Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne (Review)

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[Intervention Review]

Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

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ABSTRACT

Background

Hirsutism is the presence of excessive hair growth in women and is an important cosmetic condition often resulting in severe distress. The most common cause is by increased production of male sex hormones (androgens). It is also affected by increased sensitivity to androgens in the hair follicles, and secretory glands around hair follicles (sebaceous glands). Spironolactone is an antiandrogen and aldosterone antagonist used to treat hirsutism.

Objectives

The objective was to investigate the effectiveness of spironolactone and/or in combination with steroids (oral contraceptive pill included) in reducing excess hair growth and/or acne in women.

Search strategy

The Cochrane Menstrual Disorders and Subfertility Group (MDSG) trials register was searched (April 2008). The Cochrane MDSG register is based on regular searches of MEDLINE, EMBASE, CINAHL, PsycINFO and CENTRAL, handsearching of 20 relevant journals and conference proceedings, and searches of several key grey literature sources. In addition, all reference lists of relevant trials were searched and drug companies contacted for details of unpublished trials.

Selection criteria

All randomised controlled comparisons of spironolactone versus: placebo, steroids (oral contraceptive pill included), spironolactone of varying dosages, or spironolactone and steroids versus steroids alone when used to reduce hair growth and acne in women.

Data collection and analysis

Nine trials were included in the review, eight trials were excluded. Two other trials are awaiting assessment. Only one trial studied acne as an outcome, the remainder were concerned with hirsutism. Major outcome measures include the following: subjective observations, Ferriman and Gallwey hair scores, hormonal and biochemical parameters, side effects, sebum production measurement.

Main results

In the two trials that compared 100 mg of spironolactone with placebo significant differences were reported for subjective improvements in hair growth (OR 7.18, 95% CI 1.96 to 26.28), although not the Ferriman-Galwey score (WMD 7.20, 95% CI -10.98 to -3.42)). Data could not be otherwise pooled as only one trial reported an outcome.

Authors' conclusions

From the studies included in this review, there is some evidence to show that spironolactone is an effective treatment to decrease the degree of hirsutism but there was no evidence for effectiveness for the treatment of acne vulgaris. Studies in this area are scarce and small. Individual study data indicates some superiority of spironolactone over other drugs but results cannot be generalised.

PLAIN LANGUAGE SUMMARY

Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

The evidence suggests a lack of evidence to show whether spironolactone can reduce hirsutism and acne. Hirsutism in women (excessive hair growth) is most often caused by an increased production of male hormones. Spironolactone ('Aldactone' or 'Spirotone') is an anti-androgen, which can be taken with or without the oral contraceptive pill to try and reduce hirsutism. From the studies included in this review, there is some evidence to show that spironolactone is an effective treatment to decrease the degree of hirsutism, but insufficient evidence for the management of acne vulgaris. It appears to be more effective than finasteride 5mg/day, metformin and low dose cyproterone acetate.

BACKGROUND

Description of the condition

Hirsutism is the presence of excessive hair growth in women and is an important cosmetic condition often resulting in severe distress (Rittmaster 1995). Hair of the hirsute woman is thick, dark, terminal (coarse, adult) hair instead of fine fairer hair. Typically, hirsute women have increased body hair on the upper lip, lower jaw and neck, chest (presternal and circum-mamillary), linea alba (line between navel and symphysis), perianogenital region (around the anal and genital area) and the lower and upper extremities (Rabe 1993). Other symptoms which may accompany hirsutism are acne, alopecia (baldness) and receding frontal hairline (Rabe 1993).

Hirsutism is most often caused by increased production of male sex hormones also known as androgens. It is also affected by increased sensitivity to androgens in the hair follicles, and the secretory glands around the hair follicles, called sebaceous glands (Rittmaster 1995). Free or total testosterone concentrations are normal in approximately 50% of hirsute women. However, elevated levels of one or more androgens, namely androstenedione (which can be converted into testosterone) and dehydroepiandrosterone (the major androgen precursor in females), are present in nearly all women with hirsutism (Fox 1990). Androgens, and in particular 5 alpha dihydrotestosterone (a skin derivative of testosterone) induce hyperkeratosis (or overgrowth of skin) of the excretory ducts of the sebaceous glands and follicular infundibulum (base of the hair follicle). This can lead to acne and excessive sebum secretion, known as seborrhoea (Rabe 1993). Acne, therefore is often associated with hirsutism (Rabe 1993). Although the source of excess androgens in women probably results from defects in several metabolic and endocrine pathways at a cellular level, it is now generally accepted that the polycystic ovary is the source of these excess androgens in the majority of women with acne and hirsutism (Adams 1985; Conway 1990; Eden 1989).

