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REVIEW

Efficacy and Safety of Phosphodiesterase-5 Inhibitors for Erectile Dysfunction in Schizophrenia: A Systematic Review and Meta-Analysis

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Background: The benefits of phosphodiesterase-5 inhibitors in the treatment of sexual dysfunction and psychopathology of schizophrenia remain unclear. This systematic review and meta-analysis aimed to address the above clinical question.

Methods: Our primary outcome includes erectile dysfunction (ED) assessed using standardized questionnaires. Other efficacy outcomes involve overall sexual dysfunction, overall schizophrenia symptoms, positive symptoms, and negative symptoms. Further, we included all-cause discontinuation, discontinuation due to adverse events, discontinuation due to consent withdrawal, headache, loss of appetite, and somnolence. A meta-analysis was conducted for outcomes if at least two studies in each drug group had sufficient data to conduct a meta-analysis for a specific outcome.

Results: Our systematic review included five double-blind, randomized, placebo-controlled trials (n=155, mean age=37.18 years, male proportion=91.61%), consisting of one lodenafil, three sildenafil, and one tadalafil study. Among the three studies on sildenafil, only one reported outcomes on sexual dysfunction; however, it demonstrated that sildenafil improved ED in males with schizophrenia. Another study reported that sildenafil also outperformed placebo in terms of schizophrenia symptom improvement, especially negative symptoms. However, our meta-analysis revealed no significant differences in outcomes associated with psychopathology, all-cause discontinuation, discontinuation due to adverse events, discontinuation due to consent withdrawal, headache, loss of appetite, and somnolence between sildenafil and placebo. Tadalafil outperformed placebo in terms of ED improvement although this finding was derived from one study.

Conclusion: Sildenafil and tadalafil may be treatment options for ED, although our meta-analysis of safety outcomes did not include tadalafil. Our meta-analysis revealed that sildenafil was well accepted and well tolerated, despite involving only two studies.

Keywords: phosphodiesterase-5 inhibitors, lodenafil, sildenafil, tadalafil, schizophrenia, systematic review and meta-analysis

Introduction

The efficacy of most antipsychotic drugs is considered to be mediated by dopamine transmission attenuation through their actions as antagonists or low-efficacy partial agonists at the dopamine D_2 receptor (D_2R). However, antipsychotics have the risks of adverse events such as hyperprolactinemia-related sexual dysfunction. Prolactin production is inhibited in the hypothalamo–pituitary circuit through dopamine release and can be disinhibited by blocking D_2R. Hyperprolactinemia causes several sexual dysfunctions. Sexual dysfunctions have been one of the most frequently reported motives for treatment discontinuation in schizophrenia and have been associated with impaired quality of life in individuals with schizophrenia.[1,2] Recent systematic reviews identified erectile dysfunction (ED) as the most prevalent sexual dysfunction for men with schizophrenia.[3,4] Clinical practice guidelines recommend that individuals with sexual dysfunction consider switching from prolactin-elevating antipsychotics to prolactin-sparing antipsychotics (Table 1).[5–11]

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Table 1 Treatment Recommendation for Treatment of Erectile Dysfunction in the Clinical Practical Guidelines

APA	BAP	CPA	JSNP	NICE	RANZCP	WSFBP†
Reducing AP dose, a switch to a prolactin-sparing AP, or adding BRO to existing treatment	A switch to a prolactin-sparing AP, or adding ARI to existing treatment	No specific statement for SD	No specific statement for SD	No specific statement for SD	A switch to a prolactin-sparing AP	A switch to a prolactin-sparing AP, adding ARI to existing treatment or adding BRO to existing treatment

Notes: †The WSFBP guidelines also statederectile dysfunctions (sildenafil, vardenafil) might be effective for the treatment of antipsychotic-induced sexual dysfunction, but good evidence is still lacking.

Abbreviations: AP, antipsychotic; APA, American Psychiatric Association; ARI, aripiprazole; BAP, British Association for Psychopharmacology; BRO, bromocriptine; CPA, Canadian Psychiatric Association; JSNP, Japanese Society of Neuropsychopharmacology; NICE, National Institute for Health and Care Excellence; RANZCP, Royal Australian and New Zealand College of Psychiatrists; SD, sexual dysfunction; WSFBP, World Federation of Societies of Biological Psychiatry.

