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...
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 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, galactorrhea 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 included 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/lubrification, 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, molindone, olanzapine, perphenidol, perazine, pericyazine, pimozide, pipamperone, promazine, prothipendyl, quetiapine, reserpine, risperidone, sulpiride, thioridazine, trifluoperazine, trifluperidol, 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, tadalaflil, 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, Vasanharaj, & 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

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Scale used</th>
<th>Prolactin levels</th>
<th>Induced by</th>
<th>Study design</th>
<th>Duration (weeks)</th>
<th>N</th>
<th>Mean age (years)</th>
<th>Diagnosis</th>
<th>Intervention</th>
<th>Participants who completed the study</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byerly et al. (2008)</td>
<td>ASEX scale (sexual drive, arousal, penis erection/vaginal lubrication, ability to reach orgasm, and satisfaction with orgasm)</td>
<td>Risperidone</td>
<td>Randomized double-blind, pilot trial</td>
<td>6</td>
<td>42 (22 men, 20 women)</td>
<td>42.3</td>
<td>Schizophrenia or schizoaffective disorder</td>
<td>1. Switch to quetiapine, mean dose 280 mg/day 2. Risperidone continuation, 4.1 mg/day</td>
<td>100%</td>
<td>Sexual functioning measured by ASEX scale did not differ significantly between quetiapine switch versus risperidone continuation</td>
<td></td>
</tr>
<tr>
<td>Nakonezny et al. (2007)</td>
<td>ASEX scale (sexual drive, arousal, penis erection/vaginal lubrication, ability to reach orgasm, and satisfaction with orgasm)</td>
<td>Risperidone</td>
<td>Randomized double-blind, pilot trial</td>
<td>6</td>
<td>22 men</td>
<td>40.8</td>
<td>Schizophrenia or schizoaffective disorder</td>
<td>1. Switch to quetiapine, mean dose 280 mg/day 2. Risperidone continuation, 4.1 mg/day</td>
<td>100%</td>
<td>Higher serum prolactin level was related to greater impairment of sexual functioning in male outpatients who were treated with risperidone but not with quetiapine</td>
<td></td>
</tr>
<tr>
<td>Shim et al. (2007)</td>
<td>Prolactin-Related Adverse Event Questionnaire (menstrual disturbances and galactorrhea)</td>
<td>Hyperprolactinemia prolactin levels</td>
<td>Haloperidol</td>
<td>Randomized, double-blind, placebo controlled trial at Inje University</td>
<td>8</td>
<td>54 (22 men, 32 women)</td>
<td>39.5</td>
<td>Schizophrenia</td>
<td>1. Adjunctive aripiprazole, 15–30 mg/day 2. Placebo as adjunctive treatment</td>
<td>96.2%</td>
<td>Adjunctive aripiprazole led to prolactin level normalization in 81.6% of patients, resulting in reinstatement of menstruation in women</td>
</tr>
<tr>
<td>Study (Year)</td>
<td>Measure 1</td>
<td>Measure 2</td>
<td>Methodology</td>
<td>N</td>
<td>Diagnosis</td>
<td>Treatment 1</td>
<td>Treatment 2</td>
<td>Improvement in Sexual Function</td>
<td></td>
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<tr>
<td>Gopalakrishnan et al. (2006)</td>
<td>International Index of Erectile Function</td>
<td>Erectile dysfunction</td>
<td>Risperidone, olanzapine, clozapine, fluphenazine decanoate</td>
<td>2</td>
<td>32 men</td>
<td>35.1 Schizophrenia or delusional disorder</td>
<td>1. Adjunctive sildenafil, 25-50 mg 2. Placebo</td>
<td>96.9% Improvement in number and mean duration of erections and in combined number of satisfactory times of intercourse</td>
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<tr>
<td>Kodesh et al. (2003)</td>
<td>Sexual Functioning Scale (sexual drive, arousal, penis erection/vaginal lubrication, ability to reach orgasm, and satisfaction with orgasm)</td>
<td>Prolactin serum levels</td>
<td>Perphenazine or haloperidol</td>
<td>3</td>
<td>10 men</td>
<td>44.8 Schizophrenia</td>
<td>1. Selegiline, 15 mg/day as adjunctive treatment 2. Placebo</td>
<td>100% It was not found to be effective in improving any domain of sexual functioning, despite a significant decrease in prolactin levels</td>
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<tr>
<td>Lee et al. (1995)</td>
<td>Prolactin levels</td>
<td>Haloperidol</td>
<td>Double-blind placebo controlled trial</td>
<td>6</td>
<td>40 (20 men, 20 women)</td>
<td>34 Schizophrenia</td>
<td>1. Cyproheptadine, 24 mg/day 2. Placebo</td>
<td>87% Cyproheptadine augmentation did not reduce the plasma prolactin level but did induce a decrease in the plasma cortisol level</td>
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</tbody>
</table>

Note: ASEX = Arizona Sexual Experiences Scale.

