Antiandrogens for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials


CRD summary
The authors concluded that there was weak evidence that antiandrogens were mildly effective for treating hirsutism. Apart from the potential for publication bias, the review was well-conducted and the authors' cautious conclusions appeared reliable.

Authors' objectives
To evaluate the use of antiandrogens for hirsutism.

Searching
MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were searched from inception to May 2006. Further details of the search strategy were available on request. The reference lists of eligible studies and of narrative and systematic reviews were handsearched. Experts in the field were approached for additional studies. The search was restricted to published studies in any language.

Study selection
Randomised controlled trials (RCTs) of at least six months' duration that assessed antiandrogen treatment for varying degrees of hirsutism in women at least 12 years old were eligible for inclusion. Antiandrogens could be administered either alone or combined with oral contraceptives (OCPs) or insulin sensitisers. Controls could receive either placebo or an active intervention. Studies were required to report hirsutism as an outcome, assessed by patient, clinician (for example, Ferriman-Gallwey hirsutism score) or laboratory measures (for example, hair diameter). Studies of women receiving gonadotrophin-releasing hormone, clomiphene or glucocorticoids were excluded, as were studies in which hirsutism was secondary to conditions other than idiopathic hirsutism, polycystic ovary syndrome or presumed late-onset congenital adrenal hyperplasia.

Median participant age in the included studies was 23 years. Baseline hirsutism scores varied widely (range 11.4 to 25.1). Interventions included four androgens – spironolactone, cyproterone acetate (CPA), flutamide and finasteride – and one insulin sensitiser (metformin). OCPs included ethinyl oestradiol with either CPA or desogestrel. Duration of treatment ranged from six to 12 months. All studies reported clinician-assessed Ferriman-Gallwey scores, with or without modification. Few studies reported self-assessed outcomes.

Studies were selected by four reviewers working independently and in duplicate, with disagreements resolved by consensus.

Assessment of study quality
The factors considered in the validity assessment were: allocation concealment; blinding of patients, health care providers and outcomes assessors; and losses to follow up. The assessment was conducted by pairs of reviewers working independently.

Data extraction
Endpoint hirsutism scores or (if not available) change-from-baseline scores were extracted and mean differences (MDs) between the groups calculated, with 95% confidence intervals (CIs). For binary data (for example, proportion of responders) odds ratios (ORs) and 95% CIs were calculated. Outcomes were measured at the longest duration of complete follow up while the participants were still receiving the intervention.

Data were extracted by three reviewers working in duplicate, using a structured electronic format. Authors were contacted for missing data.
**Methods of synthesis**

Continuous data were pooled using a DerSimonian and Laird random-effects model to calculate weighted mean differences (WMD) or (where different measurement tools were used) standardised mean differences (SMD, Hedge’s g). ORs were converted to effect sizes (ES) and pooled using the inverse variance method. Pooled effect sizes were expressed in Ferriman-Gallwey units by multiplying the ES by 3.5, which was the mean standard deviation in the relevant meta-analysis. Heterogeneity was assessed using the $I^2$ statistic. Numbers needed to treat (NNTs) were also calculated. Pre-specified subgroup analyses were conducted to investigate the effect on outcomes of differences between the studies in quality, clinical characteristics and methodology.

**Results of the review**

Twelve RCTs (18 comparisons) were eligible for inclusion. The total sample size was over 506 (sample size was not reported for one study). Trial quality was low. Only one RCT reported adequate allocation concealment and only half clearly reported blinded outcome assessment. Median loss to follow up was four per cent (range 0 to 42 per cent).

**Antiandrogens versus placebo**

Hirsutism scores were significantly lower in the intervention group (WMD -3.9, 95% CI: -5.4, -2.3, NNT=3, five comparisons); there was no heterogeneity. Subgroup analysis showed no statistically significant differences in effect between spironolactone, flutamide and finasteride.

**Antiandrogens versus OCPs**

One RCT reported no statistically significant difference between the comparison groups.

**Antiandrogens versus metformin**

Scores were significantly lower in the intervention group (WMD -3.7, 95% CI: -6.8, -0.6, three RCTs), but with marked heterogeneity ($I^2$=80%), partly explained by a larger effect associated with flutamide (two RCTs) than with spironolactone (one RCT).

**Antiandrogens as add-ons**

No statistically significant difference was found between OCP plus antiandrogens (spironolactone, finasteride and CPA) and OCP alone (five comparisons). Flutamide plus metformin was associated with significantly lower scores than metformin alone (WMD -4.6, 95% CI: -7.9, -1.3, NNT=2), but with moderate heterogeneity ($I^2$=40%) that was unexplained by subgroup analyses.

**Patient self-assessments (three RCTs):**

Patient assessments were congruent with clinician assessments in two RCTs that reported both measures. A third RCT reported a trend towards improved outcomes in the intervention group ($p=0.09$).

Other subgroup analyses were reported in the review.

**Authors’ conclusions**

There was weak evidence that antiandrogens were mildly effective for treating hirsutism.

**CRD commentary**

The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies, without language restriction. However, the restriction to published studies meant that the review was at risk of publication bias (as the authors acknowledged), which was not assessed formally. Steps were taken to reduce the risk of error and bias in the processes of study selection, validity assessment and data extraction by having more than one reviewer make decisions independently. Relevant criteria were used to assess study validity and the results of validity assessment were taken into account when interpreting the findings. Appropriate statistical techniques appeared to be used to combine studies, assess heterogeneity and explore differences between the studies. Apart from the potential for publication bias, the review was well-conducted and the authors’ cautious conclusions appeared reliable.

**Implications of the review for practice and research**

Practice: the authors did not state any implications for practice.
Research: the authors stated that longer-term well-conducted and independently funded RCTs were needed to investigate different types and doses of antiandrogens in combination with other interventions for various types of hirsutism. Comparators should include biological and mechanical interventions. Primary outcomes should include blinded self-assessment of hirsutism, treatment cost and burden. RCTs should be powered to detect the minimum change in hirsutism that is meaningful to women.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.