REVIEW

Association Between 5-Alpha Reductase Inhibitor Use and The Risk of Depression: A Meta-Analysis

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Purpose: To explore the association between 5α-reductase inhibitors (5ARIs) use and risk of depression based on published literature through a meta-analysis.

Materials and methods: A comprehensive literature search was conducted by searching Pubmed, Embase, Cochrane Library, CBM, CNKI, and VIP databases up to June, 2019. Summarized risk ratios (RRs) with 95% confidence intervals (CIs) were calculated to evaluate the strength of association between 5ARIs and depression. Subgroup analyses were performed according to population, 5ARI types, degree of depression, and publication date. Registered in PROSPERO under number CRD42018096147.

Results: A total of 6 clinical studies with 265672 participants were included in our meta-analysis. The application of 5ARIs could significantly increase the risk of depression based on both pooled unadjusted (95% CI: 1.28-2.78, RR = 1.89, *P* = .001) and multivariable adjusted RRs (95% CI: 1.01-1.17, RR = 1.09, *P* = .03). In subgroup analyses, dutasteride was associated with depression significantly (95% CI: 1.37-1.70, RR = 1.53, *P* < .001), while finasteride was not. As to the degree of depression, 5ARIs mainly caused mild depression (95% CI: 1.91-2.33, RR = 2.11, *P* < .001), instead of moderate or severe depression.

Conclusion: We concluded that 5ARIs could potentially increase the risk of depression. Clinicians need to carefully consider the use of 5ARIs for benign prostatic hyperplasia and androgenic alopecia patients, especially those exhibiting risk factors for depression or those who have a previous history of depression. More studies with larger sample size and comprehensive study design are needed to further verify our outcomes.

Keywords: association; 5α-reductase inhibitors; depression; meta-analysis

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a major contributor to lower urinary tract symptoms (LUTS) due to bladder outlet obstruction in elderly men. Both European Association of Urology (EAU) and American Urological Association (AUA) guidelines recommend 5α-reductase inhibitors (5ARIs) as the primary pharmacological treatment for LUTS secondary to BPH.[1,2] 5ARIs could lower the conversion of testosterone to dihydrotestosterone (DHT) through targeting the 5α-reductase enzyme family,(3) so 5ARIs are commonly used for BPH and androgenic alopecia. Two equally efficacious 5ARIs are available for clinical use: finasteride and dutasteride. Finasteride inhibits only type 2 5α-reductase, whereas dutasteride inhibits both types 1 and 2.

The most relevant adverse effect of 5ARIs is sexual dysfunction, including reduced libido, erectile dysfunction (ED) and ejaculation disorders.[4-6] Some studies[7-9] also reported a significant increase in depressive symptoms among patients exposed to Propecia (finasteride 1 mg), which might even exist after discontinuation of the medication. These findings resulted in the addition of depression to the professional labels for Propecia in the United States. A recent population-based matched cohort study[10] indicated that the use of 5ARIs was significantly associated with increased risk of depression. However, another large population-based study showed that the risk of depression did not increase with 5ARIs.[11] Above all, the association between 5ARIs use and the risk of depression is still controversial.

So far, it is difficult to draw a solid conclusion from published studies reporting depression after 5ARIs because most of them are case series;[12-14] few controlled studies were published, and their results remained contradictory.[8,10,11] Additionally, depression is not included in the adverse effects of 5ARIs in either EAU or AUA guidelines due to inadequate levels of evidence.

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Table 1. Baseline characteristics of included studies.

