double-blind placebo-controlled trial of cyproheptadine augmentation of ongoing haloperidol treatment in 40 chronic schizophrenic in-patients. As to the neuroendocrinological effect, cyproheptadine augmentation did not reduce the plasma prolactin level.

Shim et al. (2007) investigated the effect of adjunctive treatment with aripiprazole on hyperprolactinemia and psychopathology in patients with schizophrenia maintained with haloperidol in a randomized, double-blind placebo controlled trial. Adjunctive aripiprazole treatment reversed hyperprolactinemia in both genders, resulting in reinstatement of menstruation in female patient.

There were open labels for treatment as an additional medication to antipsychotic-induced sexual dysfunction that included other medications, such as aripiprazole (Chen et al., 2009; Yasui-Furukori, Furukori, Sugawara, Fujii, & Kaneko, 2010); other phosphodiesterase-5 inhibitors, such as vardenafil (Mitsonis et al., 2008), peony-glycyrrhiza-decoction (Yuan et al., 2008); carbegoline (Cavallaro, Cocchi, Angelone, Lattuada, & Smeraldi, 2004); amantadine (Correa, Opler, Kay, & Birmasher, 1987; Valevski, Modai, Zbarski, Zemishlany, & Weizman, 1998); shakuyaku-kanzo-to (Yamada, Kanba, Yagi, & Asai, 1997); and imipramine (Aizenberg, Shiloh, Zemishlany, & Weizman, 1996); all of them showed improvement in sexual functioning and/or hormonal profile. The studies had a small sample size ( $\leq 30$  patients) and they were conducted for a short period of time ( $< 3$  months).

### Management with Switch to Other Antipsychotic

Two randomized double-blind studies have evaluated the effect of switching to quetiapine versus risperidone continuation on sexual functioning.

In a randomized, 6-week, double-blind study of 42 outpatients with schizophrenia or schizoaffective disorder who experienced risperidone associated sexual dysfunction, the authors evaluated the effect of switching to quetiapine versus risperidone continuation on sexual functioning. In this pilot trial, sexual functioning did not differ significantly between outpatients receiving quetiapine switch versus risperidone continuation, although the

quetiapine switch group had slightly lower adjusted mean ASEX total scores at Weeks 2 and 6 (Byerly et al., 2008).

Other study of management with switch to other antipsychotic examined the relation between serum prolactin level and sexual functioning in a 6-week randomized double-blind trial among 22 male outpatients and used a validated instrument (ASEX) to measure sexual functioning. The study showed a higher serum prolactin level and a greater impairment of sexual functioning in male outpatients who were treated with risperidone but not with quetiapine (Nakonezny et al., 2007).

The open-label studies that described the switch to antipsychotic with a better profile involved the switch to aripiprazole (Byerly et al., 2009; Lee, Kim, & Park, 2006; Lu, Shen, & Chen, 2008; Mir et al., 2008), ziprasidone (Montejo & Rico-Villademoros, 2008; Weiden, Daniel, Simpson, & Steven, 2003), olanzapine (Kaneda, Kawamura, Fujii, & Ohmori, 2004; Kim et al., 2002; Kinon, Ahl, Liu-Seifert, & Maguire, 2006; Lin, Wu, Pariante, & Su, 2006), and quetiapine (Byerly et al., 2004; Nakajima, Terao, Iwata, & Nakamura, 2005). All of them showed improvement in sexual function and/or prolactin levels, but few had adequate sample sizes. The switch to antipsychotic aripiprazole was the most studied strategy, and it is a promising strategy.

## DISCUSSION

In this review, we found only few randomized double-blind, controlled studies that have treated antipsychotic-induced sexual dysfunctions and/or hyperprolactinemia that represent a high level of evidence. The well-conducted studies with adjunctive treatment that showed improvement in sexual dysfunction and/or decrease of prolactin levels were sildenafil (Gopalakrishnan et al., 2006) and aripiprazole (Shim et al., 2007). The medication selegiline (Kodesh et al., 2003) and cyproheptadine (Lee et al., 1995) did not improve sexual functioning. Two randomized trials in the literature included the switch of risperidone to quetiapine. The switch to quetiapine has demonstrated that one study showed improvement in the primary outcome (Nakonezny et al., 2007), and the other did not show improvement for sexual functioning (Byerly et al., 2008).