Decreased hair growth and plasma testosterone levels in a hirsute, hyperandrogenic and hypertensive woman treated with spironolactone was first reported in 1978. Since then, many studies have been conducted to determine its effectiveness. Most of the uncontrolled investigations reported a response, but normalisation of hair density was rarely observed. Side effects were tolerated by most patients and commonly included the transient passing of a large volume of urine, chronic excessive intake of water, nausea, fatigue, breast tenderness and headaches (Rittmaster 1995).

Description of the intervention

Treatment of hirsutism and acne involves either suppressing or reducing ovarian or adrenal androgen secretion, or blocking the action of androgens in the skin with androgen receptor blockers (antiandrogens) or blocking the enzyme, 5 alpha reductase inhibitors, which converts testosterone into its skin derivative (the form used in skin) (Rittmaster 1995).

How the intervention might work

Spironolactone ('Aldactone', 'Spirotone') is an antiandrogen and aldosterone antagonist (Sciarra 1990). Its major mechanism of action is to compete with dihydrotestosterone for androgen receptors in the skin. It increases the level of proteins, called sex hormone binding globulins, which testosterone binds to in the circulation. The drug also increases the clearance of testosterone from the body, increases liver hydroxylase activity and decreases 5 alpha reductase activity (McMullen 1993).

Why it is important to do this review

The effectiveness of spironolactone in the treatment of hirsutism has not been confirmed by systematic reviews. Investigations into its effectiveness as an option for hirsute women are warranted.

OBJECTIVES

The objective of this review was to investigate the effectiveness of spironolactone alone or in combination with steroids (oral contraceptive pill included), in reducing excess hair growth and/or acne in women.

Hypotheses:

1. Spironolactone is more effective than placebo or other medical therapies in treating hirsutism and/or acne.

2. Spironolactone improves endocrine parameters when given to women with hirsutism and/or acne.

3. Spironolactone administered with additional steroids (oral contraceptive pill included) is more effective and results in greater patient satisfaction than spironolactone alone when given to women with hirsutism and/or acne .

METHODS

Criteria for considering studies for this review

Types of studies

(1) All randomised controlled comparisons of spironolactone versus placebo when used to reduce hair growth and/or acne.
(2) All randomised controlled comparisons of spironolactone versus steroids (oral contraceptive pill included) when used to reduce hair growth and/or acne.
(3) All randomised controlled comparisons of spironolactone and steroids (oral contraceptive pill included) versus spironolactone alone when used to reduce hair growth and/or acne.

(4) All randomised controlled comparisons of spironolactone versus spironolactone in varying dosages when used to reduce hair growth and/or acne.
(5) All randomised controlled comparisons of spironolactone and steroids (oral contraceptive pill included) versus steroids alone when used to reduce hair growth and/or acne.

Types of participants

CRITERIA FOR INCLUSION OF TRIALS
Women of reproductive years or postmenopausal women with hirsutism and/or acne.
Participants who subjectively classified themselves as hirsute and/or with acne, or those that are objectively diagnosed with the condition were included.
CRITERIA FOR EXCLUSION OF TRIALS
Women with:
Hirsutism secondary to a functional androgenic tumour
Iatrogenic causes of hyperandrogenism/hirsutism
Non-endocrine causes of hyperandrogenism/hirsutism

Types of interventions

Medical therapy

- Antiandrogen: spironolactone (of any dosage)
- Oral contraceptive pills and spironolactone
- Estrogen and spironolactone
- Steroids and spironolactone

Types of outcome measures

(1) SUBJECTIVE

- patients' personal observations: softer, finer hair, slower growth rates
- quality of life: subjective observation on improved quality of life provided this has been recorded in a reproducible and validated format
- subjective improvement in sebaceous secretion of skin and scalp

(2) SEMI-OBJECTIVE

- Ferriman and Gallwey scale (grading of terminal hair density from zero to four at eleven different androgenic sites)
- Pleiwig and Klingman scale (acne score)
- changes in hair removal frequency
- changes in hair distribution score

(3) OBJECTIVE

- hair shaft diameter
- hair shaft length
- hair shaft weight (changes in hair shaft length and weight are expressed in per unit of time to estimate growth rate)
- objective measurement of sebum production
- number of inflamed lesions

