

Drug-induced gynecomastia: A systematic review and meta-analysis of randomized clinical trials

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Summary

Objective: To review the evidence concerning treatment-related gynecomastia in patients

taking spironolactone, antiandrogens, 5 alpha-reductase inhibitors, lipid-lowering and psychotropic drugs.

Material and methods: A search of Medline and EMBASE was performed up to 30 June 2021. We included randomized controlled trials comparing the effects of a drug belonging to these classes versus placebo or versus a drug of the same class.

Results: A total of 32 randomized controlled trials were included in the final review. There was an increased odds of gynecomastia in men receiving antiandrogens (OR = 17.38, 95% CI: 11.26 to 26.82; 6 trials, 9599 participants) and 5 alpha-reductase inhibitors compared to controls (OR = 1.77, 95% CI: 1.53 to 2.06; 7 series out of 6 trials, 34860 participants). The use of spironolactone in mixed gender populations was characterized by significantly higher odds of having gynecomastia compared to controls (OR = 8.39, 95% CI: 5.03 to 13.99; 14 trials, 3745 participants). No placebo-controlled trials focusing on the risk of gynecomastia in patients taking antipsychotic drugs was available, although there was a significant difference in the odds of having gynecomastia in a comparison between risperidone and quetiapine (OR = 4.32, 95% CI: 1.31 to 14.27; 3 trials, 343 participants). Limited evidence about the effects of statins on mammary glands was found.

Conclusions: Antiandrogens and to a lesser extent 5 alpha-reductase inhibitors and spironolactone are associated with an increased risk of developing gynecomastia. Such effect can be explained by a modification of the testosterone to estradiol ratio. Gynecomastia (and galactorrhea) associated to the use of conventional and certain atypical antipsychotics can be related to high prolactin levels.

KEY WORDS: Gynecomastia; Breast enlargement; Spironolactone; Antiandrogens; 5 alpha-reductase inhibitors; Psychotropic drugs; Statins.

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INTRODUCTION

Gynecomastia is a condition in which the male breast is enlarged due to an increase in ductal tissue, stroma, or fat. Histological observation shows a proliferation of the

mammary ducts embedded in a fibroconnective tissue stroma. Gynecomastia is associated with medical conditions such as extreme obesity, hypogonadism, liver, and kidney failure. In addition, the administration of certain drugs is a known risk factor for gynecomastia. According to Food and Drug Administration (FDA) Adverse Event Reporting System, gynecomastia is most frequently reported after administration of inhibitors of 5alpha-reductase (dutasteride, finasteride), spironolactone, antipsychotics, lipid-lowering agents (rosuvastatin, atorvastatin, and simvastatin) and antiandrogens (1).

Other drugs causing gynecomastia include antiretrovirals (protease inhibitors and nucleoside reverse transcriptase inhibitors), histamine2-receptor blockers (cimetidine), antimycotics (long-term use of ketoconazole), calcium channel blockers, and chemotherapeutic agents.

Gynecomastia was also reported after intake of exogenous hormones (estrogens) or steroids (in adolescent boys), and after environmental exposure to phenothrin or intake of phytoestrogens (e.g., large quantities of phytoestrogen-containing soy products).

There are numerous reports on the association between the intake of certain drugs and gynecomastia, but no meta-analysis has so far assessed the extent of the risk of gynecomastia linked to specific classes of drugs.

The aim of this work was to review the scientific evidence on the risk of gynecomastia after administration of the drugs that are most frequently associated with the occurrence of this side effect.

MATERIALS AND METHODS

Electronic databases (e.g., PubMed and EMBASE) were searched for articles published up to 30 June 2021. Five separate searches were performed using the following MESH terms: "spironolactone AND gynecomastia", "antiandrogens AND gynecomastia", "(finasteride OR dutasteride) AND gynecomastia", "psychotropic agents AND gynecomastia", "statins AND gynecomastia". Title and abstract and full-text screening were performed independently by two authors. We included randomized controlled trials (RCTs),

with an open-label or single/double blinded design, which enrolled patients treated for at least 6 weeks with antiandrogens, 5 alpha-reductase inhibitors, spironolactone, psychotropic drugs, and statins. Included studies should include a primary or secondary safety endpoint focusing on the side effects of treatment.