However, several individuals with schizophrenia responded to only prolactin-increasing antipsychotics. Hence, the development of novel treatments underscoring improving sexual dysfunctions is a pressing issue in schizophrenia research. Phosphodiesterase-5 inhibitors (PDE5-Is) are generally recommended for ED in the general population.[12,13] PDE5-Is work by increasing levels of cyclic GMP (cGMP) in smooth muscle cells, leading to vasodilation. Specifically, they inhibit the enzyme PDE5, which normally breaks down cGMP. By preventing this breakdown, PDE5 inhibitors allow cGMP to accumulate, causing smooth muscle relaxation and vasodilation. In the context of ED, this vasodilation occurs in the corpus cavernosum of the penis, facilitating increased blood flow and an erection.[14] Commonly reported adverse effects associated with PDE5-Is therapy include headache, facial flushing, dyspepsia, disturbances in color vision, hypotension, dizziness, and nasal congestion.[14] This systematic review and meta-analysis aimed to identify the PDE5-I that is better for sexual dysfunction treatment in individuals with schizophrenia.

Methods

This systematic review was conducted under the PRISMA statement (Table S1)[15] and was registered at the Open Science Framework (https://osf.io/2jdn5).

Search Strategy, Inclusion Criteria, and Data Extraction

This systematic review included only double-blind, randomized, placebo controlled trials (DBRPCTs). Figure S1 summarizes the formal literature search and selection flow of PDE5-Is trials. A formal systematic literature review was conducted using the Patient, Intervention, Comparison, and Outcome strategy. Participants included individuals with schizophrenia spectrum and other psychotic disorders who received antipsychotics. The intervention involves avanafil, icariin, lodenafil, osajin, sildenafil, tadalafil, udenafil, vardenafil, yonkenafil, and zaprinast which were introduced as a PDE5-Is in our previous review.[16] We conducted a comparison with placebo, and outcomes are presented as follows. At least two authors simultaneously and independently performed the literature search and data extraction, the obtained data were input into a spreadsheet for analysis, and assessed all data for accuracy. We included all DBRPCTs that matched the aforementioned PICO criteria. A DBRPCT including both male and female participants was also included. An open-label study was excluded.

Outcome Measures and Data Synthesis

Our primary outcome includes ED assessed using standardized questionnaires. Other efficacy outcomes involve overall sexual dysfunction, overall schizophrenia symptoms (Positive and Negative Syndrome Scale (PANSS)[17] and Brief Psychiatric Rating Scale (BPRS),[18] positive symptoms (PANSS and BPRS), and negative symptoms (PANSS and BPRS). Further, we included all-cause discontinuation, discontinuation due to adverse events, discontinuation due to consent withdrawal, headache, loss of appetite, and somnolence.

Our meta-analysis primarily utilized data based on the intention-to-treat or full analysis set principles. We did not obtain any unpublished data.

Meta-Analysis Methods

A random-effects pairwise meta-analysis was conducted according to the aforementioned outcomes to compare a specific drug with a placebo.[19] Effect sizes were risk ratios for dichotomous outcomes and standardized mean differences for continuous outcomes. The heterogeneity of the included trials was assessed using the I^2 statistic.[20] The risk of bias was assessed using the Cochrane risk-of-bias tool for randomized trials version 2.[20] We did not evaluate a publication bias because only three studies were conducted on sildenafil.[20] Comprehensive Meta-Analysis version 4 (Biostat Inc., Englewood, NJ, USA) was used for statistical analysis of our meta-analysis.

Results

Literature Search

The result of literature search was shown in Figure S1. Our systematic review and meta-analysis included five trials that involved a total of 155 individuals (Figure S1).[21–25] Table 2 shows the study characteristics. Concerning the overall risk of bias, four studies were assessed as some concern and one study as low risk (Table S2).

Systematic Review

Lodenafil

Nunes Study (Brazil)

This was a 16-week, double-blind, randomized, crossover, placebo-controlled trial with lodenafil that included male patients with stable psychotic symptoms of schizophrenia and schizoaffective disorder comorbid ED (n = 50, mean age ± standard deviation [SD] = 37.26 ± 8.89 years). Lodenafil did not outperform the placebo in terms of the Arizona Sexual Experiences Scale (ASEX)[26] total score, ASEX penile erection subscale score, International Index of Erectile Function (IIEF)[27] total score, IIEF erectile function subscale score, and PANSS total score.

