ORIGINAL ARTICLE

The role of aripiprazole in improvement of penile erection in schizophrenia patients with erectile dysfunction

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ABSTRACT

Aim To provide evidence regarding the effectiveness of aripiprazole in improving penile erection with a therapeutic strategy of add-on or switching therapy in patients with schizophrenia.

Methods. PubMed, Cochrane, Clinical Key, ProQuest, EBSCOhost, and ScienceDirect were searched for any design study that evaluated aripiprazole only or versus control (placebo or other antipsychotic) for erectile dysfunction in patients with schizophrenia. Three studies were identified and analysed from 295 initial articles. Data were then extracted from the studies and summarized descriptively.

Results Two hundred ninety-five articles were screened, and three studies were identified and eventually selected. After the add-on or switching antipsychotic therapy to aripiprazole, the prevalence of erectile dysfunction and the score of erectile dysfunction or penile erection assessed by Nagoya and Sexual Function Questionnaire (NSFQ) and Arizona Sexual Experience Scale (ASEX) decreased.

Conclusion Aripiprazole was effective to improve penile erectile function in patients with schizophrenia. The therapeutic strategy is adjunctive treatment or switching therapy to aripiprazole.

Key words: penile erection, prevalence, schizophrenia, sexual behaviour

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INTRODUCTION

Schizophrenia is a severe psychiatric disorder that has a profound effect on individuals and society in the form of complex, heterogeneous behavioural and cognitive syndromes, which originate from brain development disorders caused by genetic, environmental, or both factors (1). Schizophrenia has the most prominent symptoms including delusions and hallucinations, which are also called psychotic symptoms. The symptoms are loss of contact with reality and also experiencing negative symptoms that occur specifically such as impaired motivation, decreased speech, and withdrawal from the social environment (2). The incidence of schizophrenia in industrialized countries is 10-70 new cases per 100,000 population per year (1,3). Based on Indonesian Basic Health Research data, there is an increase in schizophrenia incidence in Indonesia, which was 7 per 1000 adults in 2018, compared to 1.7 per 1000 adults in 2013 (4).

Typical antipsychotic drugs have a greater level of affinity, risk of extrapyramidal side effects, and hyperprolactinemia (5). Besides, one of the common side effects is sexual dysfunction, with prevalence of 45-80% of male patients (6). Sexual dysfunction includes a reduction in desire or libido, reduced arousal, decreased frequency of sexual intercourse or inability to reach orgasm, retrograde ejaculation, and erectile dysfunction (7). Atypical antipsychotic drugs have a greater affinity for serotonin receptors than dopamine receptors. Most atypical antipsychotic drugs cause side effects such as weight gain and fat metabolism disruption (8).

Antipsychotic drugs have the potential to cause hyperprolactinemia because the inhibition of dopamine release effectively removes negative feedback loops for prolactin secretion from the anterior pituitary gland. Increased serum prolactin levels have shown to have profound effects on reproductive health and sexual function, including hypogonadism, decreased libido in both genders, amenorrhoea and infertility in women and low sperm counts and reduced muscle mass in males (9). The prevalence of sexual dysfunction was up to 50% for first-generation antipsychotic drugs groups (10). However, aripiprazole is the only antipsychotic with partial agonist activity against dopamine D2; this difference determines the pharmacological profile and aripiprazole side effects (11). Aripiprazole is known to have a low risk of extrapyramidal side effects and decrease the risk of sexual dysfunction, including erectile dysfunction (11).

Treatment strategies for schizophrenic patients with sexual dysfunction have been proposed. Lowering the dose of antipsychotic drugs, adjunctive treatment with dopamine agonists, and switching to prolactin-sparing drugs are a useful option (5). The ability of aripiprazole to reduce the incidence of erectile dysfunction can be seen in several studies (7,12,13). Erectile dysfunction was significantly reduced 12 weeks after switching therapy to aripiprazole (12). Decreased erectile dysfunction also occurred from 8 to 26 weeks after the treatment with aripiprazole compared to other antipsychotics based on total Arizona Sexual Experience Scale (ASEX) scores (13). Also, the prevalence of erectile dysfunction is less frequent in patients treated with aripiprazole (15.38%) than with haloperidol (45.83%) (14).