Included Studies	Country	Ethnicity	Study Duration	Study Design	LOE	Type Of 5ARIs	Diagnosis of Depression		No. Participants	Mean Age (Yr)	Mean Follow-Up Time (Mo)	No. Depression (%)	NOS Scores[a]
Irwig et al, 2012[18]	USA	Mixed	2010-2011	Prospective cohort study	2b	Finasteride	Beck Depression Inventory	5ARI users	61	31	37	46 (75.41%)	********
								non-5ARI users	29	26.2	10	3 (10.34%)	
Pietrzyk et al, 2015[19]	Poland	European	2012-2013	Cross-sectional study	4	NM	Beck Depression Inventory	5ARI users	1623	65	-	519 (31.98%)	-
								non-5ARI users	1918			208 (10.84%)	
Unger et al, 2016[20]	USA	Mixed	1993-1997	Retrospective cohort study	3	Finasteride	Electronic medical records	5ARI users	6941	63.5	120	1227 (17.68%)	**********
								non-5ARI users	6994	63.6		1231 (17.6%)	
Welk et al, 2017[10]	Canada	European	2003-2013	Retrospective cohort study	3	Dutasteride, finasteride	Electronic medical records	5ARI users	89844	75	18.84	1750 (1.95%)	**********
								non-5ARI users	89844	75	19.2	1231 (1.37%)	
Hagberg et al, 2017[11]	USA	Mixed	1992-2013	Retrospective cohort study	3	Dutasteride, finasteride	Electronic medical records	5ARI users	3044	69.2	147.1	195 (6.41%)	********
								non-5ARI users	65334			2213 (3.39%)	
Catalano et al, 2019[21]	Italy	European	2017-2018	Cross-sectional study	4	Dutasteride	Beck Depression Inventory	5ARI users	20	73	30	NA	-
								non-5ARI users	20	71			

Abbreviations: 5ARI 5α-reductase inhibitor, LOE: level of evidence, NOS: Newcastle-Ottawa scale, NM: not mentioned.
a Newcastle-Ottawa scale points, one star means one point.

[1,2] Consequently, we performed this meta-analysis to clarify the association between 5ARIs use and the risk of depression based on current original controlled studies, hoping to provide some references for clinicians and 5ARIs users.

MATERIALS AND METHODS

This meta-analysis was conducted in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) guidelines. The protocol of this analysis was registered in PROSPERO, and the registration number is CRD42018096147.

Search strategy

A comprehensive electronic literature search using the Pubmed, Embase, Cochrane Library, CBM, CNKI, and VIP databases was performed to identify controlled studies investigating the association between 5ARIs use and the risk of depression. The date limit of this search was from the inception of these databases to June 2019. Search terms were "'5-alpha reductase inhibitors' or '5α-reductase inhibitors' or '5-a reductase inhibitors' or '5ARI' or '5-ARI' or 'finasteride' or 'dutasteride'" in combination with "'depression' or 'depressive'". References of relevant studies were also checked to identify potential records. No language restrictions existed in this search.

Inclusion and exclusion criteria

Only controlled clinical studies exploring the association between 5ARIs use and the risk of depression were included in this meta-analysis. Accordingly, studies without the control group of non-5ARI users were excluded. Meanwhile, studies as abstracts, case reports, conference proceedings, reviews, animal experiments, or repeated publications were also excluded.

Relevant studies' search and screen, quality assessment and data extraction were performed by two reviewers (T.D. and X.D.) independently. Discrepancies were resolved via open discussion.

Study quality assessment and data extraction

The level of evidence (LOE) of all eligible studies was assessed by the criteria provided by the Oxford Centre for Evidence-based Medicine.[15] The quality of non-randomized controlled studies included was evaluated using the Newcastle-Ottawa scale (NOS).[16]

Data from all eligible studies were attentively extracted as follows: study country, population, institution and period, research methodology, type of 5ARIs, diagnostic criteria of depression, characteristics of participants, follow-up time, and related outcomes. Authors of relevant studies were contacted to obtain incomplete data.