The following information was extracted from each study: author(s), publication year; study design; population; intervention; rate of gynecomastia (or breast enlargement or breast tenderness or pain or galactorrhea).

Two authors independently performed the quality assessment by identifying potential biases using the Cochrane risk of bias tool (2), focusing on the following items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcomes, selective reporting and other biases. The *risk of bias* (ROB) was graded as high, low or unclear. Publication bias was assessed by visual inspection of funnel plots and by the Egger's regression test. Dichotomous data (presence/absence of gynecomastia) and number of per-protocol or intent-to-treat patients were extracted to calculate *odds ratios* (OR), *confidence intervals* (CI) to odds-ratios, and Z statistics according to the Mantel-Haenszel method. Meta-analysis was performed using a random-effects model. Heterogeneity was assessed

by I2 statistics, reported with 95% CIs, and interpreted as of lesser importance ($\leq 40\%$), moderate (30%-60%), substantial (50%-90%) or considerable ($\geq 75\%$), according to Cochrane criteria. The review (PROSPERO registration number: CRD42021276781) was conducted in accordance with PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) guidelines (3).

Statistical analysis was performed using the RevMan5 software. The Egger's test was performed using the MetaEssentials software (Rotterdam School of Management, Erasmus University, The Netherlands).

RESULTS

Database search for the association between gynecomastia and treatment with spironolactone, antiandrogens, alpha-reductase inhibitors, and antipsychotics retrieved 74, 215, 42 and 74 papers respectively. A total of 68 papers was screened by title/abstract. After full-text screening with removal of duplicates or of articles describing series reported in other reports we included 32 papers in this systematic review (4-35). Out of them 30 reports were included in the quantitative analysis (4-33).

A PRISMA flow-chart of the study selection process is shown in Figure 1. The supplementary appendix provides