1 Determined by the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.).
2 Determined by the International Classification of Diseases-10.
3 Original number of participants was 46; however, 6 dropped out, yielding 40 participants.
<table>
<thead>
<tr>
<th>Sexual dysfunction</th>
<th>Induced by</th>
<th>Number of patients and gender</th>
<th>Therapy, dose, and duration</th>
<th>Study design</th>
<th>Number of participants who completed the study (%)</th>
<th>Primary outcome</th>
<th>Author and year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hyperprolactinemia</td>
<td>Risperidone</td>
<td>16 women</td>
<td>Adjunctive treatment with aripiprazole, 3–12 mg/day</td>
<td>Open-label study</td>
<td>12 (100%)</td>
<td>Aripiprazole reduces the prolactin levels</td>
<td>Yasui-Furukori et al. (2010)</td>
</tr>
<tr>
<td>2. Hyperprolactinemia</td>
<td>Risperidone</td>
<td>21 men</td>
<td>Adjunctive aripiprazole, 10 mg</td>
<td>Open-label study</td>
<td>19 (90.4%)</td>
<td>Aripiprazole reduces the prolactin levels</td>
<td>Chen et al. (2009)</td>
</tr>
<tr>
<td>3. Hyperprolactinemia</td>
<td>Risperidone, olanzapine</td>
<td>269 men and women</td>
<td>Switch from risperidone or olanzapine to aripiprazol (10–30 mg/day), 8 weeks</td>
<td>Randomized open-label study</td>
<td>199 (74%)</td>
<td>Mean prolactin levels decreased significantly</td>
<td>Byerly et al. (2009)</td>
</tr>
<tr>
<td>4. Libido, erectile, ejaculatory, menstrual dysfunction, satisfaction in overall sexual functioning, and hyperprolactinemia</td>
<td>Antipsychotic (not aripiprazole)</td>
<td>27 (14 men, 13 women)</td>
<td>Switch to aripiprazole or the addition of aripiprazole (15–30 mg/day) to another antipsychotic regime, 26 weeks</td>
<td>Open-label study</td>
<td>22 (81%)</td>
<td>Improvement in sexual performance and reduction in prolactin</td>
<td>Mir et al. (2008)</td>
</tr>
<tr>
<td>5. Hyperprolactinemia</td>
<td>Risperidone, sulpiride</td>
<td>23 women</td>
<td>Switch from risperidone or sulpiride to aripiprazol (10–30 mg/day), 4 weeks</td>
<td>Open-label noncontrolled drug study</td>
<td>20 (87%)</td>
<td>Reduced serum prolactin levels and restoring menstruation</td>
<td>Lu et al. (2008)</td>
</tr>
<tr>
<td>6. Hyperprolactinemia, oligomenorrhea, or amenorrhea</td>
<td>Risperidone</td>
<td>20 women</td>
<td>Peony-glycyrrhiza decoction with bromocriptine for 4 weeks each, with an interval of 4-week washout period</td>
<td>Randomized crossover study</td>
<td>2 (90%)</td>
<td>Peony-glycyrrhiza decoction treatment produced a significant decrease in serum Prolactin levels</td>
<td>Yuan et al. (2008)</td>
</tr>
<tr>
<td>7. Sexual dysfunction of any type</td>
<td>Antipsychotics (the most frequent were risperidone and olanzapine)</td>
<td>41 patients</td>
<td>Switch to ziprasidone, mean dose of 140 mg/day, 3 months</td>
<td>Multicenter, non-comparative observational, and naturalistic study</td>
<td>41 (100%)</td>
<td>Normalization on sexual function. 50% of patients had much or very much improvement on sexual function and 24% a slight improvement</td>
<td>Montejo and Rico-Villademoros (2008)</td>
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<td>8. Erectile dysfunction</td>
<td>Clozapine, risperidone, amisulpride, olanzapine, haloperidol, aripiprazole</td>
<td>25 men</td>
<td>Vardenafil 5–20 mg/day, 12 weeks</td>
<td>Flexible-dose open-label study</td>
<td>21 (84%)</td>
<td>Improvement in sexual function and in quality of life</td>
<td>Mitsonis et al. (2008)</td>
</tr>
<tr>
<td>9. Hyperprolactinemia</td>
<td>Risperidone, amisulpride</td>
<td>7 women</td>
<td>Switch to aripiprazole (10–20 mg/day), 8 weeks</td>
<td>Noncontrolled open-label trial</td>
<td>5 (71%)</td>
<td>Serum prolactin levels were normalized and hyperprolactinemia symptoms were resolved in all patients</td>
<td>Lee et al. (2006)</td>
</tr>
<tr>
<td>10. Prolactin levels</td>
<td>Risperidone or olanzapine</td>
<td>8 women, 9 men</td>
<td>Switch risperidone to olanzapine or olanzapine to risperidone, 3 months</td>
<td>Observational, noncontrolled, and crossover study</td>
<td>17 (100%)</td>
<td>When patients switched from risperidone to olanzapine, serum prolactin level decreased significantly</td>
<td>Lin et al. (2006)</td>
</tr>
<tr>
<td>11. Hyperprolactinemia and comorbid symptoms</td>
<td>Conventional antipsychotics or risperidone</td>
<td>26 men, 28 women</td>
<td>Switch from conventional antipsychotics or risperidone to olanzapine (5–20 mg/day), 4 months</td>
<td>Open-label, prospective, and randomized study</td>
<td>41 (76%)</td>
<td>Reduction in serum prolactin and improvement in sexual and reproductive comorbid symptoms</td>
<td>Kinton et al. (2006)</td>
</tr>
<tr>
<td>12. Hyperprolactinemia</td>
<td>Conventional antipsychotics</td>
<td>25 women</td>
<td>Switch from conventional antipsychotics to quetiapine, 8 weeks</td>
<td>Open-label study</td>
<td>17 (68%)</td>
<td>Serum prolactin levels were significantly decreased without any</td>
<td>Nakagima et al. (2005)</td>
</tr>
</tbody>
</table>