Sildenafil

Akhondzadeh Study (Iran)

This was an 8-week, double-blind, randomized, placebo controlled trials with sildenafil that included male (90.00%) and female patients with schizophrenia with acute exacerbation (n = 40, mean age ± SD = 33.36 ± 8.27 years). Sildenafil outperformed placebo in terms of PANSS total, negative subscale, and general subscale scores but not PANSS positive subscale scores. This study did not assess sexual dysfunction-related outcomes.

Goff Study (USA)

This was a 2-day, double-blind, randomized, crossover, placebo-controlled trial with sildenafil that included male (47.06%) and female patients with stable psychotic symptoms of schizophrenia (n = 17, mean age ± SD = 49.7 ± 0.6 years). Sildenafil did not outperform placebo in terms of BPRS total score and positive, negative, and depression subscale scores. This study did not assess sexual dysfunction-related outcomes.

Gopalakrishnan Study (India)

This was a 4-week, double-blind, randomized, crossover, placebo-controlled trial with sildenafil that included male patients with stable psychotic symptoms of schizophrenia and delusional disorder comorbid ED (n = 32, mean age ± SD = 35.1 ± 5.5 years). Sildenafil outperformed placebo in terms of the number of adequate erections, sexual intercourse satisfaction, and erection duration when assessed using the Global Efficacy Questionnaire.[28] This study did not assess for psychopathology-related outcomes.

Tadalafil

de Boer Study (Netherlands)

This was a 6-week, double-blind, randomized, crossover, placebo-controlled trial with tadalafil that included male patients with schizophrenia and schizoaffective disorder comorbid ED (n = 16, mean age ± SD = 37.4 ± 6.6 years). Tadalafil outperformed placebo in terms of Improvement Global Usefulness and Antipsychotics and Sexual Functioning

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Table 2 Study Characteristics

Study† (country), sponsorship	Patient's characteristic (diagnostic criteria)	Study duration	Total n	% male	Mean age ±SD	Mean PANSS-T ±SD at baseline	AP (%)	AP dose (mean±SD, mg/day)	PDE5-I (dose, mg/day)	The result for erectile function	The result for psychopathology
LOD study											
Nunes 2013 (Brazil),[25] industry	Stable SA or SZ (DSM-IV)+ED	8 weeks	50	100.00	37.26±8.89	59.72±11.39	APs (NR)	NR	LOD (80)	IIEF: no difference between the treatments	PANSS-T: no difference between the treatments
SIL studies											
Akhondzadeh 2011 (Iran),[21] academia	SZ with acute exacerbation (DSM-IV-TR)	8 weeks	40	90.00	33.36±8.27	112.75±10.20	RIS (100.00)	6	SIL (75)	NR	PANSS-T: SIL outperformed PLA
Goff 2009 (USA),[23] academia	Stable SZ (DSM-IV)	1 day	17	47.06	49.7±0.6	NR	ARI (11.76), CLO (11.76), FGAs (11.76), OLA (29.41), QUE (5.88), RIS (11.76), OLA+ZIP (5.88), PER+ZIP (5.88), QUE +FLUPH (5.88)	NR	SIL (50), SIL (100)	NR	BPRS-T: no difference among the treatments
Gopalakrishnan 2006 (India),[24] academia	SZ or DD (ICD-10) +ED	2 weeks	32	100.00	35.1±5.5	40.8±6.0	CLO (3.13), FLUPH (6.25), OLA (37.50), RIS (53.13)	556.3±198.6 (CHL-eq)	SIL (25 or 50)	GEQ: SIL outperformed PLA	NR
TAD study											
de Boer 2014 (Netherlands),[22] industry	SA or SZ (DSM-IV-TR)+ED	3 weeks	16	100.00	37.4±6.6	NR	OLA (26.67), CLO (26.67), FLUPE (26.67), ZUC (13.33), RIS (6.67)	NR	TAD (10) 3 times/ week	IIEF: no difference between the treatments	PANSS-T: no difference between the treatments

Notes: †The underlined study is a crossover study (the information was shown before crossover).