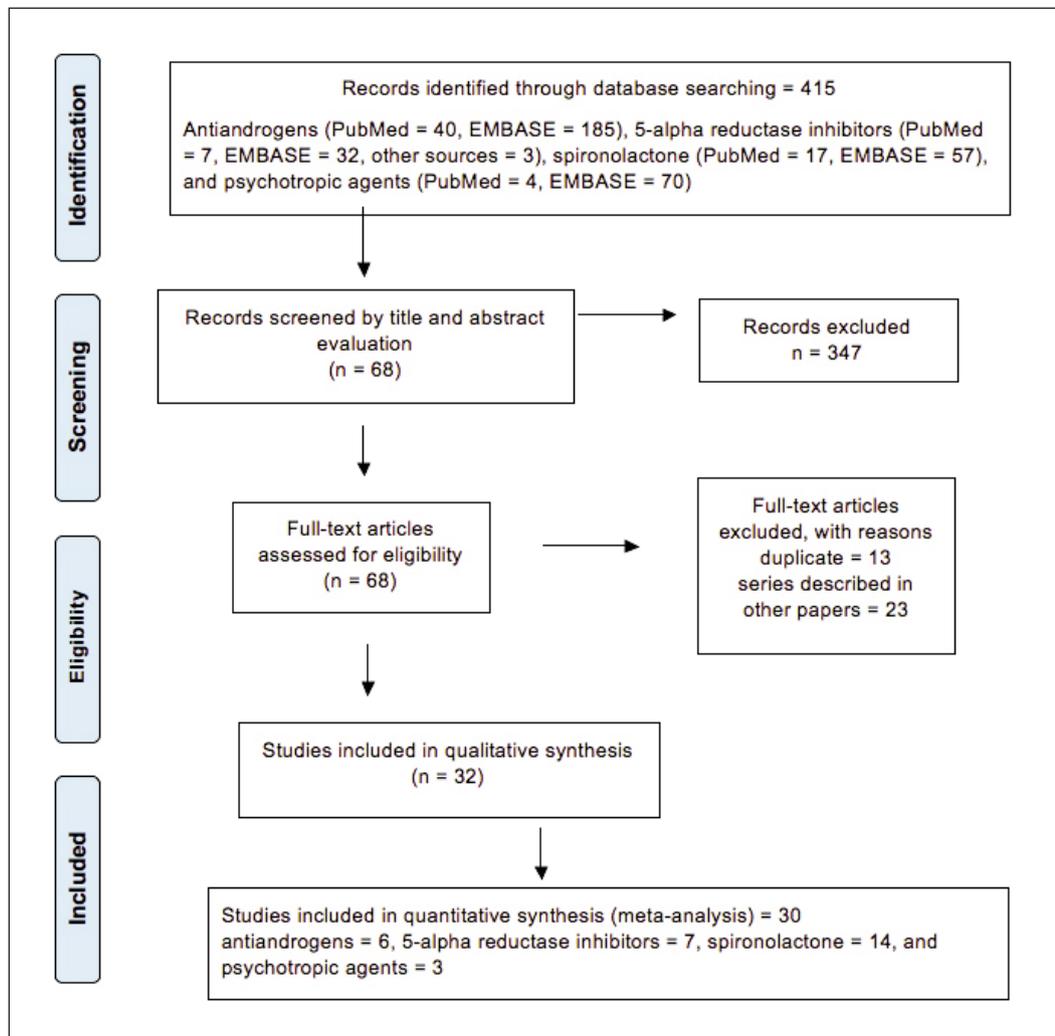


Figure 1. PRISMA flow chart summary of the study selection procedure.

Table 1.

Drugs compared with placebo or active comparators - endpoint: gynecomastia.

Patient or population: various.

Settings: outpatient.

Intervention: antiandrogens, 5-alpha reductase inhibitors, spironolactone, risperidone, quetiapine.

Comparison: placebo or active comparator.

Comparisons	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies or comparisons)	Quality of the evidence (GRADE)	Comments
	Assumed control risk	Corresponding intervention risk				
	Placebo/active drug	Intervention				
Antiandrogens vs. placebo	81.24 per 1000	605.8 per 1000 (498.91 to 703.40)	OR 17.38 (11.26 to 26.82)	9599 (6)	⊕⊕⊕⊕ Moderate	Reasons for upgrading: - large magnitude of effect Reasons for downgrading: - indirectness of evidence - risk of bias
5-alpha reductase inhibitors vs. placebo	19.54 per 1000	34.07 per 1000 (29.59 to 39.44)	OR 1.77 (1.53 to 2.06)	34860 (7)	⊕⊕⊕⊕ Low	Reasons for upgrading: none Reasons for downgrading: - risk of bias - indirectness of evidence
Spironolactone vs. placebo	6.5 per 1000	52.09 per 1000 (31.89 to 83.94)	OR 8.39 (5.03 to 13.99)	3745 (14)	⊕⊕⊕⊕ Moderate	Reasons for upgrading: - large magnitude of effect Reasons for downgrading: - risk of bias - indirectness of evidence
Risperidone vs. quetiapine	19.35 per 1000	78.56 per 1000 (25.20 to 219.75)	OR 4.32 (1.31 to 14.27)	343 (3)	⊕⊕⊕⊕ Moderate	Reasons for upgrading: - large magnitude of effect Reasons for downgrading: - imprecision (small sample size, wide 95%CI) - risk of bias - indirectness of evidence

The corresponding intervention risk (and its 95% confidence interval) is based on the assumed control risk in the comparison group and the relative effect of the intervention (and its 95% CI). It is calculated from the odds ratio using the formula: $OR/[1-ACR \times (1-OR)]$.
 CI: Confidence Interval. OR: Odds Ratio. ACR: Assumed Control Risk.
 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.

a list of included studies (**Supplementary Materials**), characteristics of the included trials and the risk-of-bias assessment.

We included the most recent paper reporting the cumulative results at 10-year follow-up of three studies of the administration of bicalutamide in the frame of the *Early Prostate Cancer* (EPC) program which includes three large, randomized trials conducted in the *United States, Europe, Mexico and Australia* (4).

Random-effects meta-analysis revealed that antiandrogen therapy is associated with significantly higher odds of gynecomastia (odds ratio, OR = 17.38, 95% CI: 11.26 to 26.82; 6 trials, 9599 participants) compared with placebo (4, 5, 7-9) or no treatment (6) (Figure 2A).