Statistics analysis

For the included case-control studies, odds ratios (ORs)

Table 2. Results of subgroup analyses

	Subgroups	Number of Included Studies	No. Participants	Heterogeneity I^2	Heterogeneity *P*	RR (95% CI)
Study population	European population	2	183229	99%	< .001	2.04 (1.00-4.17)
	USA population	3	82403	97%	< .001	1.85 (1.01-3.38)
5ARI type	Finasteride	3	99923	94%	< .001	1.34 (0.96-1.87)
	Dutasteride	1	93790	NA		1.53 (1.37-1.70)
Degree of depression	Mild depression	2	3631	0%	.32	2.11 (1.91-2.33)
	Moderate and severe depression	2	3631	85%	.01	4.74(0.14-162.14)
Study publication date	Before 2015	2	3631	62%	.10	3.93 (1.72-8.98)
	After 2015	3	262001	98%	< .001	1.39 (1.00-1.91)

Abbreviations 5ARI: 5α-reductase inhibitor, RR: risk ratio, CI: confidence interval, NA: not applicable.
Bold numbers mean the *P*-value is < .05.

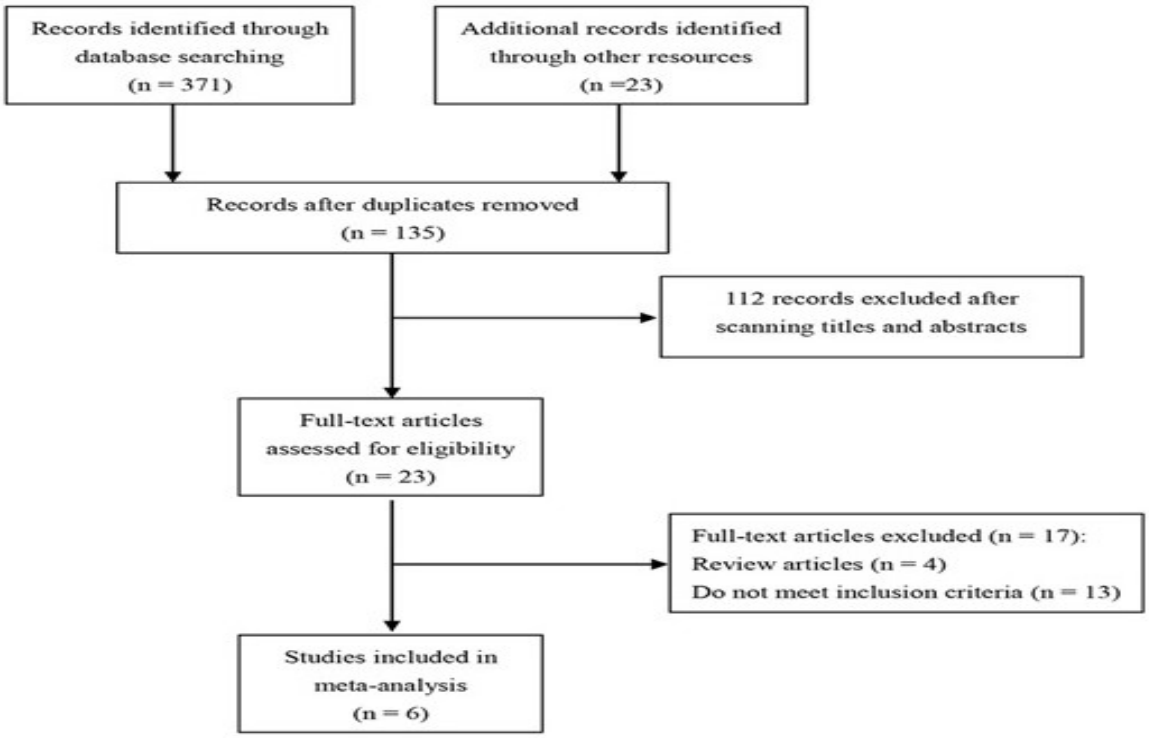

Figure 1. Flow diagram of study selection.