(Continued on next page)
<table>
<thead>
<tr>
<th>Sexual dysfunction</th>
<th>Induced by</th>
<th>Number of patients and gender</th>
<th>Therapy, dose, and duration</th>
<th>Study design</th>
<th>Number of participants who completed the study (%)</th>
<th>Primary outcome</th>
<th>Author and year</th>
</tr>
</thead>
<tbody>
<tr>
<td>13. Hyperprolactinemia</td>
<td>Risperidone</td>
<td>19 patients</td>
<td>Cabergoline, 0.125–0.250 mg/week, 8 weeks</td>
<td>Open-label pilot study</td>
<td>19 (100%)</td>
<td>Decrease in plasma prolactin levels and 11 patients showed remission of clinical signs with prolactin values within the normal range</td>
<td>Cavallaro et al. (2004)</td>
</tr>
<tr>
<td>14. Sexual drive, arousal, penis erection/vaginal lubrication, ability to reach orgasm, and satisfaction with orgasm, prolactin serum levels</td>
<td>Risperidone, haloperidol</td>
<td>8 men</td>
<td>Switch outpatients with schizophrenia and antipsychotic-induced sexual dysfunction to open-label quetiapine treatment (300–800 mg/day), 6 weeks</td>
<td>Open-label trial</td>
<td>6 (75%)</td>
<td>Clinically and statistically significant improvement in ASEX total scores; Plasma prolactin levels tended to decrease.</td>
<td>Byerly et al. (2004)</td>
</tr>
<tr>
<td>15. Prolactin levels</td>
<td>First generation antipsychotics (bromperidol, chlorpromazine, fluphenazine, haloperidol, levomepromazine, mosapramine, pipamperone, sulpiride, timiperone, zotepine)</td>
<td>30 men</td>
<td>Switch to olanzapine, perospirone, or quetiapine, 6 weeks</td>
<td>Prospective open-label study</td>
<td>30 (100%)</td>
<td>Reduced elevated prolactin without affecting the gonadal hormones and in improving quality of life</td>
<td>Kaneda et al. (2004)</td>
</tr>
<tr>
<td>16. Erectile dysfunction</td>
<td>Risperidone</td>
<td>12 men</td>
<td>Sildenafil 25–75 mg, 6 weeks</td>
<td>Open-label noncontrolled drug study</td>
<td>9 (75%)</td>
<td>Improvements in all sexual Function domains</td>
<td>Aviv et al. (2004)</td>
</tr>
<tr>
<td></td>
<td>Prolactin levels</td>
<td>Olanzapine, risperidone, and conventional antipsychotic</td>
<td>270 (177 men, 93 women)</td>
<td>Switch to ziprasidone (40–160 mg/day), 6 weeks</td>
<td>Open label</td>
<td>205 (76%)</td>
<td>Prolactin levels decreased among those switched from risperidone or conventional, but not for patients switched from olanzapine</td>
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<tr>
<td>18. Erectile dysfunction</td>
<td>Olanzapine</td>
<td>10 men</td>
<td>Sildenafil 50–100 mg, 4 weeks</td>
<td>Noncontrolled open-label study</td>
<td>10 (100%)</td>
<td>Sildenafil use is effective and well-tolerated in patients with olanzapine-induced ED</td>
<td>Atmaca et al. (2002)</td>
</tr>
<tr>
<td>19. Menstrual disturbances, galactorrhea, and/or sexual dysfunction</td>
<td>Risperidone</td>
<td>20 women</td>
<td>Switch from risperidone to olanzapine (5–20 mg/day), 10 weeks</td>
<td>Noncontrolled open-label study</td>
<td>20 (100%)</td>
<td>Reversed hyperprolactinemia, decrease in amenorrhea, improved cycle regularity, and a decrease in sexual side effects.</td>
<td>Kim et al. (2002)</td>
</tr>
<tr>
<td>20. Sexual drive, erection, ejaculation, and satisfaction with sexual performance</td>
<td>First-generation antipsychotics (haloperidol, thioridazine, fluphenazine, propriciazine)</td>
<td>12 men</td>
<td>Amantadine 100 mg/day, 6 weeks</td>
<td>Open-label noncontrolled drug study</td>
<td>12 (100%)</td>
<td>Improvement in all events evaluated except ejaculation. Decreased serum prolactin.</td>
<td>Valevski et al. (1998)</td>
</tr>
<tr>
<td>21. Hyperprolactinemia and sexual dysfunction</td>
<td>Neuroleptic</td>
<td>20 men</td>
<td>Shakuyaku-kanzo-to (TJ-68) 7.5 g, 8 weeks</td>
<td>Noncontrolled open-label study</td>
<td>20 (100%)</td>
<td>Decreased prolactin levels in 5 patients, improvement in sexual desire 50% returned to previous ejaculatory function</td>
<td>Yamada et al. (1997)</td>
</tr>
<tr>
<td>22. Orgasmic</td>
<td>Thioridazine</td>
<td>8 men</td>
<td>Imipramine 25–50 mg/day, 2 weeks</td>
<td>Open-label noncontrolled drug study</td>
<td>8 (100%)</td>
<td></td>
<td>Aizenberg et al. (1996)</td>
</tr>
</tbody>
</table>