Furthermore, the majority of studies had short periods of time of evaluation and small sample sizes. The sildenafil (Gopalakrishnan et al., 2006) and the selegiline (Kodesh et al., 2003) studies were crossover studies, which are not the best ones for evaluation of sexual dysfunction. The crossover studies are best for conditions that are stable and for interventions with no psychological carryover (Berner, Hagen, & Kriston, 2007).

The only randomized, placebo-controlled trial with sildenafil (Gopalakrishnan et al., 2006) showed good evidence. The researchers reported

that this drug is an effective treatment of antipsychotic-induced sexual dysfunction in men with increasing number of erections sufficient for penetration, the mean duration of erections, and the frequency of satisfactory intercourse. The majority of the patients completed the trial (96.9%). The study included outpatients in India and there is no indication that problems differ by region or race (Tharyan & Gopalakrishan, 2006). The study did not report on adverse effects. It is, therefore, impossible to tell how safe sildenafil is when added to antipsychotic drugs. The study did not have washout between treatment periods. There were two open-label noncontrolled studies that described the use of sildenafil in patients with schizophrenia and showed improvement in sexual function (Atmaca, Kuloglu, & Tezcan, 2002; Aviv, Shelef, & Weizman, 2004). Although the studies in this review were important, they have limited data to be source of robust evidence.

The only double-blind placebo-controlled trial found in the literature with selegiline did not show any effectiveness in improving sexual functioning, despite a significant decrease in prolactin levels (Kodesh et al., 2003). The comparison of selegiline and placebo contained only one sample size of 10 patients, and the study was conducted across only 3 weeks. Selegiline did not lead to more likely adverse effects than did placebo as regards to extrapyramidal movement disorders and exacerbation of schizophrenic symptoms.

There was one double-blind placebo-controlled trial (Lee et al., 1995) with the use of cyproheptadine in 46 patients in use of haloperidol that had high prolactin levels, and the augmentation did not reduce the plasma prolactin level.

Adjunctive treatment with low-dosage aripiprazole has been widely reported as effective for the treatment of antipsychotic-induced hyperprolactinemia (Ishitobi, Kosaka, Shukunami, Murata, & Wada, 2010; Kane et al., 2007). Adjunctive or switch to aripiprazole had satisfactory response in the following studies: Byerly et al., 2009; Chen et al., 2009; Lee et al., 2006; Lu et al., 2008; Mir et al., 2008; Shim et al., 2007; and Yasui-Furukori et al., 2010.

There are few open labels that studied bromocriptine in sexual dysfunction and/or hyperprolactinemia (Beau & Guillard, 1980; Matsuoka, Nakai, Miyake, Hirai, & Ikawa, 1986) and all had satisfactory results, but small sample sizes. Further evidence is needed to confirm these findings.

Several case reports and small studies have been published, mostly in the Japanese literature, describing the use of herbal supplements in the treatment of hyperprolactinemia associated with antipsychotics (Wehring & Kelly, 2009). There are very small, noncontrolled, open-labels that described the use of shakuyaku-kanzo-to (TJ-68) and peony-glycyrrhiza decoction and found reduction in prolactin levels and hormonal side effects.

There was a lack of high level evidence on the use of amantadine, imipramine, and carbegoline for the treatment of antipsychotic-induced



sexual dysfunction. In this systematic review, there are only open-label noncontrolled studies that used these medications, all of them with very small sample sizes (fewer than 20 patients).

In terms of limitations of our review, the extensive search was planned to be highly sensitive, however, we may have failed to find some relevant publications. There were three articles in Chinese and one in Polish that we excluded, so the information was limited to articles written only in English, Spanish, Portuguese, or French. We also excluded meeting abstracts. We did not search for psychological treatment or therapy for sexual dysfunction and/or hyperprolactinemia, and we know the effectiveness of these techniques in clinical practice.