of 5ARIs use on the risk of depression were extracted and converted to risk ratios (RRs) based on the formula RR=OR/((1-P"0")+(P"0" ×OR)) (P0 indicates the incidence of the outcome of interest in the nonexposed group) according to the Cochrane Handbook.[17] Summarized unadjusted RRs with 95% confidence intervals (CIs) were calculated to assess the strength of association between 5ARIs and the risk of depression. Available adjusted RRs of depression risk and mean differences (MDs) of the Beck Depression Inventory-second edition (BDI-II) score in eligible studies were also pooled as references. Chi-square test-based Q- and I2- statistic was used to test the heterogeneity among included studies.[18] The fixed-effect model was used when no significant heterogeneity existed with a ^{P} value > 0.10. Otherwise, the random-effect model was applied. All results in this meta-analysis were considered significant with a two-sided *P* value < 0.05. Subgroup analyses were performed based on the study population, type of 5ARI, degree of depression, and study publication date. Sensitivity analyses were conducted by excluding every single eligible study in turn. The publication bias among eligible studies was assessed through the inverted funnel plot visual inspection and the Egger's test. All statistical analyses were conducted by RevMan (version 5.3; Cochrane Collaboration, Oxford, UK) and STATA (version 13.0; StataCorp, College Station, Texas, USA) software.

RESULTS

Characteristics and quality assessments of eligible studies

After article reviewing and screening carefully, six controlled clinical studies[8,10,11,19,20,21] were included in this meta-analysis (**Figure 1**). And a total of 265672 participants were involved. Table 1 showed the baseline characteristics of all eligible studies. Among them, 4[8,10,11,20] were cohort studies and 2[19,21] were cross-sectional study. As to the study regions, 3 studies[8,11,20] were conducted in the USA, and the other 3 were performed in Canada[10], Poland[19], and Italy[21] respectively. Regarding to the study publication date, 2 studies[8,19] were published before 2015, while 4 studies[10,11,20,21] were published after 2015. Among the six included studies, the depression rates among 5ARI users ranged from 1.95% to 75.41%, with an average rate of 3.68% (3737/101513); whereas the average rate of depression among non-5ARI users was 2.98% (4886/164119) with a range of 1.37% to 17.6%.

LOEs of all 6 included articles were listed in Table 1. Among the 6 clinical studies, 4[8,10,11,20] of them were considered as high quality with a NOS score more than 6 stars.

Meta-analysis

Unadjusted RRs of 5ARIs use on the risk of depression could be extracted or calculated from 5 clinical studies[8,10,11,19,20]. Result of the meta-analysis showed that the use of 5ARIs could significantly increase the risk of depression (95% CI: 1.28-2.78, RR = 1.89, *P* = .001), with significant heterogeneity among them (I2 = 98%, *P* < .001) (**Figure 2**). No obvious publication bias was detected through either inverted funnel plot or Egger's test (t = 1.44, *P* = .245).

Multivariable adjusted RRs were available in 2 clinical studies(11,20). And the summarized adjusted RR and its 95%CI also indicated that 5ARIs use could significantly increase the risk of depression (95% CI: 1.01-1.17, RR = 1.09, *P* = .03) without heterogeneity (I2 = 0%, *P* = .53) (**Figure 3**).

Mean differences of BDI-II score were also available

Table 2. Results of subgroup analyses

Excluded study	Included participants		Heterogeneity	RR (95% CI)
	I^2	*P*		
Irwig et al, 2012(8)	265542	98%	< .001	1.67 (1.13-2.48)
Pietrzyk et al, 2015(19)	262091	97%	< .001	1.56 (1.12-2.17)
Unger et al, 2016(20)	251697	97%	< .001	2.27 (1.49-3.46)
Welk et al, 2017(10)	85944	99%	< .001	2.21 (1.18-4.13)
Hagberg et al, 2017(11)	197254	98%	< .001	1.91 (1.20-3.03)

Abbreviations: RR: risk ratio, CI: confidence interval.
Bold numbers mean the *P*-value is < 0.05.

in 2 clinical studies[8,21]. However, no significant difference was found in BDI-II scores between 5ARI and non-5ARI groups (95% CI: -8.62 to 26.25, MD = 8.81, *P* = .32) (**Figure 4**).