(Continued on next page)
<table>
<thead>
<tr>
<th>Sexual dysfunction</th>
<th>Induced by</th>
<th>Number of patients and gender</th>
<th>Therapy, dose, and duration</th>
<th>Study design</th>
<th>Number of participants who completed the study (%)</th>
<th>Primary outcome</th>
<th>Author and year</th>
</tr>
</thead>
<tbody>
<tr>
<td>23. Hyperprolactinemia</td>
<td>Neuroleptic</td>
<td>10 (4 women, 6 men)</td>
<td>Amantadine 200–300 mg/day, 7 weeks</td>
<td>Open-label reversal drug study</td>
<td>10 (100%)</td>
<td>Improvement on parameters: serum prolactin levels, body weight, gynecomastia/galactorrhea, breast tenderness, decreased libido, and amenorrhea</td>
<td>Correa et al. (1987)</td>
</tr>
<tr>
<td>24. Amenorrhea, galactorrhea, and impotence</td>
<td>First-generation antipsychotics, on the basis of the date of the study</td>
<td>35 (24 women, 11 men)</td>
<td>Bromocriptine 5.0–7.5 mg/day</td>
<td>Open-label noncontrolled drug study</td>
<td></td>
<td>Return of menstrual cycle in 70%, relief of galactorrhea in 80% and improvement of impotence in 60%</td>
<td>Matsuoka et al. (1986)</td>
</tr>
<tr>
<td>25. Erection, ejaculation, libido, amenorrhea, galactorrhea, and weight change</td>
<td>Fluphenazine, pipotiazine, levomepromazine, cyamemazine, sulpiride</td>
<td>30 (20 women, 10 men)</td>
<td>Bromocriptine 5–10 mg/day</td>
<td>Open-label noncontrolled drug study</td>
<td>30 (100%)</td>
<td>Decreased serum prolactin, weight loss, normalization of menstrual cycle, relief in galactorrhea, and little improvement of erectile and ejaculatory dysfunction</td>
<td>Beau and Guillard (1980)</td>
</tr>
</tbody>
</table>

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 vardenafl (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 (≤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, Fuji, & 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.

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reproductive side effects in patients with schizophrenia treated with risperidone, olanzapine, quetiapine, or haloperidol. *Journal of Sex & Marital Therapy, 29*, 125–147.


