General Psychiatry

Adjunctive Peony-Glycyrrhiza decoction for antipsychotic-induced hyperprolactinaemia: a meta-analysis of randomised controlled trials

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ABSTRACT

Background Hyperprolactinaemia is a common adverse effect of antipsychotics (APs). The results of Peony-Glycyrrhiza decoction (PGD) as a potentially useful adjunctive treatment for hyperprolactinaemia are inconsistent.

Aim This meta-analysis of randomised controlled trials (RCTs) examined the efficacy and safety of adjunctive PGD therapy for AP-induced hyperprolactinaemia.

Methods English (PubMed, Embase, Cochrane Library, PsycINFO) and Chinese (Chinese National Knowledge Infrastructure, Wanfang Data) databases were systematically searched up to 10 June 2018. The inclusion criteria were based on PICOS—*P*articipants: adult patients with schizophrenia; *I*ntervention: PGD plus APs; *C*omparison: APs plus placebo or AP monotherapy; *O*utcomes: efficacy and safety; *S*tudy design: RCTs. The weighted mean difference (WMD) and risk ratio (RR) along with their 95% CIs were calculated using Review Manager (RevMan) V.5.3 software.

Results Five RCTs (n=450) were included and analysed. Two RCTs (n=140) were double-blind and four RCTs (n=409) reported 'random' assignment with specific description. The PGD group showed a significantly lower serum prolactin level at endpoint than the control group (n=380, WMD: −32.69 ng/mL (95% CI −41.66 to 23.72), $p<0.00001$, $I^2=97\%$). Similarly, the superiority of PGD over the control groups was also found in the improvement of hyperprolactinaemia-related symptoms. No difference was found in the improvement of psychiatric symptoms assessed by the Positive and Negative Syndrome Scale (n=403, WMD: −0.62 (95% CI −2.38 to 1.15), $p=0.49$, $I^2=0\%$). There were similar rates of all-cause discontinuation (n=330, RR 0.93 (95% CI 0.63 to 1.37), $p=0.71$, $I^2=0\%$) and adverse drug reactions between the two groups. According to the Grading of Recommendations Assessment, Development and Evaluation approach, the level of evidence of primary and secondary outcomes ranged from 'very low' (14.3%), 'low' (42.8%), 'moderate' (14.3%), to 'high' (28.6%).

Conclusions Current evidence supports the adjunctive use of PGD to suppress elevated prolactin and improve prolactin-induced symptoms without significant adverse events in adult patients with AP-induced hyperprolactinaemia. High-quality RCTs with longer duration are needed to confirm these findings.

Trial registration number 42016037017.

INTRODUCTION

Hyperprolactinaemia induced by antipsychotics (APs), defined as an abnormally high serum prolactin level of greater than 25 ng/mL for men and 20 ng/mL for women,[1 2] is a common adverse drug reaction (ADR).[3] APs induce hyperprolactinaemia by enhancing prolactin secretion through their dopamine-blocking action in the tuberoinfundibular system.[4] The prevalence of hyperprolactinaemia is up to 76%–86% in patients receiving AP treatment.[5] Hyperprolactinaemia could result in severe menstrual irregularities, including amenorrhoea, gynaecomastia, galactorrhoea, sexual dysfunction, infertility and decreased bone mineral density, all of which would contribute to poor treatment adherence and reduced quality of life.[6 7]

Several treatment strategies have been suggested to suppress hyperprolactinaemia and improve the associated symptoms, although some of these strategies remain controversial. The frequently used treatment options include (1) dopamine agonists, such as bromocriptine (BMT), amantadine and cabergoline, all of which could induce abnormal involuntary movements;[1 8] (2) metformin, which may cause gastrointestinal symptoms;[9] (3) aripiprazole, which may cause sedation, insomnia and headache;[10–12] (4) using the lowest possible therapeutic dose of AP; however, this strategy may increase the risk of relapse;[13] and (5) switching to another AP, risking the occurrence of other ADRs, such as metabolic syndrome and sedation.[14 15]

In the past two decades growing evidence has suggested that Peony-Glycyrrhiza decoction (PGD), an herbal medicine formula consisting of Paeonia and Glycyrrhiza radices (shaoyao-gancao-tang in Chinese and shakuyaku-kanzo-toin in Japanese, TJ-68),