Abbreviations: AP, antipsychotic; ARI, aripiprazole; BPRS-T, Brief Psychiatric Rating Scale total score; CHL-eq, chlorpromazine equivalent; CLO, clozapine; DD, delusional disorder; DSM(-TR), Diagnostic and Statistical Manual of Mental Disorders(-Text Revision); ED, erectile dysfunction; FGA, first-generation antipsychotic; FLUPE, flupentixol; FLUPH, fluphenazine; GEQ, Global Efficacy Questionnaire; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th; IIEF, International Index of Erectile Function; LOD, lodenafil; n, number of individuals; NR, not report; OLA, olanzapine; PANSS-T, Positive and Negative Syndrome Scale total score; PDE5-I, phosphodiesterase 5 inhibitor; PER, perphenazine; PLA, placebo; QUE, quetiapine; RIS, risperidone; SA, schizoaffective disorder; SD, standard deviation; SIL, sildenafil; SZ, schizophrenia; TAD, tadalafil; USA, United States of America; ZIP, ziprasidone; ZUC, zuclopenthixol.

Questionnaire[29,30] total score but not IIEF total score, IIEF erectile function subscale score, PANSS total score, and PANSS positive, negative, and general subscale scores.

Meta-Analysis Including Sildenafil Studies

Only sildenafil, which had three trials, was assessed for its characteristics using a meta-analysis. However, our meta-analysis did not include efficacy outcomes for sexual dysfunction due to insufficient data. No significant differences in other outcomes were found between sildenafil and placebo (Figure 1 and Table 3).