Although the more favorable benefit–risk ratio of the new antipsychotics represents a major improvement over the older neuroleptics, differences need to be addressed and more clearly documented. There was a lack of randomized controlled trials on the clinical management of antipsychotic-induced sexual dysfunction in the literature, and no proper comparisons of the efficacy of agents (Costa, Lima, & Mari, 2006).

### Implications for Actions

Researchers should investigate studies involving patients who are on antipsychotic drugs and who present with difficulties in obtaining sexual functioning. Then, the dosage of antipsychotic may be reduced or the antipsychotic can be switched to another one with better sexual profile as quetiapine or adjunctive treatments can be associated.

The adjunctive treatments that have been reported as effective for the management of antipsychotic-induced sexual dysfunction were sildenafil and aripiprazol. To reduce hyperprolactinemia, which is induced by antipsychotic treatment, the studies suggest adjunctive treatment with low dosage of aripiprazole because of its partial agonistic actions to dopamine D2 receptor with high affinity. For men with schizophrenia who take antipsychotic medication and who experience erectile dysfunction, the use of phosphodiesterase-5 inhibitors may be useful treatment options as additional medication. Men should be aware that this conclusion is based on such limited data and that long-term effects are unknown.

### Conclusion

This reviewed data has suggested that the management of antipsychotic-induced sexual dysfunction and/or hyperprolactinemia should be treated with attention, different antipsychotics agents lead to different sexual dysfunction risk. The use of adjunctive treatment or switching to other antipsychotics can benefit sexual dysfunction among patients receiving antipsychotics.

The use of adjunctive medication for the treatment of sexual dysfunction in patients with schizophrenia currently appear to be either initiating treatment with prolactin-sparing antipsychotics, switching to antipsychotic with a better profile (as quetiapine) or decreasing prolactin levels through the use of dopamine agonists such as aripiprazole. The use of phosphodiesterase-5 inhibitors may be useful for patients with erectile dysfunction, or cases with a less clear association between sexual dysfunction and elevated prolactin, particularly in men who smoke or have clinical diseases such as diabetes.

We should be cautious in the management of patients with sexual dysfunction receiving antipsychotic agents. It is necessary to mention that only small open-label studies and a few small, randomized, placebo-controlled studies have been published. Randomized controlled trials are needed to provide evidence for the effects of different strategies: dose reduction, adjunctive treatment, and switching. The outcomes must include data on quality of life, partner satisfaction with the intervention, and economic outcomes. The trials are necessary in order to have a better compliance and reduce the distress among patients with schizophrenia.

## REFERENCES

- Aizenberg, D., Modai, I., Landa, A., Gil-Ad, I., & Weizman, A. (2001). Comparison of sexual dysfunction in male schizophrenic patients maintained on treatment with classical antipsychotics versus clozapine. *Journal of Clinical Psychiatry*, *62*, 541–544.
- Aizenberg, D., Shiloh, R., Zemishlany, Z., & Weizman, A. (1996). Low-dose imipramine for thioridazine-induced male orgasmic disorder. *Journal of Sex & Marital Therapy*, *22*, 225–229.
- Atmaca, M., Kuloglu, M., & Tezcan, E. (2002). Sildenafil use in patients with olanzapine-induced erectile dysfunction. *International Journal of Impotence Research*, *14*, 547–549.
- Aviv, A., Shelef, A., & Weizman, A. (2004). An open-label trial of sildenafil addition in risperidone-treated male schizophrenia patients with erectile dysfunction. *Journal of Clinical Psychiatry*, *65*(1), 97–103.
- Beau, Y., & Guillard, P. (1980). Essai de traitement par la bromocriptine des effets secondaires endocriniens des traitements psychotropes [Trial therapy with bromocriptine of secondary endocrine effects after psychotropic treatment]. *Annales Medico-Psychologiques*, *138*, 179–186.
- Berner, M., Hagen, M., & Kriston, L. (2006). A systematic review of research on strategies for the management of antipsychotic-induced sexual dysfunction: High level evidence is needed. *Journal of Clinical Psychiatry*, *67*, 1649–1650.
- Berner, M., Hagen, M., & Kriston, L. (2007). Management of sexual dysfunction due to antipsychotic drug therapy. *Cochrane Database of Systematic Reviews*, *1*. doi: 10.1002/14651858.CD003546.pub2.
- Bobes, J., Garcia-Portilla, M. P., Rejas, J., Hernandez, G., Garcia-Garcia, M., Rico-Villademoros, F., & Porras, A. (2003). Frequency of sexual dysfunction and other