Subgroup analysis

Subgroup analyses of unadjusted RRs of 5ARIs use on the risk of depression were conducted according to the study populations, 5ARI type, degree of depression, and study publication date. Table 2 showed the results of all subgroup analyses. Positive association between 5ARIs use and increased risk of depression was only found in USA population (95% CI: 1.01-3.38, RR = 1.85, *P* < .05), dutasteride (95% CI: 1.37-1.70, RR = 1.53, *P* < .001), mild depression (95% CI: 1.91-2.33, RR = 2.11, *P* < .001), and study published before 2015 (95% CI: 1.72-8.98, RR = 3.93, *P* = .001) subgroups.

Sensitivity analysis

Sensitivity analyses of summarized unadjusted RRs of 5ARIs use on the risk of depression were conducted to evaluate the stability and reliability of our results by excluding every single eligible study in turn. As shown in Table 3, no matter which eligible study was excluded, the pooled result remained significant, which means our results are stable and reliable. However, in the sensitivity analyses, we did not find the source of heterogeneity among the five included studies, cause the exclusion of any single study could not reduce the heterogeneity.

DISCUSSION

In our meta-analysis, we included 6 clinical studies with 265672 participants. We found that the application of 5ARIs may increase the risk of depression. From our subgroup analyses, dutasteride was associated with the existence of depression, while this relationship could not be observed with finasteride. As to the degree of depression, 5 ARIs mainly caused mild depression, instead of moderate or severe depression. Sensitivity analyses indicated that our results are stable and reliable.

According to our unadjusted results from 5 studies, BPH or androgenic alopecia patients having a history of 5ARIs had a significant higher tendency to suffer from depression. In a study conducted by Unger et al, an increase in the existence of depression was detected in finasteride users.[20] A large observational study based on the General Practice Research Database also reported similar results, showing a probable positive relationship between 5ARIs and depression.[22] Several clinical researches discovered the occurrences of depression in their patients receiving 5ARIs and their findings should not be ignored, which need further necessary analysis. Although with different affinities with 5α-reductase, finasteride and dutasteride had similar mechanisms when causing potential risk of depression.[23] First, 5α-reductase participates in the synthesis of some neuroactive steroids.[24] These are not only produced by the central nervous system itself, but also by the gonads and adrenal glands and then transported to the brain.[25] 5ARIs, including finasteride and dutasteride, can pass the blood-brain barrier and inhibit the activity of 5α-reductase, so the concentration of a variety of neuroactive steroids reduces.[26-28] Second, γ-aminobutyric acid (GABA) is an important inhibitory neurotransmitter. 5α-reductase promotes the formation of allopregnanolone, which is responsible for depression, tension and anxiety, owing to its binding to GABA receptor.[29,30] Therefore, the