(4) HORMONAL/BIOCHEMICAL PARAMETERS

- testosterone levels
- dehydroepiandrosterone levels (DHEA, DHEA-S) (other hormones, along with testosterone that are produced by the adrenal gland and ovaries)
- sex hormone binding globulin levels (SHBG) (binds testosterone)
- free testosterone levels (determines androgenicity)
- free androgens index
- androstenedione (converts to form testosterone)

(5) SIDE EFFECTS

- hyperkalemia (increased potassium in the blood)
- change in menstrual cycle regularity:

-metrorrhagia (development of frequent but irregular uterine bleeding)
-amenorrhoea (abnormal stoppage of menses)
-oligomenorrhoea (infrequent menstrual flow)
-induction of cycle regularity

- breast symptoms
- polyuria/polydipsia (passing large amount of urine/excessive intake of water)
- fatigue
- nausea
- headache
- decreased libido/sexual dysfunction
- breast cancer

Search methods for identification of studies

This is an update of a pervious version of the review. The authors searched the Cochrane Menstrual Disorders and Subfertility Group trials register (April 2008). The Cochrane Menstrual Disorders and Subfertility Group register is based on regular searches of MEDLINE, EMBASE, CINAHL, PsycINFO and CENTRAL, the handsearching of 20 relevant journals and conference proceedings, and searches of several key grey literature sources. A full description is given in the Group's module on the Cochrane Library. In addition, the following terms were included in the MEDLINE electronic search strategy Appendix 1
The following electronic databases were also searched using comparable search terms:
Bioabstracts
PsycLIT
CINAHL
Social Sciences Index
Dissertation Abstracts
Current Contents (1995-1996)
EMBASE
In addition, all reference lists of relevant trials were searched and drug companies contacted for details of unpublished trials. Searle Medical provided a list of references unfound in other databases.

Data collection and analysis

All assessments of the quality of trials and data extraction were performed unblinded and independently by at least two reviewers. One or more of these reviewers was an expert in the content matter. Selection of trials for inclusion in the review were performed by one of the reviewers, after employing the search strategy described previously. A second reviewer assessed any trials where there was uncertainty regarding eligibility. Where necessary, additional information was sought from the principal investigators of trials which appear to meet the eligibility criteria.

Quality of the included trials was assessed by both of the reviewers separately. Any discrepancies were assessed by a third reviewer. The quality of allocation concealment was graded as either A (adequate), B (unclear) or C (inadequate). For each of the included trials information was collected regarding the method of randomisation, allocation concealment, blinding, whether an intention to treat analysis could possibly be performed and relevant interventions and outcomes. If information was not recorded in the article, efforts were made to contact authors for the required data. Data were extracted independently by the two reviewers using forms designed according to the Cochrane guidelines.

Data were extracted in the most accurate way possible. In cases where results were presented in graphs and no actual data were available, the data were extracted from the graphs by taking measurements from the figures directly.

No outcome had data from more than one trial. If data from future trials become available, the heterogeneity between trial design, population studied and trial results will be tested subjectively, by clinical judgement of differences, and objectively using appropriate statistical tests. Depending on the results of the heterogeneity assessments, some of the outcomes will be pooled statistically using appropriate techniques.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

This is an update of a previous version of the review. Seventeen trials were identified which fulfilled the criteria for inclusion in the review. Seven trials were subsequently excluded as they did not meet inclusion criteria for quality and information. Additional information was sought from trialists involved in five of the included studies (Muhlemann 1986; Lobo 1985; Lumachi 2003; Walton 1986; McLellan 1989; Prezelj 1989) but only one (Prezelj 1989) provided adequate additional data. Two additional studies were identified in the update Gainie 2004 and Wong 1995.

Included studies

Seven of the included trials involved women with hirsutism. Women with a significant degree of hirsutism but minimal abnormalities in blood androgen levels were included in one trial (Lobo 1985). One trial (McLellan 1989) only treated women with idiopathic hirsutism. It did not state the age of the participants. In only one trial was acne graded by the Cunliffe and Burke method (Burke 1984) (Walton 1986). Women with androgen secreting tumours, congenital adrenal hyperplasia were excluded in one trial (Prezelj 1989). Women with thyroid dysfunction and hypercorticism were also excluded in one trial (Prezelj 1989).