Similarly, alpha-5-reductase inhibitors (OR = 1.77, 95% CI: 1.53 to 2.06; 6 trials, 34860 participants) and spironolactone (OR = 8.39, 95% CI: 5.03 to 13.99; 14 trials, 3745 participants) were significantly associated with gynecomastia (10-16) (Figures 2B-2C).

It is known that dutasteride can inhibit the activity of both type I and II reductases, whereas finasteride is not active on isoform II. This might suggest an increased risk of gynecomastia in patients taking dutasteride. However, the comparison between dutasteride and finasteride resulted in non-significantly different ($p = 0.31$) odds of gynecomastia (OR = 0.66, 95% CI 0.30-1.48; 2 trials; 1697 participants) (Forest plot not shown). Risperidone

was significantly ($p = 0.02$) associated with higher odds of gynecomastia compared to quetiapine (OR = 4.32, 95% CI: 1.31 to 14.27; 3 trials, 343 participants) (Figure 2D), but not olanzapine (Forest plot not shown).

Figure 3 shows the funnel plots for publication bias. No significant bias was identified by visual inspection and statistical analysis of funnel plots. Accordingly, the Egger's test (antiandrogens/placebo, $p = 0.43$; 5-alpha reductase inhibitors/placebo, $p = 0.37$; spironolactone/placebo, $p = 0.53$; risperidone/quetiapine, $p = 0.17$). Between-study heterogeneity was moderate for the antiandrogens vs. controls comparison ($I^2 = 49\%$), and of lesser importance for all other analyses.

Table 1 presents the summary of the findings of our pooled analyses, also including an evaluation of the quality of the evidence, performed according to GRADE criteria.

DISCUSSION

Mechanisms regulating the growth of the breast tissue are complex and not fully elucidated (36, 37).

The breast tissue expresses receptors for both estrogens and androgens, which can induce the proliferation or inhibition of the growth and differentiation of the mammary gland, respectively. Gynecomastia can be caused either by overt reduction of circulating estrogen levels or

Figure 2.

Pooled analysis of the comparisons between antiandrogens and placebo (panel A), 5-alpha-reductase inhibitors and placebo (panel B) and Risperidone and Quetiapine (panel D). The diamonds show the position of the pooled odds-ratios, extending to the 95% confidence interval limits. Values to the right of the no-effect vertical axis show increased odds for gynecomastia.