This research aimed to review the effectiveness of the therapeutic strategy aripiprazole as an adjunctive or switching therapy for patients with schizophrenia focusing on a comparison of evidence regarding the effectiveness of aripiprazole in improving penile erectile function.

MATERIALS AND METHODS

Materials and study design

A comprehensive search was performed in July 2020 in which we searched the Wiley Online Library, PubMed, Cochrane, ProQuest, and ScienceDirect databases, using keywords related to schizophrenia, aripiprazole, and erectile dysfunction without language restrictions. The following keywords were used in searches of all the databases: "Schizophrenia" and "Aripiprazole" and "Erectile Dysfunction."

This study reviews evidence from any design study with open-label treatment published in the period between 2005 and 2020 to assess the effect of aripiprazole on erectile dysfunction of schizophrenic patients. The patients reviewed were male patients younger than 65 years. Race and duration of follow-up were not considered.

The criteria for inclusion and exclusion were determined before the search. We included studies

with add-on therapy or switching to aripiprazole with or without other control or antipsychotic groups. Studies with relevant titles are then collected and filtered. Studies found in more than one database were removed. Full-paper manuscripts were then studied, and manuscripts that were irrelevant to the theme are excluded. Three studies were included in a systematic review.

Methods

This systematic review was written based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting the events evaluated by interventions and health care behaviours (15). Population, intervention, control, and outcome (PICO) questions (16) used in this systematic review were: P (population): schizophrenia patient, I (intervention): the use of aripiprazole, C (comparison/control): without or with other antipsychotic or placebo and O (outcome): erectile dysfunction.

Statistical analysis

Relevant information was extracted from selected studies. Relevant information included study types, patient characteristics, intervention regimens, comparative regimens (placebo or other antipsychotic treatments), side effects of erectile dysfunction, and methods used to analyse the results. The primary outcome assessed was the efficacy of aripiprazole treatment, classified as a decreased percentage of erectile dysfunction, compared with baseline.

RESULTS

The search on the database was resulted in 295 initial articles (93 articles from Wiley Online Library, 42 from PubMed database, four from Cochrane Online Library, 108 from ProQuest and 48 articles from ScienceDirect). Because of the irrelevant titles, 279 articles were excluded, and nine articles were removed because of duplicate titles. After the discussion among the authors, another four articles were excluded because of several reasons (among them, three were not found and attempts to contact the authors were unsuccessful). The title and the abstract of the articles were reviewed, and according to the results, only three fitted the eligibility criteria stated in this systematic review (Figure 1).

All three selected studies were conducted in Korea (18), India (19) and Japan (17). There were 34 schizophrenic patients with sexual dysfunction in these studies. Two studies were on add-on therapy