All trials involved spironolactone as part of the intervention. Spironolactone at a dosage of 100 mg was compared to placebo in two trials (Moghetti 2000; McLellan 1989). Topical spironolactone of varying concentrations was compared with the metabolite of spironolactone, carenoate in another trial (Walton 1986). Spironolactone at a dosage of 200 mg plus 0.5 mg dexamethasone was tested against 200 mg spironolactone in a trial (Prezelj 1989). One dosage trial was included (Lobo 1985) which compared 100 mg spironolactone against 200 mg spironolactone. Duration of treatment varied: the shortest trial (Walton 1986) lasting 2 months, the remaining trials lasting from three to nine months. In one trial six women were on the oral contraceptive pill during the study (Muhlemann 1986). The most recent trial compared three different treatments (Lumachi 2003) , 100mg spironolactone, 12.5 mg/day of cyproterone acetate (first ten days of cycle) and finasteride five mg/day for 12 months and then reported follow up 12 months after the end of treatment. Finasteride 5mg was also compared with spironolactone 100mg by Wong 1995 and spironolactone 50mg was compared with metformin 1000mg daily by Gainie 2004.

Gonadotropin levels were measured by four trials while testosterone levels were measured in all the trials concerned with hirsutism. Dehydroepiandrosterone levels and androstenedione levels were reported by four trials (Prezelj 1989; Lobo 1985; McLellan 1989; Gainie 2004). Various other hormone levels, the Ferriman and Gallwey hair scores and side effects of the drugs were other parameters measured. Acne was assessed by sebum secretion rate in one trial (Walton 1986) and by the mean number of lesions in another.

Excluded studies

Eight studies were excluded based on lack of true randomisation or lack of randomisation to the drug of interest.

Risk of bias in included studies

Four studies (Prezelj 1989; Muhlemann 1986; Lobo 1985; Lumachi 2003) reported randomisation procedures in sufficient detail to be rated A for their attempts to control selection bias. The remaining trials did not report how randomisation was performed and were therefore given a quality score of B. The majority of the authors were not able to provide more information as the original

data was no longer available. Only one of the trials included an intention to treat analysis (Moghetti 2000) although two trials (McLellan 1989) and (Prezelj 1989) described the individual reasons for withdrawals. All trials were of adequate duration. The number of participants in each trial was small. The largest trial (Gainie 2004) involved 82 women.

Three trials (McLellan 1989; Muhlemann 1986; Moghetti 2000), were double blind. There was one cross over study. Six trials (Walton 1986; Lobo 1985; Prezelj 1989, Lumachi 2003; Gainie 2004; Wong 1995) did not mention blinding and three trials (Moghetti 2000; Muhlemann 1986; McLellan 1989) did not mention the method of randomisation. Concealment of allocation was unclear in six trials (Moghetti 2000; Prezelj 1989; Lumachi 2003; Lobo 1985; Walton 1986; Gainie 2004; Wong 1995).

Inclusion and exclusion criteria were clearly stated in three trials (Lumachi 2003; Prezelj 1989; Moghetti 2000). One trial (McLellan 1989) matched participants for menstrual irregularities, duration and degree of hirsutism, family history of hirsutism, age of menarche and presence of acne. However, the age of participants was mentioned in three trials (Moghetti 2000; Gainie 2004; Wong 1995). None of the trials used the body mass index as an inclusion or exclusion criteria even though weight may influence the severity of hirsutism. However, one trial (Lobo 1985) matched the weight between the two groups of participants.

Effects of interventions

Only two trials compared spironolactone (100 mg) with placebo (McLellan 1989; Moghetti 2000). The mean difference between two groups at the end of treatment was analysed rather than the mean change within the two groups before and after treatment. The included trials involved only small sample populations, therefore confidence intervals were wide. Significant differences were reported for subjective improvements in hair growth (OR 7.18, 95% CI 1.96 to 26.28) Analysis 1.1, Ferriman-Galwey score (WMD 7.20, 95% CI -10.98 to -3.42) Analysis 1.2.

There was a statistically significant decrease in sebum excretion rate using spironolactone in the results comparing 3% topical spironolactone with 3% topical carenoate at two months. However, the trial (Walton 1986) was very small, involving only 11 female patients. The results showed that no treatment achieved significance in decreasing acne severity. Both outcomes have wide confidence intervals and were not, therefore, accurate indications of treatment effectiveness in the area.

One dosage trial (Lobo 1985) reported testosterone levels and hair diameter as percentage changes with the mean and standard error before and after treatment. Percentage of unbound testosterone was unchanged in both groups of patients receiving either 100 mg (42% +/- 5%) or 200 mg (45.8% +/- 4%) spironolactone. Hair shaft diameter decreased in both groups by 19% +/- 8% and 30% +/- 3%. The article stated that this was a significant decrease. However, according to the Cochrane statistical analysis, there was no statistically significant difference between the two dosages.