- reproductive side effects in patients with schizophrenia treated with risperidone, olanzapine, quetiapine, or haloperidol. *Journal of Sex & Marital Therapy*, *29*, 125–147.
- Byerly, M., Lescoufflair, E., Weber, M. T., Bugno, R. M., Fisher, R., Carmody, T., . . . Rush, A. J. (2004). An open-label trial of quetiapine for antipsychotic-induced sexual dysfunction. *Journal of Sex & Marital Therapy*, *30*, 325–332.
- Byerly, M., Marcus, R. N., Tran, Q. V., Eudicone, J. M., Whitehead, R., & Baker, R. A. (2009). Effects of aripiprazole on prolactin levels in subjects with schizophrenia during cross-titration with risperidone or olanzapine: Analysis of a randomized, open-label study. *Schizophrenia Research*, *107*, 218–222.
- Byerly, M., Nakonezny, P., Bettcher, B., Carmody, T., Fisher, R., & Rush, A. J. (2006). Sexual dysfunction associated with second-generation antipsychotics in outpatients with schizophrenia or schizoaffective disorder: An empirical evaluation of olanzapine, risperidone, and quetiapine. *Schizophrenia Research*, *86*, 244–250.
- Byerly, M., Nakonezny, P., & Rush, A. J. (2008). Sexual functioning associated with quetiapine switch vs. risperidone continuation in outpatients with schizophrenia or schizoaffective disorder: A randomized double-blind pilot trial. *Psychiatry Research*, *159*, 115–120.
- Cavallaro, R., Cocchi, F., Angelone, S. M., Lattuada, E., & Smeraldi, E. (2004). Cabergoline treatment of risperidone-induced hyperprolactinemia: A pilot study. *Journal of Clinical Psychiatry*, *65*, 1429–1431.
- Chen, J. X., Su, Y. A., Wang, S. L., Bian, Q. T., Liu, Y. H., Wang, N., . . . Zhang, X. Y. (2009). Aripiprazole treatment of risperidone-induced hyperprolactinemia. *Journal of Clinical Psychiatry*, *70*, 1058–1059.
- Correa, N., Opler, L. A., Kay, S. R., & Birmasher, B. (1987). Amantadine in the treatment of neuroendocrine side effects of neuroleptics. *Journal of Clinical Psychopharmacology*, *7*(2), 91–95.
- Costa, A. M. N., Lima, M. S., Faria, M., Filho, S. R., Oliveira, I. R., Mari, J. J. (2007). A naturalistic, 9-month follow-up, comparing olanzapine and conventional antipsychotics on sexual function and hormonal profile for males with schizophrenia. *Psychopharmacology*, *21*, 165–170.
- Costa, A. M. N., Lima, M. S., & Mari, J. J. (2006). A systematic review on clinical management of antipsychotic-induced sexual dysfunction in schizophrenia. *São Paulo Medical Journal*, *124*, 291–297.
- Cutler, A. J. (2003). Sexual dysfunction and antipsychotic treatment. *Psychoneuroendocrinology*, *28*, 69–82.
- Gonzalez, A. L. M., Villademoros, R., & Tafalla, M. (2005). A 6-month prospective observational study on the effects of quetiapine on sexual functioning. *Journal of Clinical Psychopharmacology*, *25*, 533–538.
- Gopalakrishnan, R., Jacob, K. S., Kuruvilla, A., Vasantharaj, B., & John, J. K. (2006). Sildenafil in the treatment of antipsychotic-induced erectile dysfunction: A randomized, double-blind, placebo-controlled, flexible-dose, two-way crossover trial. *The American Journal of Psychiatry*, *163*, 494–499.
- Haddad, P. M., & Sharma, S. G. (2007). Adverse effects of atypical antipsychotics. *CNS Drugs*, *21*, 911–936.
- Haddad, P. M., & Wieck, A. (2004). Antipsychotic-induced hyperprolactinaemia: Mechanisms, clinical features and management. *Drugs*, *64*, 2291–2314.