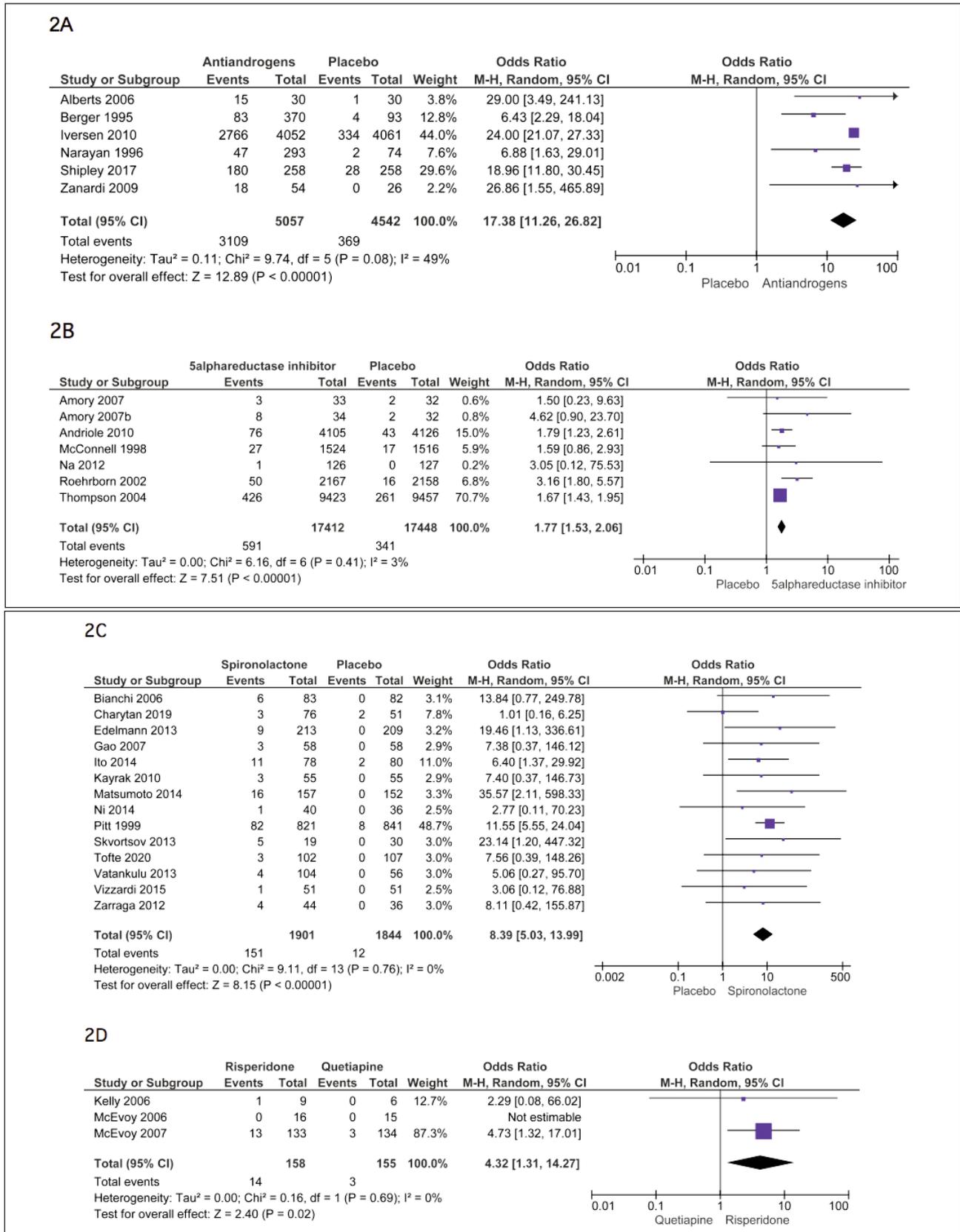
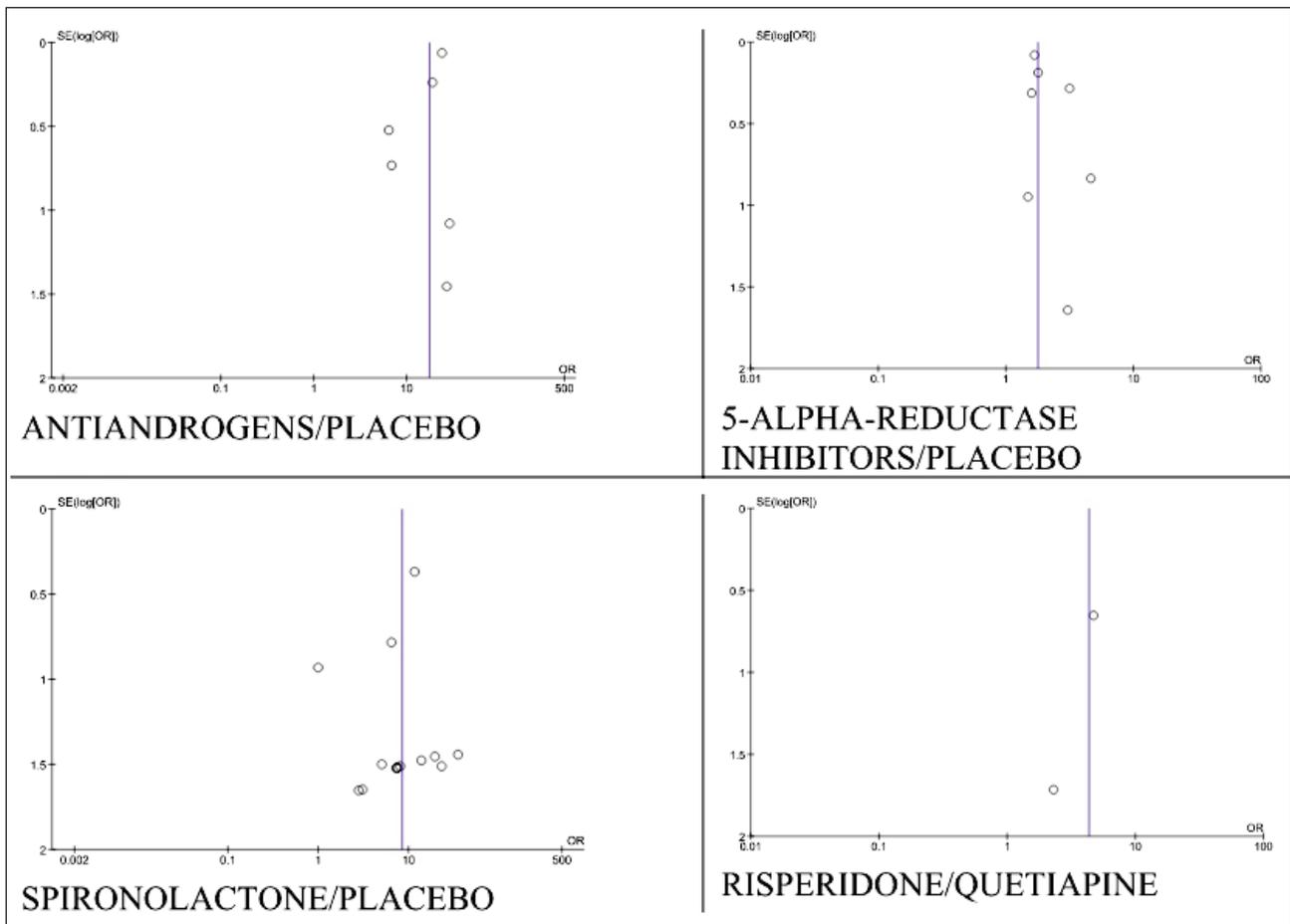