Data of luteinising hormone levels from the trial involving dexamethasone and spironolactone (Prezelj 1989) differed considerably from the conventional reference levels of radioimmunoassays. The study stated a normal range of luteinising hormone levels for women to be between 10.5 and 20 IU/l where the conventional assays have a reference range of 2 to 15 IU/l. It appeared that the second IRP-HMG assay was used in the trial. Results can be converted to the more conventional assay - WHO 68/40, by dividing the data by two. The converted results for luteinising hormone level after six months of therapy becomes 8.0 IU/l for women who took 200 mg spironolactone plus 0.5 mg dexamethasone and 10.6 mg IU/l for the women who received only 200 mg spironolactone. After conversion, the results were still not statistically significant.

Two of the three included trials recorded the number of patients withdrawing from the studies. Two patients receiving 0.5 mg dexamethasone plus 200 mg spironolactone daily discontinued treatment after two to three months (Prezelj 1989) One withdrew due to clinical signs of iatrogenic Cushing's syndrome and the other because of polymenorrhea. Sixteen out of thirty-eight patients withdrew from one trial (McLellan 1989). The patients receiving 100 mg spironolactone were paired with women of comparable hirsute scores receiving placebo treatment. As one patient withdrew, the patient receiving the placebo also discontinued with the trial. Two pairs were withdrawn due to non-compliance in the actively treated subjects. Three withdrawals were due to spironolactone-induced menorrhagia. These three patients were also recorded in the section where menorrhagia was one of the side effects in the outcome category. Another three patients opted to withdraw for personal reasons unrelated to drug therapy.

In one crossover study of women with acne treated with either 200 mg of spironolactone or placebo (Muhlemann 1986) data extraction was not possible because incomplete data was available from the period before and after crossover (authors were contacted but no data available). At the end of three months of treatment with 200 mg of spironolactone the mean number of inflamed lesion was 18 (standard error of mean = 5) and in the placebo group it was 22 (standard error of mean = three) which was not significantly different. The actual number of patients in each arm of the study prior to crossover was not available making further analysis impossible.

In the one study that compared three different treatments (Lumachi 2003) , 100mg spironolactone, 12.5 mg/day of cyproterone acetate (first ten days of cycle) and finasteride 5 mg/day, there was a statistically significant difference 12 months after the end of treatment in those women who received spironolactone compared to cyproterone acetate and finasteride in favour of spironolactone . There was no statistically significant difference in adverse events between the three treatments; two of the patients who received finasteride reported loss of libido during the first three to four months, three of the patients who received spironolactone experienced transient polyuria and headache but this resolved with long-term use.

One study compared Metformin 1000mg and spironolactone 25mg daily (Gainie 2004). The Ferriman-Gallwey score was significantly lower at 6 months in the spironolactone group. There was no difference in the levels of serum testosterone or DHEAS. A number of side effects were reported of which menstrual irregularity was more common in the spironolactone group and diarrhoea was more common in the metformin group.
Wong 1995 compared spironolactone100mg with finasteride 5mg daily and reported no statistical difference between the two groups for self reported improvements in hirsutism at 3 or 6 months.

DISCUSSION

The trials included in this review varied in the type of comparisons and outcome measures. A large number of trials studying spironolactone were not randomised and controlled. Seven trials were excluded due to poor design. No study investigated both hirsutism and associated acne although these conditions are frequently both present in clinical practice (Rabe 1993). None of the hirsutism trials included decreased acne severity as an outcome and no trial studying acne included decreased hirsutism as an outcome.

Six months treatment with 100 mg spironolactone compared with placebo was associated with a statistically significant subjective improvement in hair growth and a decrease in Ferriman-Galwey scores.

All of the studies concerned with hirsutism have measured biochemical markers of androgenicity but the techniques of measurement differed. One trial (Prezelj 1989) sampled luteinising hormone levels and used different reference levels from the conventional radioimmunoassays. This may be due to the particular method used in preparing the samples using the assaying kit, Biodata. This was not a conventional radioimmunoassay kit. Furthermore, the assay may be less sensitive compared to the more conventional assays. However, after converting the data into the more conventional assaying method - WHO-68/40, the results were still not statistically significant.