- Haro, J. M., & Carulla, L. S. (2006). The SOHO (Schizophrenia Outpatient Health Outcome) study: Implications for the treatment of schizophrenia. *CNS Drugs*, *20*, 293–301.
- Heald, A. (2010). Physical health in schizophrenia: A challenge for antipsychotic therapy. *European Psychiatry*, *25*, S6–S11.
- Heald, A., Montejo, A. L., Millar, H., De Hert, M., McCrae, J., & Correll, C. U. (2010). Management of physical health in patients with schizophrenia: practical recommendations. *European Psychiatry*, *25*, S41–S45.
- Ishitobi, M., Kosaka, H., Shukunami, K., Murata, T., & Wada, Y. (2010). Adjunctive treatment with low-dosage aripiprazole for blonanserin-induced hyperprolactinemia in a female patient with schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *34*, 1361–1362.
- Kane, J. M., Meltzer, H. Y., Carson, W. H., McQuade, R. D., Marcus, R. N., & Sanchez, R. (2007). Aripiprazole for treatment resistant schizophrenia: Results of a multicenter, randomized, double-blind, comparison study versus fluphenazine. *Journal of Clinical Psychiatry*, *68*, 213–223.
- Kaneda, Y., Kawamura, I., Fujii, A., & Ohmori, T. (2004). Impact of a switch from typical to atypical antipsychotic drugs on quality of life and gonadal hormones in male patients with schizophrenia. *Neuroendocrinology Letters*, *25*(1–2), 35–40.
- Kelly, D. L., & Conley, R. R. (2006). A randomized double-blind 12-week study of quetiapine, risperidone or fluphenazine on sexual functioning in people with schizophrenia. *Psychoneuroendocrinology*, *31*, 340–346.
- Kim, K. S., Pae, C. U., Chae, J. H., Bahk, W. M., Jun, T. Y., Kim, D. J., & Dickson, R. A. (2002). Effects of olanzapine on prolactin levels of female patients with schizophrenia treated with risperidone. *Journal of Clinical Psychiatry*, *63*, 408–413.
- Kinon, B. J., Ahl, J., Liu-Seifert, H., & Maguire, G. A. (2006). Improvement in hyperprolactinemia and reproductive comorbidities in patients with schizophrenia switched from conventional antipsychotics or risperidone to olanzapine. *Psychoneuroendocrinology*, *31*, 577–588.
- Knegtering, H., van den Bosch, R., Castelein, S., Bruggeman, R., Sytema, S., & van Os, J. (2008). Are sexual side effects of prolactin-raising antipsychotics reducible to serum prolactin? *Psychoneuroendocrinology*, *33*, 711–717.
- Kodesh, A., Weizman, A., Aizenberg, D., Hermesh, H., Gelkopf, M., & Zemishlany, Z. (2003). Selegiline in the treatment of sexual dysfunction in schizophrenic patients maintained on neuroleptics: A pilot study. *Clinical Neuropharmacology*, *26*, 193–195.
- Lambert, M., Conus, P., Eide, P., Mass, R., Karow, A., & Moritz, S. (2004). Impact of present and past antipsychotic side effects on attitude toward typical antipsychotic treatment and adherence. *European Psychiatry*, *19*, 415–422.
- Lambert, M., Haro, J. M., Novik, D., Edgell, E., Kennedy, L., Ratcliffe, M., & Naber, D. (2005). Olanzapine vs other antipsychotics in actual out-patient settings: Six months tolerability results from the European schizophrenia out-patient health outcomes study. *Acta Neuropsychiatrica Scandinavica*, *111*, 232–243.
- Laumann, E. O., Paik, A., & Posen, R. C. (1999). Sexual dysfunction in the United States: Prevalence and predictors. *JAMA*, *281*, 537–554.