Figure 3.

Funnel plots for publication bias analysis. Top-left, antiandrogens vs. placebo; top-right, 5-alpha-reductase inhibitors vs. placebo; bottom-left, spironolactone vs. placebo; bottom-right, risperidone vs. quetiapine.



by an increase of androgen serum levels. In addition, imbalances between estrogen and androgen levels, which may retain serum concentrations within the normal ranges, may cause such effects. Furthermore, activity of estrogens and androgens can be locally modulated in the breast tissue (i) by increased local production of estrogens or decreased inactivation of estrogens, (ii) by decreased local production of androgens, or (iii) by changes in the number and/or activity of androgen or estrogen receptors. Besides androgens and estrogens, other hormones can interfere with the growth of men's breast tissue, which presents receptors for prolactin, progesterone, *insulin-like growth factor* (IGF)-1, IGF-2, *luteinizing hormone* (LH) and/or *human chorionic gonadotropin* (hCG). Our meta-analysis confirmed that antiandrogens are associated with the highest risk of gynecomastia.

Antiandrogens are used for the treatment of prostate cancer as monotherapy or in combination with LHRH inhibitors. Bicalutamide is the most used antiandrogen, though other agents, either steroidal like cyproterone acetate or non-steroidal like flutamide, have also been used for the treatment of prostate cancer. These agents bind to androgen receptors competitively, thus inhibiting testosterone or dihydrotestosterone receptor binding and activity. The administration of non-steroidal antiandrogens, as bicalutamide, causes an increase in the synthesis of testos-

terone due to the inhibition of the negative feedback of the hypothalamic-pituitary-gonadal axis. Increased availability of testosterone causes an increase in estradiol levels due to aromatization of testosterone. These hormonal changes explain the high risk of gynecomastia, which tends to occur in the first year of administration. The evaluation at different time intervals of the rates of gynecomastia in patients taking bicalutamide included in the same series of *Early Prostate Cancer* program showed rates of gynecomastia and breast pain of 64.9% and 65.1% after a median follow up of 2.6 years (38), 66.3% and 67.9% at 5.1 years (39) and 66.8 and 73.7% at 9.7 years (40). Cyproterone acetate is expected to involve a lower risk of gynecomastia because, in contrast to nonsteroidal antiandrogens, it can decrease estrogen levels via inhibition of the secretion of gonadotropins. However, a comparative study by EORTC described similar gynecomastia rates in patients treated with cyproterone or flutamide, though the latter was more frequently associated with painful gynecomastia (35). Inhibitors of 5-alpha-reductase are widely used for the treatment of benign prostatic hyperplasia. These agents inhibit the conversion of testosterone to dihydrotestosterone through inhibition of the 5-alpha-reductase enzyme, thus reducing prostate cell proliferation. They also cause an increase in the synthesis of testosterone and, consequently, of estrogen through aromatization of

testosterone. Spironolactone may induce gynecomastia by several mechanisms: (i) increased peripheral conversion of testosterone to estradiol, (ii) displacement of testosterone from SHBG, or (iii) binding to peripheral androgen receptors to competitively inhibit testosterone and dihydrotestosterone. Our meta-analysis confirms that spironolactone and 5-alpha-reductase inhibitors are associated with an increased risk of gynecomastia, although to a lesser extent than antiandrogens.