Four studies (McLellan 1989; Lobo 1985; Moghetti 2000; Wong 1995) measured hair shaft diameter. Although it appears to be an objective measure of hair growth, it is an extremely difficult technique with which to obtain reproducible and valid results. One of the studies (McLellan 1989) stated that the hair shavings were taken from the thigh and the other trial (Lobo 1985) stated that hairs were plucked from facial and abdominal areas of the patients. However, hair growth in these areas are not all due to androgens, therefore it is also difficult to ensure that the hair examined is androgen dependent hair. Furthermore, hair growth is affected by factors such as ethnicity and temperature. No study stated what time of the year the trials were conducted at. One trial (McLellan 1989) did not state the severity of hirsutism of their participants before the start of treatment.

It has been postulated that a high body mass index (BMI) may increase the severity of hirsutism. Randomisation in treatment allocation should have ensured that treatment groups had comparable body mass indexes. Thus, if patients lost weight during the trial, their condition may improve but not due to the effects of the therapy. One trial (McLellan 1989) published the weight of all patients, another two trials (Prezelj 1989; Moghetti 2000) presented the mean BMI of the patients. No trial measured change in BMI after treatment.

In the only trial comparing topical spironolactone to placebo (Walton 1986), it was found that 3% topical spironolactone significantly decreased sebum excretion rate after two months of treatment. However, only the results of the 11 female patients were analysed. The original trial which included male participants, found that there was no reduction in sebum excretion rate after two months of treatment. Moreover, the small sample size and wide confidence interval implied that the result, though significant, is not a reliable indication of the effectiveness of spironolactone in this area.

In the only study that compared 100mg/day spironolactone with 12.5 mg/day cyproterone acetate (first ten days of cycle) and 5mg/day finasteride, spironolactone was superior in reducing the Ferriman-Galwey scores after 12 months of treatment and 12 months after the end of treatment (Lumachi 2003). However, the dose of cyproterone acetate was a quarter of the normal dose (50mg/day) and therefore it is not possible to conclude that spironolactone is superior to a higher dose of cyproterone acetate. Another Cochrane review on cyproterone acetate (Van der Spuy 2003) reported that cyproterone acetate was effective in improving hair growth when measured subjectively but the dosages were 25 mg/day - 50 mg/day.

From the studies included in this review, there is some evidence to show that oral spironolactone is an effective therapy for treating hirsutism but insufficient evidence for the effectiveness for the management of acne vulgaris. It is difficult to draw conclusions from the limited number of studies available in this review.

AUTHORS' CONCLUSIONS

Implications for practice

From the studies included in this review, there is some evidence to show that spironolactone is an effective treatment to decrease the degree of hirsutism, but insufficient evidence for the management of acne vulgaris. It is also clear that there are not appropriate tools to evaluate the effectiveness of these treatments adequately. Poor standard of research makes it difficult to determine the effectiveness of spironolactone in treatment of hirsutism and/or acne.

Implications for research

The limited number of randomised controlled studies on spironolactone highlights the need for more well designed studies involving a large sample size to investigate the properties of the drug. Outcome measures of acne and hirsutism need to be validated as accurate indications of severity of the conditions. The use of other drugs such as cyproterone acetate, said to be of comparative effectiveness to spironolactone, is investigated by another Cochrane review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Gainie 2004

Methods	This was a randomised trial comparing Metformin and Spironolactone. It was an open labelled study. Randomisation was computer generated. There was no blinding. There is no mention of exclusion after randomisation. Three patients were lost to follow up, 2 from the metformin group and 1 from the spironolactone group.In total 6 patients were not analysed in the metformin group and 7 were not analysed in the spironolactone group
Participants	The trial was conducted in India. It consisted of 82 women out of 168 who were screened. Mean age was 22.9 +/- 5.3 for the metformin group and 23.3 +/- 5.2 for the spironolactone group. Women were included if they had the presence of menstrual disturbance and hirsuitism after ruling out endocrine disturbances and neoplasms. Other exclusions included use of drugs known or suspected to affect reproductive or metabolic functions within 60 days of study entry or those having diabetes mellitus, or renal, hepatic or cardiac dysfunction.
Interventions	Metformin 500 mg twice daily orally (n= 41) versus Spironolactone 25 mg twice daily orally for six months (n=41).
Outcomes	Modified Ferriman-Gallwey score, biochemical and hormonal profiles, menstrual cycle frequency recorded at 3 and 6 months of treatment. Adverse events
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation was computer generated.
Allocation concealment?	Unclear	B-unclear
Blinding? All outcomes	No	open label study
Incomplete outcome data addressed? All outcomes	Yes	All attrition accounted for