- Lee, B. H., Kim, Y. K., & Park, S. H. (2006). Using aripiprazole to resolve antipsychotic-induced symptomatic hyperprolactinemia: A pilot study. *Progress in Neuro-Psychopharmacology and Biological*, *30*, 714–717.
- Lee, H. S., Song, D. H., Kim, J. H., Lee, Y. M., Han, E. S., & Yoo, K. J. (1995). Cyproheptadine augmentation of haloperidol in chronic schizophrenic patients: A double-blind placebo-controlled study. *International Clinical Psychopharmacology*, *10*(2), 67–72.
- Lin, C. Y., Wu, P. L., Pariante, C. M., & Su, K. P. (2006). A crossover study of prolactin changes associated with risperidone and olanzapine. *Journal of Clinical Psychiatry*, *67*, 1470–1471.
- Lu, M. L., Shen, W. W., & Chen, C. H. (2008). Time course of the changes in antipsychotic-induced hyperprolactinemia following the switch to aripiprazole. *Progress in Neuro-Psychopharmacology and Biological*, *32*, 1978–1981.
- MacDonald, S., Halliday, J., MacEvan, T., Sharkey, V., Farrington, S., Wall, S., & McCreadie, R. G. (2003). Nithsdale Schizophrenia Surveys 24: Sexual dysfunction: Case-control study. *The British Journal of Psychiatry*, *182*, 50–56.
- Matsuoka, I., Nakai, T., Miyake, M., Hirai, M., & Ikawa, G. (1986). Effects of bromocriptine on neuroleptic-induced amenorrhea, galactorrhea and impotence. *Journal of Psychiatric & Neurology*, *40*, 639–646.
- Mir, A., Shivakumar, K., Williamson, R. J., McAllister, V., O'Keane, V., & Aitchison, K. J. (2008). Change in sexual dysfunction with aripiprazole: A switching or add-on study. *Journal of Psychopharmacology*, *22*, 244–253.
- Mitsonis, C. I., Mitropoulos, P. A., Dimopoulos, N. P., Kararizou, E. G., Psarra, V. V., Tsakiris, F. E., & Katsanou, M. N. (2008). Vardenafil in the treatment of erectile dysfunction in outpatients with chronic schizophrenia: A flexible-dose, open-label study. *Journal of Clinical Psychiatry*, *69*, 206–212.
- Montejo, A. L., & Rico-Villademoros, F. (2008). Changes in sexual function for outpatients with schizophrenia or other psychotic disorders treated with ziprasidone in clinical practice settings: A 3-month prospective, observational study. *Journal of Clinical Psychopharmacology*, *28*, 568–570.
- Nakajima, M., Terao, T., Iwata, N., & Nakamura, J. (2005). Switching female schizophrenic patients to quetiapine from conventional antipsychotic drugs: Effects on hyperprolactinemia. *Pharmacopsychiatry*, *38*(1), 17–19.
- Nakonezny, P. A., Byerly, M. J., & Rush, A. J. (2007). The relationship between serum prolactin level and sexual functioning among male outpatients with schizophrenia or schizoaffective disorder: A randomized double-blind trial of risperidone vs. quetiapine. *Journal of Sex & Marital Therapy*, *33*, 203–216.
- Olfson, M., Uttaro, T., Carson, W. H., & Tafesse, E. (2005). Male sexual dysfunction and quality of life in Schizophrenia. *Journal of Clinical Psychiatry*, *66*, 331–338.
- Peuskens, J., Sienaert, P., & De Hert, M. (1998). Sexual dysfunction: The unspoken side effects of antipsychotics. *European Psychiatry*, *13*(Suppl. 1), 23–30.
- Rosenberg, K. P., Bleiberg, K. L., Koscis, J., & Gross, C. (2003). A survey of sexual side effects among severely mental ill patients taking psychotropic medication: Impact on compliance. *Journal of Sex & Marital Therapy*, *29*, 289–296.
- Shim, J. C., Kelly, D. L., Jung, D. U., Seo, Y. S., Liu, K. H., Shon, J. H., & Conley, R. R. (2007). Adjunctive treatment with a dopamine partial agonist, aripiprazole, for antipsychotic-induced hyperprolactinemia: a placebo-controlled trial. *The American Journal of Psychiatry*, *164*(9), 1404–1410.