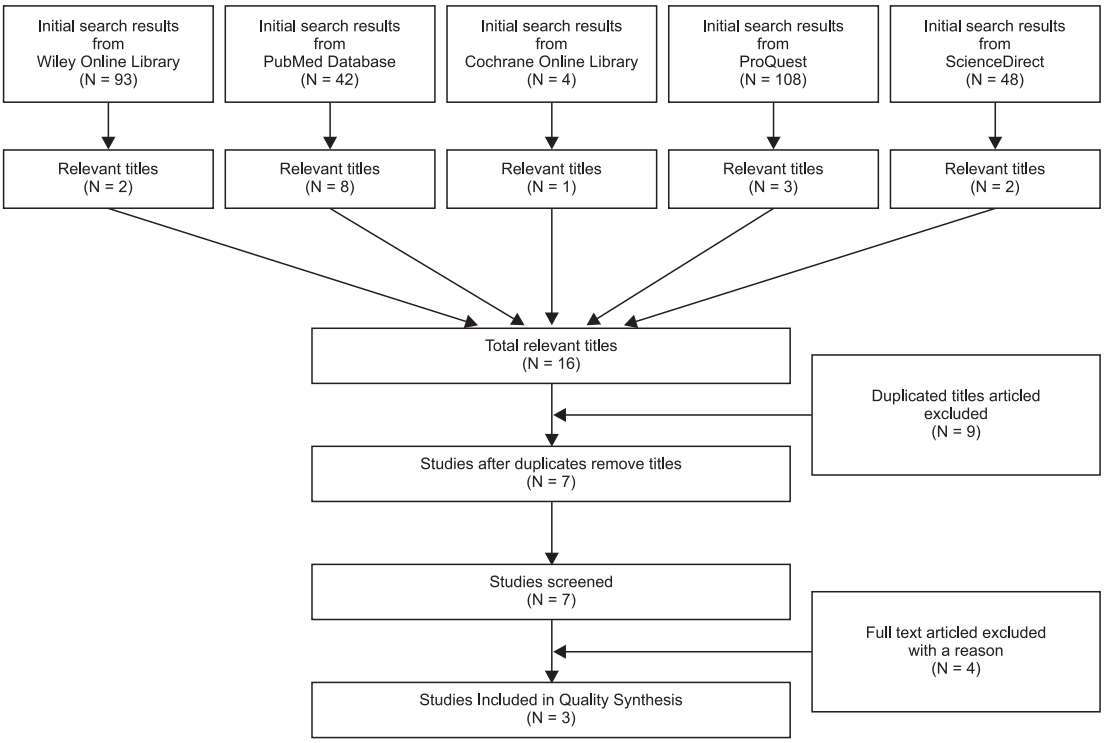

Figure 1. Diagram flow of the article's selection

Table 1. Summary of data description from the included studies

Study	Subject criteria and study design	Intervention	Length of follow up	Outcome
Jeong et al. 2012 (Korea) (18)	**Subject criteria:** Taking a single second-generation oral antipsychotic (especially risperidone, olanzapine, or amisulpride), complaining of significant sexual dysfunction since taking antipsychotic medication and patients aged 20–55 years. **Study design:** Prospective, open-label study without control group	Switching to aripiprazole on sexual dysfunction of 10 male schizophrenia patients, who had been treated with atypical antipsychotics, risperidone (n =6), amisulpride (n=3), and olanzapine (n=1)	12 weeks	Penile erection improved significantly over the study period (score: baseline = 3.8±1.14, week 6 = 3.1±0.99, week 12 =3.3±1.16; w2=9.33; p =0.009).
Raghuthaman et al. 2015 (India) (19)	**Subject criteria:** Aged 15–45 years, patients were being prescribed a stable dose of risperidone for at least 12 weeks. **Study design:** A double-blind, placebo-controlled study	Adjunctive treatment with 10 mg aripiprazole on sexual side-effects in patients with schizophrenia symptomatically maintained on risperidone	8 weeks	Aripiprazole improved erectile dysfunction in five out of six patients. In contrast, one additional patient developed erectile dysfunction in the placebo group at follow-up (p=0.01)
Fujioi et al. 2017 (Japan) (17)	**Subject criteria:** 9 males were 65 years of age or younger, hyperprolactinemia and a score of 3 or higher on any of the NSFQ items **Study design:** Open-label and naturalistic design without a control group	Adjunctive treatment with aripiprazole on sexual side-effects in patients with schizophrenia	24 weeks	Erectile dysfunction improved by week 24 (mean = 2.6±1.1 vs 2.0±1.1; p=0.049)

with aripiprazole, and one study was on switching therapy to aripiprazole. Erectile dysfunction was assessed with the Nagoya and Sexual Function Questionnaire (NSFQ) (17) and Arizona Sexual Experience Scale (ASEX) (18,19).

Erectile dysfunction or penile erection was one of several items assessed from the two questionnaires (NSFQ and ASEX). The NSFQ is a self-administered sexual function scale that consists of 7 items, which for males include pulsating sensation in the breast/mammary area, galactorrhea, interest in women, sexual interest, sexual self-confidence, erectile dysfunction and ejaculatory dysfunction (20), while the Arizona Sexual Experience Scale (ASEX) consists of 5 items comprising strength of sex drive, ease of sexual arousal, penile erection, ability to reach orgasm, and satisfaction with orgasm (21).

Two open-label studies without a control group and one double-blind study with placebo-controlled were conducted in 2012, 2015, and 2017. The patient's age ranged between 15 - 65 years. One of the open-label studies without the control group used the NSFQ to assess erectile dysfunction, and the other used the ASEX. Various lengths of follow up were from 8 weeks (19), 12 weeks (18), and 24 weeks (17) (Table 1).

Jeong et al. (18) found that the score of penile erection in 10 male schizophrenia patients after switching to aripiprazole improved significantly over the study period from a mean value of 3.8±1.14 at baseline to 3.1±0.99 at week 6, and continued to improve at week 12 to 3.3±1.16 (p=0.009).