Lobo 1985

Methods	This was a randomised controlled dosage trial of spironolactone. Method of allocation was by a table of random numbers. No blinding was mentioned. There was no mention of exclusion after randomisation. There were no losses to follow-up although unbound testosterone was only measured in 9 of the patients, no explanation was given. Patients in the two groups have similar hair scores, also, a group of 15 normal women were matched for weight and age acted as control.
Participants	The trial was conducted in USA. It consisted of 30 women between the age of 20 to 35. Women with significant degree of hirsutism but minimal abnormalities in blood androgen levels were included. Patients did not receive any treatment for hirsutism in the last 6 months. No exclusion criteria was stated.
Interventions	Group 1 of 15 women received 100mg spironlactone daily. Group 2 of 15 women received 200mg spironolactone daily. The trial lasted 3 months.
Outcomes	Free testosterone levels Androstenedione levels Dehydroepiandrosterone sulphate levels Hair diameter
Notes	Spironolactone versus spironolactone

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Method of allocation was by a table of random numbers.
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Unclear	No blinding was mentioned.

Lumachi 2003

Methods	Randomised controlled trial Method of randomisation was by random number table.
Participants	41 women, median age 21 years, with idiopathic hirsutism who were on the oral contraceptive pill (minimum of two years).
Interventions	Group 1 received cyproterone acetate (12.5mg/day for first days of cycle), Group 2 received finasteride (5 mg/d), Group 3 received spironolactone (100 mg/day) for 12 months

Lumachi 2003 (*Continued*)

Outcomes	Ferriman-Gallwey score at 6 and 12 months and 1 year after the end of treatment, androgenic profile after treatment
Notes	no blinding

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Method of randomisation was by random number table.
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Unclear	No evidence

McLellan 1989

Methods	This was a double blind randomised trial. Concealment of allocation was adequate. Method of allocation was not stated. Patients were matched for menstrual regularity, duration and degree of hirsutism, family history of hirsutism, age of menarche and presence of acne to ensure equal allocation to the treatment groups of any patients with unrecognised polycystic ovary syndrome. Of the 38 patients, 8 pairs or 16 patients withdrew: three pairs due to menorrhagia, two pairs due to non compliance, three pairs due to personal reasons. Duration of trial was 9 months
Participants	38 female patients in the United Kingdom participated, age was not stated. Patients were included for presumptive diagnosis of idiopathic hirsutism. Exclusion criteria was not stated.
Interventions	100 mg oral spironolactone daily or placebo for 9 months.
Outcomes	hair diameter withdrawal from trials side effects-menorrhagia (change in menstrual cycle regularity) subjective assessment of hair growth. serum testosterone levels serum androstenedione levels serum dehydroepiandrosterone levels serum sex hormone binding globulin levels serum luteinising hormone levels serum follicular stimulating hormone levels
Notes	

McLellan 1989 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	Patients accounted for

Moghetti 2000

Methods	Randomised double blind placebo controlled trial of spironolactone, flutamide and finasteride
Participants	women with severe hirsutism n=40 21 women had polycystic ovarian syndrome mean age = 20 years BMI 24.5
Interventions	1. spironolactone 100mg daily for 6 months versus 2. flutamide 250 mg daily 3. finasteride 5 mg daily 4. placebo tablets
Outcomes	hirsutism and hormonal parameters were measured at the beginning and after 6 months treatment
Notes	

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not clear
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Double blind

Muhlemann 1986

Methods	Double blind, placebo controlled crossover trial, random allocation , sealed envelope
Participants	Women with moderate to severe acne (n=29), 8 patients withdrew (2 stated side effects and 6 failed to return).
Interventions	Spironolactone (200mg) versus placebo, co intervention possible as 6 women continued previously prescribed oral contraceptive pills
Outcomes	Mean lesion count, change in acne - improved, unchanged and worse, number of inflamed lesions
Notes	No data on mean lesion count or subjective improvement before or after crossover period.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	random allocation
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	Patients accounted for

Prezelj 1989

Methods	This was a randomised parallel study. Randomisation was conducted by computer generated pseudo-random numbers thus concealment of allocation was adequate. Blinding was unclear. Two patients in treatment group A withdrew, one due to signs of Cushings Syndrome, one due to polymenorrhea.
Participants	25 female patients aged between 17 and 34 participated in the trial. Women with hirsutism score of 7 or more (Ferriman and Gallwey score), menstrual disorder(olig or amenorrhea), and at least one of the following androgen levels elevated:serum and salivary testosterone, serum androstenedione and dehydroepiandrosterone sulphate. Androgen secreting tumours , thyroid dysfunction, hypercortisolism and congenital adrenal hyperplasia were excluded.
Interventions	Duration of trial was 6 months Treatment involved 100mg spironolactone twice a day and 0.5mg dexamethasone daily Control: 100mg spironolactone twice a day