- Tharyan, P., & Gopalakrishnan, G. (2006). Erectile dysfunction. *BMJ Clinical Evidence*, *15*, 1227–1251.
- Uçok, A., Incesu, C., Aker, T., & Erkoç, S. (2007). Sexual dysfunction in patients with schizophrenia on antipsychotic medication. *European Psychiatry*, *22*, 328–333.
- Uçok, A., Incesu, C., Aker, T., & Erkoç, S. (2008). Do psychiatrists examine sexual dysfunction in schizophrenia patients? *Journal of Sexual Medicine*, *5*, 2000–2001.
- Valevski, A., Modai, I., Zbarski, E., Zemishlany, Z., & Weizman, A. (1998). Effect of amantadine on sexual dysfunction in neuroleptic-treated male schizophrenic patients. *Clinical Neuropharmacology*, *21*, 355–357.
- Van Bruggen, M., Amelvoort, T., Wouters, L., Dingemans, P., Haan, L., & Linszen, D. (2009). Sexual dysfunction and hormonal changes in first episode psychosis patients on olanzapine or risperidone. *Psychoneuroendocrinology*, *34*, 989–995.
- Volavka, J., Czobor, P., Cooper, T. B., Sheitman, B., Lindenmayer, J. P., Citrome, L., & Lieberman, J. A. (2004). Prolactin levels in schizophrenia and schizoaffective disorders patients treated with clozapine, olanzapine, risperidone, or haloperidol. *Journal of Clinical Psychiatry*, *65*, 57–61.
- Wehring, H., & Kelly, D. L. (2009). Sexual dysfunction and schizophrenia. In J. M. Meyer & H. D. Nasrallah (Eds.), *Medical illness and schizophrenia* (2nd ed., pp. 303–342). Washington, DC: American Psychiatric Publishing.
- Weiden, P. J., Daniel, D. G., Simpson, G. R., & Steven J. (2003). Improvement in indices of health status in outpatients with schizophrenia switched to ziprasidone. *Journal of Clinical Psychopharmacology*, *23*, 595–600.
- Yamada, K., Kanba, S., Yagi, G., & Asai, M. (1997). Effectiveness of herbal medicine (Shakuyaku-kanzo-to) for neuroleptic-induced hyperprolactinemia. *Journal of Clinical Psychopharmacology*, *17*, 234–235.
- Yasui-Furukori, N., Furukori, H., Sugawara, N., Fujii, A., & Kaneko, S. (2010). Dose-dependent effects of adjunctive treatment with aripiprazole on hyperprolactinemia induced by risperidone in female patients with schizophrenia. *Journal of Clinical Psychopharmacology*, *30*, 596–599.
- Yuan, H. N., Wang, C. Y., Sze, C. W., Tong, Y., Tan, Q. R., Feng, X. J., . . . Zhang, Z. J. (2008). A randomized, crossover comparison of herbal medicine and bromocriptine against risperidone-induced hyperprolactinemia in patients with schizophrenia. *Journal of Clinical Psychopharmacology*, *28*, 264–370.
- Zemishlany, Z., & Weizman, A. (2008). The impact of mental illness on sexual dysfunction. *Advances in Psychosomatic Medicine*, *29*, 89–106.