Search terms (in the title or abstract): ("Peony-Glycyrrhiza"[MeSH] OR paeonia lacliflora and Glycyrrhiza uralensis OR shakuyaku-kanzo-to OR shaoyao gancao OR glycyrrhiza OR paeoniae) AND ("prolactin"[MeSH] OR hyperprolactinemia OR prolactin OR amenorrhea OR menstrual irregularities OR oligomenorrhea OR galactorrhea OR gynecomastia)

A total of 241 articles published by June 10, 2018 were identified from PubMed (n=26), Embase (n=91), PsycINFO (n=7), and Cochrane Library (n=18), China Knowledge Network (n=32), and WanFang Database (n=67)

61 duplicate reports excluded

The titles or abstract of the 180 articles were screened

163 reports excluded

The full text of 17 articles were examined to determine whether or not they reported the efficacy and safety of adjunctive PGD for antipsychotic-induced Hyperprolactinaemia

Full-text articles excluded (n = 12):
-Overlapping data (n=3)
-Case report (n=2)
-Open label (n=4)
-PGD versus bromocriptine (n=1)
-PGD versus Guifu Dihuang pill (n=1)
-PGD versus biperiden (n=1)
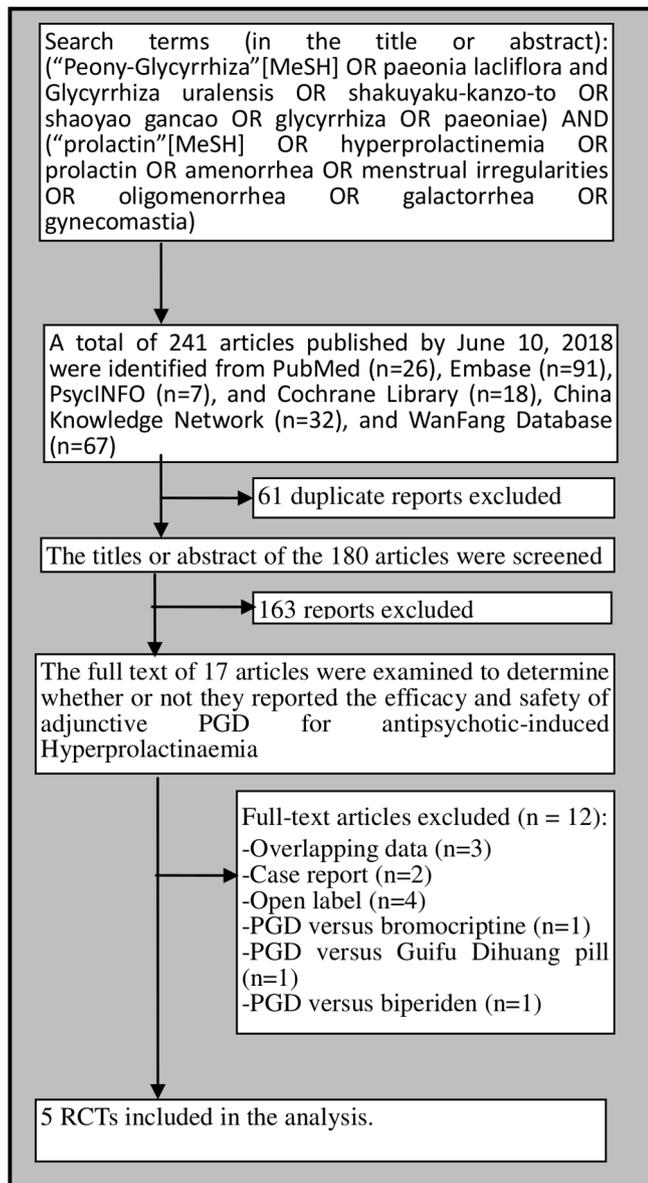
5 RCTs included in the analysis.

Figure 1 Flow chart of identification of studies. PGD, Peony-Glycyrrhizadecoction; RCT, randomized controlled trial.

can significantly improve prolactin-induced symptoms in patients with AP-induced hyperprolactinaemia.[1 16–22] A number of case reports,[21 22] observational studies[17–20] and randomised controlled trials (RCTs)[16 23–26] of adjunctive PGD for AP-induced hyperprolactinaemia have been published with mixed results.

This meta-analysis set out to assess the efficacy and safety of adjunctive PGD in the treatment of AP-induced hyperprolactinaemia, including recent studies published in Chinese-language and English-language journals.