Raghuthaman et al. (19) enrolled fifteen male patients who had been prescribed a stable dose of risperidone for at least 12 weeks, nine patients received adjunctive treatment with aripiprazole, and six patients received placebo. In the aripiprazole group, six (66.7%) males had erectile dysfunction at baseline, only one (11.1%) still had erectile dysfunction after eight weeks. In contrast, in the placebo group four (66.7%) males had erectile dysfunction at baseline, which increased to five (83.3%) males after eight weeks. The difference in the proportion of men with erectile dysfunction at follow-up between the two groups was statistically significant (p=0.01).

Fujioi et al. (17) reported a significant improvement of erectile dysfunction in nine male schizophrenia patients after adjunctive treatment with aripiprazole. The score of erectile dysfunctions improved from mean value of 2.6±1.1 at baseline to 2.0±1.1 at week 24 (mean difference=0.6 with 95% CI=0.003–1.2; p=0.049).

DISCUSSION

Based on three studies that have been analysed, two studies were related to add-on therapy, and the remaining one was related to switching therapy to aripiprazole. Erectile dysfunction or penile erection was one of several items assessed from the two questionnaires (NSFQ and ASEX). A significant

improvement of erectile dysfunction was found in add-on therapy with aripiprazole at week 24 (17) and week 8 (19) after adjunctive therapy. It can be concluded that adjunctive aripiprazole reduces prolactin levels in schizophrenic patients treated with risperidone and may be a potential treatment for hyperprolactinemia following treatment with second-generation antipsychotics.

Switching therapy with aripiprazole could be considered in patients with schizophrenia. The study in Korea (18) found improvement in penile erection after switching to aripiprazole. It can be determined that sexual dysfunction in patients with schizophrenia in this study appeared to improve after switching to aripiprazole from other atypical antipsychotics.

Erection is a neurovascular condition that is influenced by hormones, consists of arterial dilatation, relaxation of the trabecular smooth muscles, and activation of the corporal veno-occlusive mechanism (22). The National Institutes of Health (NIH) Consensus Development Conference on Impotence defines erectile dysfunction as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance (23).

Blockade of dopamine receptors in the tuberoinfundibular pathway results in decreased dopamine tone. Besides, inhibition of dopamine release effectively removes the negative feedback loop for prolactin secretion from the anterior pituitary gland, thereby increasing the secretion of prolactin. Elevated serum prolactin levels have profound effects on reproductive health and sexual function, including erectile dysfunction (24, 25).

Jeong et al. (18) reported that by switching therapy to aripiprazole, penile erection improved significantly after 12 weeks. This is also the case with the adjunctive therapy with aripiprazole, Raghuthaman et al. (19) reported adjunctive therapy with aripiprazole improved erectile dysfunction in five out of six patients after eight weeks of treatment. Besides, Fujioi et al. (17) reported an improvement of erectile dysfunction after 24 weeks of adjunctive treatment with aripiprazole. After the addition or switching therapy to aripiprazole, the incidence of erectile dysfunction and the score of erectile dysfunction or penile erection decrease.

Despite the evidence of overall improvement of erectile dysfunction after adjunctive or switch therapy to aripiprazole, there were several limitations on these studies (17,18,19). The results of Jeong's et al. study is based on a small sample, and this will result in possible type II error/ false negative (26). Also, this study was unable to show whether improvements in sexual function persisted after 12 weeks. Fujioi's study included only participants in the aripiprazole group without a control group. The statistical power for some assessment items is underpowered because of the small sample size. All patients had varied sexual functions; the therapeutic environment (in and out of the hospital) can also affect the results. For further research, the sample size should be more extensive, and long-term research is recommended to ensure whether improvements in sexual function persisted overtime.

This study's limitation was that a small number of studies proved the effectiveness of aripiprazole in improving erectile function in patients with schizophrenia, because only three studies fitted the eligibility criteria.

In conclusion, dopamine blockade, as an antipsychotic mechanism of action in the tuberoinfundibular pathway, can cause hyperprolactinemia. Addition or switching of therapy to aripiprazole decreases the incidence of erectile dysfunction and the score of erectile dysfunction or penile erection, thereby improving erectile function.

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