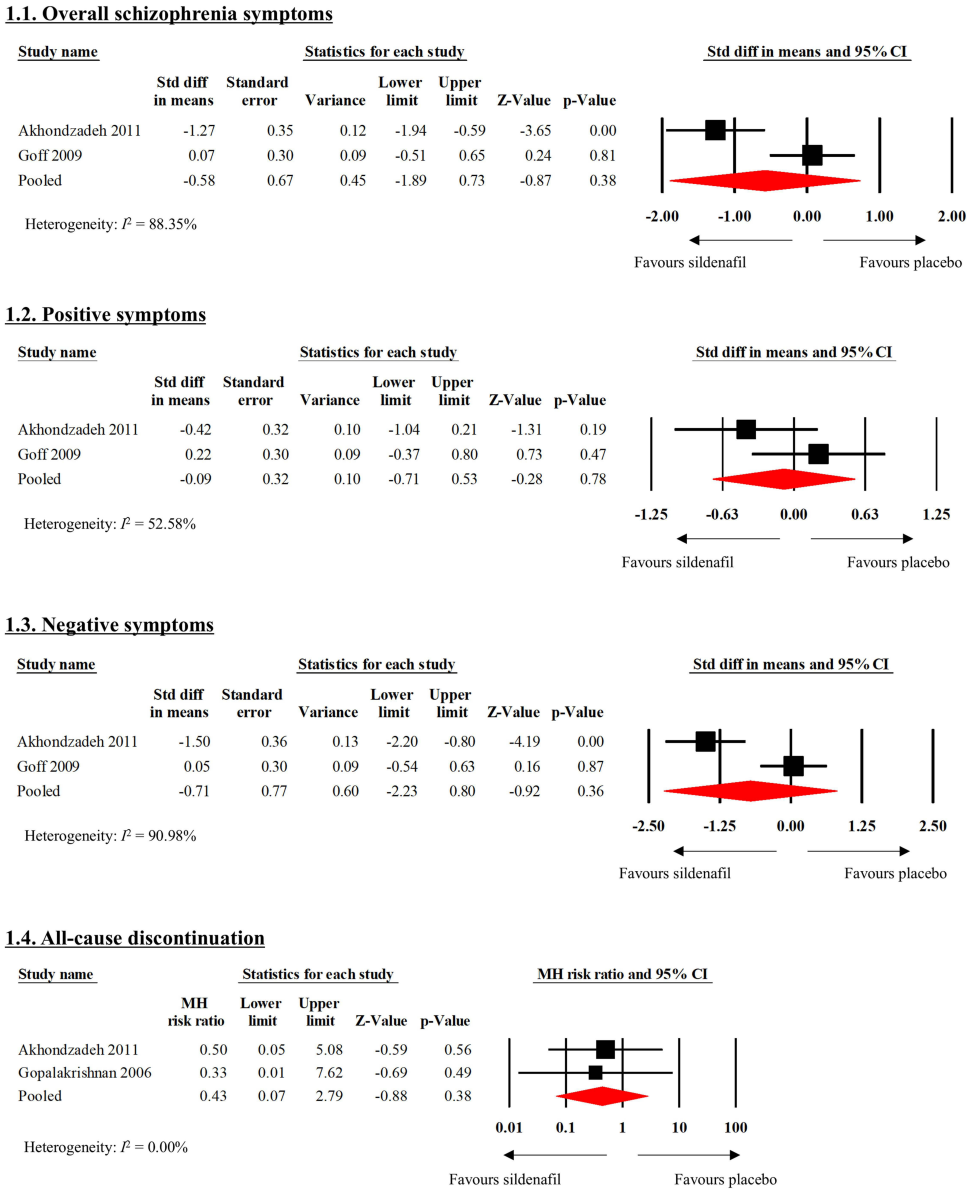

Figure 1 Continued.

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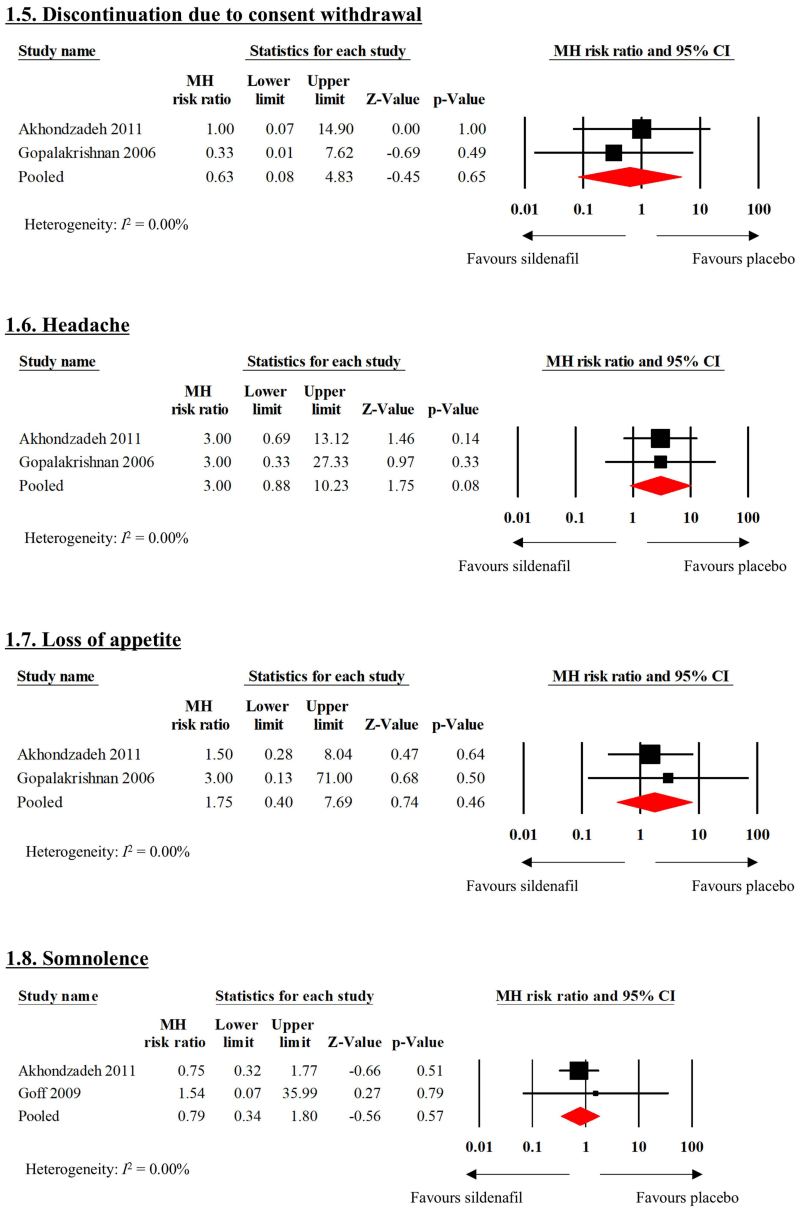

Figure 1 Forest plots.
Abbreviations: 95% CI, 95% confidence interval; MH, Mantel-Haenszel; Std diff in means, standardized difference in means.