METHODS
Inclusion and exclusion criteria
Two independent investigators (WZ, D-BC) assessed and screened the eligibility of studies based on the following criteria of PICOS: Participants: adult patients with schizophrenia; Intervention: PGD plus APs; Comparison: APs plus placebo or AP monotherapy; Outcomes: the primary outcome measures were efficacy of treatment (serum prolactin level and prolactin-related symptoms: reduction in the severity of galactorrhoea, amenorrhoea and oligomenorrhoea)—key secondary outcomes were improvement of psychiatric symptoms assessed by the Positive and Negative Syndrome Scale (PANSS)[27] or the Brief Psychiatric Rating Scale,[28] ADRs assessed using the Treatment Emergent Symptom Scale (TESS),[29] and all-cause discontinuation; Study design: only RCTs examining the efficacy and safety of adjunctive PGD for AP-induced hyperprolactinaemia. Case report/series, observational studies and meta-analyses and systematic reviews were excluded.

Search strategy
Two reviewers (WZ, D-BC) independently searched PubMed, Embase, Cochrane Library, PsycINFO, Chinese National Knowledge Infrastructure and Wanfang Data for trials evaluating adjunctive PGD for AP-induced hyperprolactinaemia from inception of these databases until 10 June 2018. The keywords used for the searches included the following: ("Peony-Glycyrrhiza" (MeSH) OR paeonia lacliflora and Glycyrrhiza uralensis OR shakuyaku-kanzo-to OR shaoyao gancao OR glycyrrhiza OR paeoniae) AND ("prolactin" (MeSH) OR hyperprolactinemia OR prolactin OR amenorrhea OR menstrual irregularities OR oligomenorrhea OR galactorrhea OR gynecomastia). Reference lists from relevant review articles for additional studies were hand-searched. The two reviewers (WZ, D-BC) independently assessed all trials by judging their clinical, methodological and statistical heterogeneity to decide which ones to include in the qualitative or quantitative synthesis. Any disagreement was discussed with a third reviewer (Y-TX).

Data extraction
Data of each study were independently identified, checked and extracted by the two reviewers (WZ, D-BC). Results based on intention-to-treat were preferred to observed cases data. Inconsistencies were resolved by consensus involving a third reviewer. In addition, missing information was obtained by contacting the first or corresponding authors, or was extracted from graphs or figures of included RCTs if possible.

Evaluation of quality of included studies
The included RCTs were assessed by two reviewers (WZ, D-BC) using the Cochrane risk of bias with seven dimensions as follows: (1) random sequence generation; (2) allocation concealment; (3) blinding of the subjects and the treatment providers; (4) blinding of the result evaluators; (5) incomplete results data; (6) selective reporting; and (7) other potential risks.[30] The quality of evidence and strength of recommendations of outcome measure of PGD for hyperprolactinaemia were assessed using the Grading of Recommendations Assessment, Development

Table 1 Characteristics of the included studies

Study	Duration (weeks)	Patients, n (intervention/control) Male, n (intervention/control)	Age (years)*	AP	PGD dose	Change of serum prolactin level (ng/mL)	Hyperprolactinaemia-induced adverse effects at endpoint†
Gu et al, 2016[23]	8	120 (60/60) 53 (28/25)	30	Olanzapine	Paeoniae Radix Alba (15 g) and Glycyrrhizae Radix Et Rhizoma (15 g)	PGD: −19.98±7.17 Control: −0.48±6.81	NA
Man et al, 2016[24]	16	99 (49/50) 0	30	AP‡	Paeoniae Radix Alba and Glycyrrhizae Radix Et Rhizoma: 45.0 g/d§	PGD: −5.90±70.46 Placebo: −19.90±57.59	PGD: 68% Placebo: 54%
Xie et al, 2015[16]	12	120 (80/40) 0	32	Risperidone	A group: Paeoniae Radix Alba (30 g) and Glycyrrhizae Radix Et Rhizoma (30 g) B group: Paeoniae Radix Alba (30 g) and Glycyrrhizae Radix Et Rhizoma (15 g)	PGD (A group): −54.70±20.91 PGD (B group): −55.40±24.62 Control: 9.77±23.20	NA
Yang et al, 2017[25]	8	41 (21/20) 0	28	Amisulpride	Paeoniae Radix Alba (60 mg) and Glycyrrhizae Radix Et Rhizoma (30 mg)	PGD: −22.62±4.92 Placebo: −0.98±5.35	PGD¶: 79% Placebo: 0%
Yue, 2016[26]	4	70 (35/35) 35 (17/18)	32	AP**	Paeoniae Radix Alba (15 g) and Glycyrrhizae Radix Et Rhizoma (10 g)	PGD: −14.97±8.09 Control: 4.33±10.00	NA