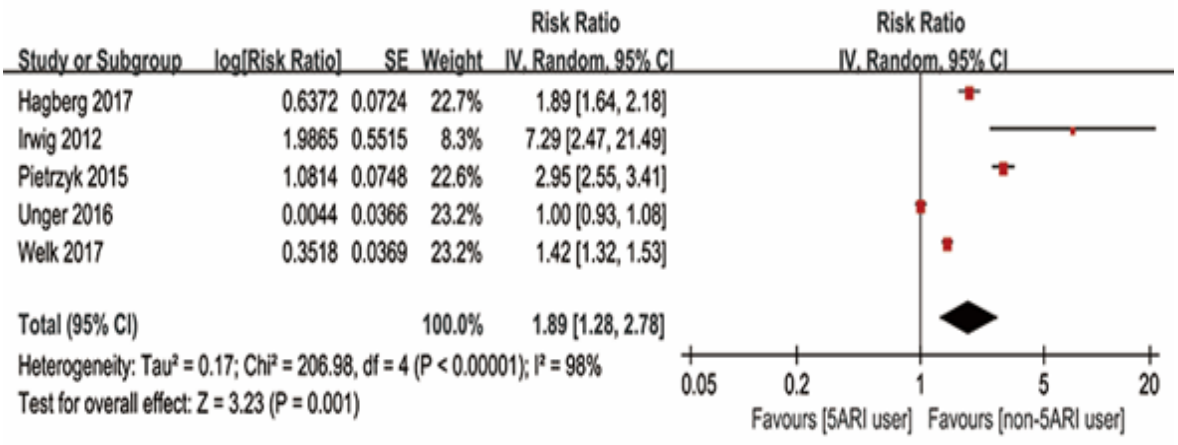

Figure 2. Forest plot of unadjusted RR and 95% CIs of 5ARI use for risk of depression.

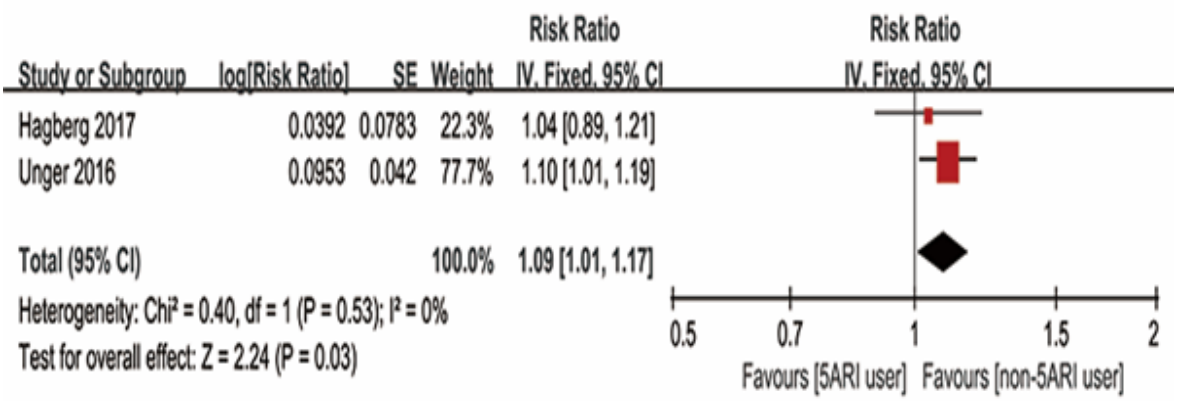

Figure 3. Forest plot of multivariable adjusted RR and 95% CIs of 5ARI use for risk of depression.

application of 5ARIs decreases the secretion of allopregnanolone and suppresses GABA's function. Third, in laboratory tests, levels of neuroactive steroids were lower in BPH patients who received finasteride.31 This phenomenon was also observed among patients with depression,32 further proving the potential association between 5ARIs and depression. Furthermore, some experiments were conducted on animals. Rodents tended to have anxiolytic and depressive behaviors after being given finasteride. They were also shown to have a lower level of plasma allopregnanolone compared to controls.[33,34] Except for the pharmacological pathways, 5ARIs have other adverse events, such as loss of libido and ED, which may also lead to depression. Taken together, these clinical findings and the experimental research provided some evidence for the increased risk caused by 5ARIs, confirming our results to some extent.

After adjusting for confounding factors, our results still showed that 5ARIs use was significantly associated with an increased risk of depression. BPH and depression could share some kinds of co-risk factors, including old age, smoking, and the presence of chronic disease.[35] Apart from this, BPH itself could induce depression due to LUTS. Pietrzyk and colleagues confirmed the association between LUTS and depression, indicating that the severity of urinary urgency, frequency, and increased nocturia really influenced male patients' quality of life drastically.[19] In our meta-analysis, we adjusted our data for confounding factors based on 2 original studies; however, we did not know the details in the factors included in their researches. In addition, pooled mean differences of BDI-II score were also calculated by combining two studies, however, no significant difference was found between the two groups. Since these data from only 2 articles were not adequate for a valid conclusion, these results should be taken into thorough consideration.