Discussion

Among the three studies on sildenafil, only one reported outcomes on sexual dysfunction; however, it demonstrated that sildenafil improved ED in males with schizophrenia. In addition, the sole study on tadalafil also found that tadalafil was effective in improving ED in males with schizophrenia. Taken together, our systematic review suggested that sildenafil and tadalafil might represent potential treatment options for ED in males with schizophrenia. Furthermore, the results of our meta-analysis indicated that sildenafil was generally well-accepted and well-tolerated. However, these findings were based on only two studies, highlighting the need for further research.

One study of sildenafil for schizophrenia with acute exacerbation reported that sildenafil improved psychopathology, especially negative symptoms; however, other sildenafil studies for stable schizophrenia did not demonstrate such findings. Further, tadalafil did not improve psychopathology for stable schizophrenia. Thus, the discrepancy in efficacy

Table 3 Results of Meta-Analysis Including Sildenafil Studies

	K (n)	SMD (95% CI)	P	I^2 (%)†
Overall schizophrenia symptoms	2 (91)	−0.58 (−1.89, 0.73)	0.38	88.35
Positive symptoms	2 (91)	−0.09 (−0.71, 0.53)	0.78	52.58
Negative symptoms	2 (91)	−0.71 (−2.23, 0.80)	0.36	90.98
	K (n)	**RR (95% CI)**	**P**	**I^2 (%)†**
All-cause discontinuation	2 (72)	0.43 (0.07, 2.79)	0.38	0.00
Discontinuation due to adverse events	2 (72)	No incidence in each treatment group		
Discontinuation due to consent withdrawal	2 (72)	0.63 (0.08, 4.83)	0.65	0.00
Headache	2 (104)	3.00 (0.88, 10.23)	0.08	0.00
Loss of appetite	2 (104)	1.75 (0.40, 7.69)	0.46	0.00
Somnolence	2 (91)	0.79 (0.34, 1.80)	0.57	0.00

Notes: †The heterogeneity of the included trials was assessed using the I^2 statistic, with I^2 of ≥50% as considerable heterogeneity.[20]
Abbreviations: 95% CI, 95% confidence interval; K, number of studies; n, number of individuals; RR, risk ratio; SMD, standardized mean difference.

results for psychopathology may be explained by the difference in the patient's condition (ie, acute phase or maintenance phase). However, at least PDE5-Is are unlikely to make psychopathology in individuals with schizophrenia worse.

Individuals with schizophrenia have a higher risk of coronary artery disease.[31] The drug insert package states that "patients should not use sildenafil and tadalafil if sexual activity is inadvisable due to cardiovascular status."[32] Therefore, clinicians should carefully check the heart conditions of patients before providing these PDE5-Is.

A recent meta-analysis reported that adding aripiprazole to existing treatment significantly decreased prolactin levels.[33] However, aripiprazole has a risk of akathisia and somnolence although the effect sizes were low when compared with placebo.[34,35]

Our study had several limitations. First, only one study revealed the positive results. Second, the study duration of each trial was short. A longer-duration study involving a larger sample is warranted as individuals with schizophrenia have a long-term treatment period. Third, the scales for sexual dysfunction used in each study were not consistent. The characteristics of each scale may have affected sexual dysfunction-related outcomes (eg, questions that are affected by whether or not a patient has a partner). Finally, we did not assess whether PDE5-Is had a benefit for sexual dysfunction treatment in women with schizophrenia.

In conclusion, our systematic review suggested that sildenafil and tadalafil might represent potential treatment options for ED in males with schizophrenia. Furthermore, the results of our meta-analysis indicated that sildenafil was generally well-accepted and well-tolerated. However, these findings were based on only two studies, highlighting the need for further research. Clinicians should address the cause of ED, such as antipsychotic-induced hyperprolactinemia, if possible.

Data Sharing Statement

Data used for the current study were reported in articles as cited in this paper.

Ethical Approval

The requirement for ethical approval was waived in this study because it did not involve any human subjects, and the data retrieved for synthesis was collected from published studies.

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