*Available data were extracted based on mean baseline value of each included trials.
†Percentage of improvement.
‡Including risperidone, paliperidone, sulpiride, amisulpride, lanzapine, ziprasidone, quetiapine, perphenazine, clozapine and chlorpromazine.
§Paeonia and Glycyrrhiza radices in a ratio of 1:1 in weight.
¶Including 2 (amenorrhoea), 4 (abnormal menstruation), 3 (galactorrhoea), 4 (reduced libido) and 2 (sexlessness).
**No detailed use of AP.
AP, antipsychotic ; NA, not available; PGD, Peony-Glycyrrhiza decoction.

and Evaluation (GRADE) system as 'very low', 'low', 'moderate' or 'high'.[31 32]

Statistical methods

The meta-analysis was performed according to the recommendations of the Cochrane Collaboration using Review Manager (RevMan) (V.5.3) (http://www.cochrane.org). For continuous outcomes and dichotomous outcomes, weighted mean differences (WMDs) and risk ratios (RRs) with their 95% CIs were reported, respectively. The heterogeneity of meta-analytic pooling was measured using the χ^2 ($p<0.1$) or I^2 ($<50\%$) statistics. A random-effect model by DerSimonian and Laird[33] was used in all cases. One RCT[16] with three study arms was included in the meta-analysis, and in order to include each of the two adjunctive PGD arms separately we included the AP monotherapy condition twice in the analysis, but assigned half of the total patients randomised to each PGD arm

in order to not inflate the number of AP monotherapy patients, as recommended by prior studies.[34 35]

Publication bias was assessed using funnel plots and the Egger's test.[36] All analyses were two-tailed, with alpha set to 0.05.

RESULTS

Search results

Figure 1 presents the flow chart of study selection. Altogether 241 potentially relevant published studies from English (142 trials) and Chinese (99 trials) databases were identified. Of them, three RCTs that compared PGD with BMT,[1] Guifu Dihuang pill[37] or biperiden,[38] respectively, were excluded. Finally, five RCTs[16 23–26] were included in this meta-analysis.

Table 2 Evaluation of risk of bias in the included studies

Study	Random sequence generation	Allocation concealment	Blinding of participants and providers	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting	Other biases
Xie *et al*, 2015[16]	Low	High	High	High	Low	Unclear	Unclear
Gu *et al*, 2016[23]	Low	High	High	High	High	Unclear	Unclear
Man *et al*, 2016[24]	Low	Low	Low	Low	Unclear	Low	Unclear
Yue, 2016[26]	Low	High	High	High	Low	Unclear	Unclear
Yang *et al*, 2017[25]	Unclear	Unclear	Unclear	Low	Low	Low	Unclear

Study characteristics

All five RCTs[16 23–26] (n=450) were conducted in China (table 1). These RCTs had a sample size of 90.0 (30.6) (range=41–120, median=99) and an average length of 9.6 (4.1) (range=4–16, median=8) weeks. Participants were 30.4 (1.5) (range=28–32, median=30) years old and 80.4% were female. Only one RCT[24] mentioned PGD fixed dose (45.0 g/day) (table 1).

Quality assessment

Although 80% (4/5) of the RCTs[16 23 24 26] reported randomisation methods with a specific description, only one RCT was rated as low risk regarding allocation concealment (table 2). Similarly, 60% (3/5) of the RCTs[16 25 26] were rated as low risk in terms of incomplete outcome data. Based on the GRADE approach, the quality of evidence presented for each outcome ranged from 'very low' (14.3%), 'low' (42.8%), 'moderate' (14.3%), to 'high' (28.6%) (table 3).