Although an increased risk of gynecomastia could be expected in patients taking dutasteride, which inhibits the activity of both type 1 and 2 reductases, our meta-analysis could not demonstrate a different risk of gynecomastia between finasteride and dutasteride (16).

Statins are inhibitors of the *3-hydroxy-3-methylglutaryl coenzyme A* (HMG-CoA) reductase, an enzyme that lowers the serum levels of lipids by blocking the pathways of cholesterol synthesis. Inhibition of adrenal and gonadal steroid synthesis may entail to an increased estradiol: testosterone ratio. A meta-analysis showed that a reduction in circulating testosterone levels in patients receiving statin (41). Our search did not retrieve randomized controlled studies that evaluated the possible occurrence of gynecomastia after treatment with statins. It was therefore not possible to investigate the potential risk of gynecomastia associated with the use of these drugs, which was observed following treatment with statins in a case-control cohort study (42). On the other hand, some case reports have suggested that pravastatin, atorvastatin, and rosuvastatin may cause gynecomastia that can be reverted by withdrawal or substitution with a less potent statin. In addition, pharmacovigilance studies include HMG-CoA reductase inhibitors among the most frequent causes of drug-induced gynecomastia (43, 44).

Some antipsychotics are correlated with the risk of gynecomastia because of their effect on prolactin secretion. Antipsychotics block pituitary dopamine D2 receptors and prevent their inhibitory effect on prolactin secretion. Hyperprolactinemia may in turn decrease the secretion of GnRH by hypothalamus feedback causing hypogonadism. Nonetheless, prolactin receptors have also been found in male breast tissue, and this may also contribute to the development of gynecomastia (45, 46).

Most first-generation antipsychotics and some second-generation antipsychotics, particularly risperidone and paliperidone, have been found to increase prolactin levels, with accompanying gynecomastia.

The onset of gynecomastia after administration of risperidone is more frequently associated with the use of high doses of the drug and can be triggered by the simultaneous administration of fluoxetine which can interfere in the metabolism of risperidone by inhibition of cytochrome P450. Our meta-analysis confirmed a greater risk of gynecomastia associated with the use of risperidone compared to another atypical antipsychotics.

A limitation of the meta-analysis evidence presented in this review is the possible under-reporting of breast enlargement or gynecomastia in the female population taking spironolactone or antipsychotics because this effect may be unnoticed or even considered a beneficial effect by female patients, while in the male population it may have been reported with more attention, as it modifies the body image

more heavily. Unfortunately, no study has provided a separate assessment of the appearance of this side effect in relation to gender. In populations of adult women who took spironolactone for the treatment of acne, the appearance of breast tenderness and breast enlargement was estimated at 2.5% and 2.1% respectively (47, 48). The prevalence of gynecomastia could therefore be underestimated in mixed gender populations taking spironolactone or antipsychotics compared to male populations receiving antiandrogens or alpha-reductase inhibitors.

In conclusion, our study confirmed the high risk of gynecomastia in patients taking antiandrogens for the treatment of prostate cancer. The frequent occurrence of gynecomastia is a limiting factor of this treatment and ablation of the breast tissue by ionizing radiation is sometimes used to prevent this effect. The risk of gynecomastia is lower but significantly higher than placebo in patients receiving spironolactone, 5-alpha-reductase inhibitors, and atypical antipsychotics (risperidone vs. quetiapine). The potential risk of gynecomastia associated with the use of statins should be better assessed with studies evaluating the long-term side effects of these drugs. In the clinical practice, the possible additive or synergic interaction of several drugs predisposing to the onset of gynecomastia must be cautiously considered.

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