In our subgroup analyses, dutasteride was shown to increase the risk of depression significantly, while finasteride did not. There are 3 kinds of 5α-reductase in this family: 5α-reductase 1, 2, and 3. Dutasteride inhibits both type 1 and 2; however, finasteride has a specific affinity with only type 2, probably explaining its weak relationship with depression. Nevertheless, because only 3 articles were included in the subgroup finasteride and 1 for dutasteride, this result was not reliable enough to provide any guidance in the application of drugs. Besides, our data suggested that 5ARIs could only evoke mild depression, but not moderate or severe. 2 studies were included in this subgroup[8,19] and both used the Beck Depression Inventory to evaluate the severity of depression. Perhaps more clinical studies with larger sample sizes were necessary to ensure the accuracy and validity of our results.

Our meta-analysis had several limitations. Firstly, only 6 articles were included for us to reach the pooled re-

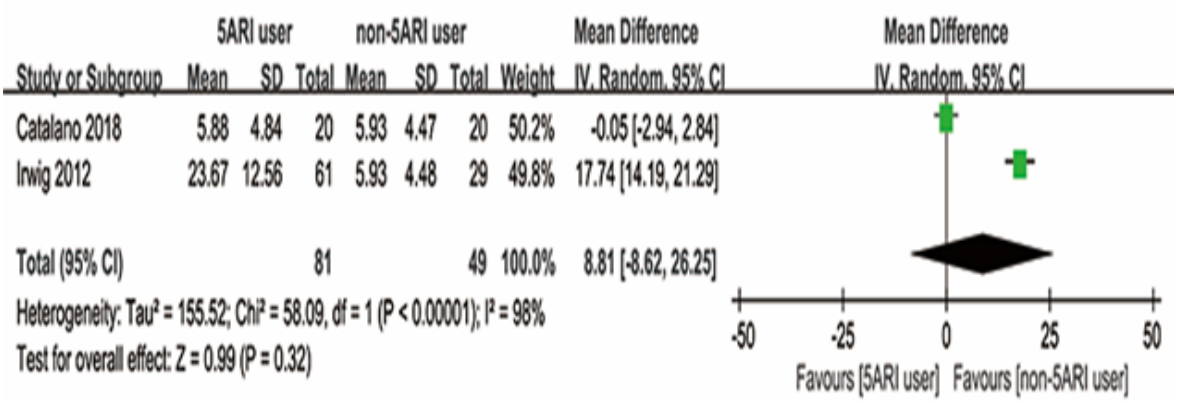

Figure 4. Forest plot of mean difference in BDI-II scores between 5ARI and non-5ARI groups.

Supplementary material 1: PRISMA checklist.

sults. The lack of original studies was a great obstacle to conduct a comprehensive meta-analysis. Subsequently, the number of studies in each subgroup was no more than 3, meaning our results cannot affect the current guidelines. Secondly, all studies were observational and no RCTs met our inclusion criteria. Selection bias and recall bias were apparent in retrospective studies, and for data extracted from databases, it was hard to guarantee the accuracy of diagnoses, because researchers could only judge the existence of disease according to the code recorded. It was also not realistic to achieve detailed information through recalling or scanning databases, such as types of the drugs, severity of diseases and so on. Thirdly, BPH and depression do share several similar risk factors, and LUTS from BPH could also cause depression. Although 2 included studies considered the confounding factors and adjusted for them, we still could not reach a valid conclusion due to the lack of enough evidences.

CONCLUSIONS

We finally conclude that 5ARIs could potentially increase the risk of depression. Based on several large observational studies and FDA's suggestions, clinicians need to carefully consider the use of 5ARIs for BPH and androgenic alopecia patients, especially those at risk for depression. More studies with a larger sample size and comprehensive study design are needed necessary to further verify our outcomes.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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