Efficacy

The PGD group had a significant decrease in the serum prolactin level at endpoint compared with the control group (5 RCTs, n=380, WMD: −32.69 ng/mL (equivalent to 693.03 mIU/L) (95% CI −41.66 to 23.72), $p<0.00001$, I^2=97%; figure 2). Only two RCTs[24 25] reported hyperprolactinaemia-induced symptoms. In one RCT,[25] 79%

Table 3 GRADE analyses: adjunctive Peony-Glycyrrhiza decoction for antipsychotic-induced hyperprolactinaemia

Outcomes	Subjects	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Overall quality of evidence*
Prolactin level	380	No	Serious†	No	No	Serious‡	Large§	+/+/+/− Moderate
PANSS total scores	403	No	No	No	No	No	No	+/+/+/+ High
Discontinuation due to any reason	330	No	No	No	No	No	No	+/+/+/+ High
TESS total scores	187	Serious¶	Serious†	No	No	Serious‡	No	+/−/−/− Very low
Akathisia	190	Serious¶	No	No	No	Serious**	No	+/+/−/− Low
Constipation	190	Serious¶	No	No	No	Serious**	No	+/+/−/− Low
Headache	190	Serious¶	No	No	No	Serious**	No	+/+/−/− Low

*GRADE Working Group grades of evidence: high quality: further research is very unlikely to change our confidence in the estimate of effect; moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: we are very uncertain about the estimate.
†Meta-analytic results presented a serious inconsistency when I^2 values were greater than 50% or $p<0.1$ in the Q statistics.
‡For continuous outcomes, N<400.
§Studies with large effects provided increased quality of evidence. Large effects=effect size ≥0.8.
¶All studies reported as having a serious bias used an open-label method, only mentioned random allocation without describing the method and withdrawal from the study.
**For dichotomous outcomes, N<300.
GRADE, Grading of Recommendations Assessment, Development and Evaluation; PANSS, Positive and Negative Syndrome Scale; TESS, Treatment Emergent Symptom Scale.
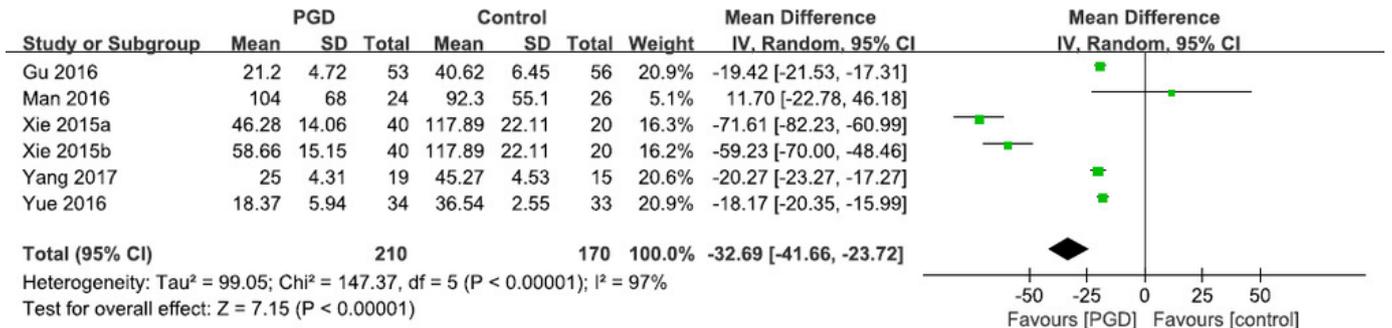
Figure 2 Adjunctive Peony-Glycyrrhiza decoction (PGD) for antipsychotic-induced hyperprolactinaemia: forest plot for serum prolactin level at endpoint (ng/mL). IV, inverse-variance.

of patients in the PGD group and 0% in the placebo group reported improvement in hyperprolactinaemia-induced adverse effects. In another RCT,[24] 68% of patients on PGD and 54% on placebo reported improvement in hyperprolactinaemia-induced adverse effects.

Psychiatric symptoms
Meta-analysis of PANSS total scores (5 RCTs, n=403, WMD: −0.62, 95% CI −2.38 to 1.15, p=0.49, I^2=0%) showed no significant difference between the PGD augmentation and AP monotherapy groups (table 4).

ADRs and discontinuation rates
Meta-analysis of akathisia, constipation and headache (p=0.53–0.78) found no significant difference between the PGD group and control group (table 4). Similarly, meta-analysis of TESS total score showed no significant difference (n=187, WMD: 6.95, 95% CI −1.23 to 15.14, p=0.10, I^2=99%; table 4).

There were similar rates regarding discontinuation due to any reason between the two groups (4 RCTs, n=330, RR: 0.93, 95% CI 0.63 to 1.37, p=0.71, I^2=0%; table 4).

Publication bias
Publication bias could not be evaluated using a funnel plot graph or the Egger's test[36] since the number of included RCTs was less than 10.[39]

DISCUSSION
Main findings
To the best of our knowledge, this was the first meta-analysis examining the efficacy and safety of adjunctive PGD

for AP-induced hyperprolactinaemia. The main finding was that adjunctive PGD significantly suppresses elevated prolactin and improved prolactin-induced symptoms, which was consistent with the results of case reports,[21 22] observational studies[17–20] and a systematic review.[40] PGD was safe and well tolerated in patients with AP-induced hyperprolactinaemia.

Implications
There are a few possible reasons for the therapeutic effect of PGD on hyperprolactinaemia. First, PGD may directly suppress the elevated prolactin and testosterone production by affecting their conversion processes and the relevant enzymes.[1] Second, PGD may modulate the expression of D2 receptor and dopamine transporter.[2 41] A recent study[42] found that paeoniflorin and liquiritin, both major constituents of PGD, are associated with the improvement of hyperprolactinaemia. Third, PGD may inhibit P450 enzymes that metabolise APs.[43] However, the mechanisms underlying PGD for hyperprolactinaemia need to be further explored.

In clinical practice, the prevalence of AP-induced hyperprolactinaemia has been often underestimated due to lack of visible signs of hyperprolactinaemia-related symptoms, patients' embarrassment with the symptoms and clinicians' lack of awareness.[42] There are no therapeutic strategies approved by the Food and Drug Administration in the treatment of AP-induced hyperprolactinaemia, although meta-analyses[12 44] have found that adjunctive aripiprazole and metformin may be effective augmentation strategies reducing elevated prolactin

Table 4 Adjunctive Peony-Glycyrrhiza decoction for antipsychotic-induced hyperprolactinaemia: secondary outcomes

Secondary outcomes	Subjects	SMDs/RRs (95% CI)	I^2 (%)	p-value
PANSS total scores	403	−0.62 (−2.38 to 1.15)	0	0.49
Discontinuation due to any reason	330	0.93 (0.63 to 1.37)	0	0.71
TESS total scores	187	6.95 (−1.23 to 15.14)	99	0.10
Akathisia	190	1.40 (0.46 to 4.22)	0	0.55
Constipation	190	1.48 (0.44 to 5.02)	0	0.53
Headache	190	0.85 (0.27 to 2.67)	0	0.78

PANSS, Positive and Negative Syndrome Scale;
RRs, risk ratios; SMDs, standard mean differences; TESS, Treatment Emergent Symptom Scale.

and improving hyperprolactinaemia-induced symptoms. We could not locate any head-to-head trials to compare PGD and aripiprazole/metformin in treating AP-induced hyperprolactinaemia.

Adjunctive PGD appears to be relatively safe and well tolerated. Unlike BMT, a dopamine agonist, adjunctive PGD does not exacerbate psychosis.[1] Ota[38] and colleagues have found that adjunctive PGD significantly improved extrapyramidal symptoms.

Strengths and limitations of this study

The majority strength of this study is the inclusion of Chinese database in the search. The results of this study need to be interpreted with caution due to several limitations. First, only five RCTs met the inclusion criteria and were included in the study. In addition, the sample sizes were relatively small and the methodology of the RCTs was heterogeneous. Second, half of quality of evidence was rated as 'very low' or low' according to the GRADE approach. However, Guyatt[45] and colleagues suggested that low-quality evidence may still result in strong recommendations as strong recommendations are not always based on high-quality evidence. Third, the dose–response effect of adjunctive PGD in suppressing the elevated prolactin was not analysed due to missing information. Fourth, only English and Chinese databases were searched in this review, while relevant studies may have also been published in other languages.

CONCLUSION

There has been no effective pharmacotherapy for hyperprolactinaemia, a frequent side effect of AP treatment. Evidence from this meta-analysis supports the use of adjunctive PGD in AP-induced hyperprolactinaemia, which has important clinical implications for the treatment of hyperprolactinaemia. Adjunctive PGD is not associated with increased ADR and exacerbation of psychosis. High-quality RCTs of PGD for hyperprolactinaemia are warranted.

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