Prezelj 1989 (*Continued*)

Outcomes	Hormone levels: follicular stimulating hormone levels luteinising hormone levels dehydroepiandrosterone levels estradiol levels estrone levels serum total testosterone levels androstenedione levels Ferriman and Gallwey score
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation was conducted by computer generated pseudo-random numbers
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Unclear	Blinding was unclear

Walton 1986

Methods	This was a randomised controlled trial. Method of randomised and blinding were unclear. Concealment of allocation was unclear. There was no loses to follow up.
Participants	The trial was conducted in the United Kingdom. Patients with moderately severe facial acne; grade 1.0-3.0 assessed by method of Cunliffe and Burke. No exclusion criteria or age of participants was stated. Patients were randomised to 3 groups to receive treatment for 2 months. 11 patients(4 men, 7 women) received treatment with 3% spironolactone. 11 patients(7 men, 4 women) received treatment with 5% spironolactone cream. 9 patients(5 men, 4 women) received treatment with 3% potassium canrenoate solution.
Interventions	3% spironolactone powder finely ground and evenly dispersed in Unguentum Merck. 5% spironolactone cream supplied by Schiapparelli Farmaceutici S.p.A., Turin, Italy. 3% potassium canrenoate solution made up in a cream with 2% acetic acid and Unguentum Merck. Patients receiving 3% spironolactone or potassium carenoate cream applied either 3mg spironolactone or 0.1gm canrenone cream to the forehead twice a day. Patients with 5% spironolactone used an unmeasured amount of the cream on the forehead twice a day. Duration of trial was 2 months

Walton 1986 (*Continued*)

Outcomes	sebum excretion rate
Notes	The author informed us that details of the results are no longer available. Hence data could only be extracted from the graphs published in the article. Results recorded after one month of treatment was excluded from statistical analysis as it was felt that the treatment period was not long enough for effects of therapy to be shown yet.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	unclear
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Unclear	unclear
Incomplete outcome data addressed? All outcomes	Yes	No losses to follow up

Wong 1995

Methods	This study was a randomised trial comparing finasteride to spironolactone for the treatment of hirsute women. Randomisation was on a 2:1 basis. Method of randomisation was not described. Allocation concealment not clear. No evidence of blinding. No details of loss to follow-up or exclusion after randomisation.
Participants	The trial was conducted in the USA. 14 women were randomised. Age range 15-40 years. Mean age was 29.3 +/-3.1 (SEM) for Finasteride group and 33.4 +/-1.3 years for the spironolactone group. Inclusion criteria was for a Ferriman Gallwey score greater or equal to 12, and not received hormonal treatment for hirsutism in the previous six months. All women had a history of long standing, slowly progressive hirsutism without evidence of virilisation, pelvic mass, or elevated 17-hydroxyprogesterone levels.
Interventions	Spironolactone (n=5) 100mg daily versus finasteride (n=9) 5 mg daily adminstered orally for six months. Evaluation took place at 3 and 6 months of treatment.
Outcomes	Ferriman-Gallwaey score, hormonal and biochemical analysis, self reported score. Hair shaft diameter.
Notes	

Risk of bias

Wong 1995 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No details
Allocation concealment?	Unclear	B-unclear
Blinding? All outcomes	Unclear	No evidence
Incomplete outcome data addressed? All outcomes	Unclear	No details

Characteristics of excluded studies *[ordered by study ID]*

Castello 1991	Comparison of spironolactone versus spironolactone and licorice. No clinical outcomes reported
Gokmen 1996	The study first randomised 173 patients into two treatment groups, cyproterone acetate and oral contraceptive. After allocating 51 patients, another two treatments were added to the treatment allocation, spironolactone and ketoconazole. Furthermore, patients who did not return for follow up were subsequently excluded from the study. This caused an uneven distribution of patients among groups: 48 receiving oral contraceptives, 65 receiving cyproterone acetate, 12 receiving spironolactone and 16 receiving ketaconazole. Therefore, the trial was excluded.
Gomez 1987	Although this is a placebo-controlled study in 12 women, there was no mention of randomisation. Results of the study was not given. All authors were contacted but none replied to supply additional information. Thus we classified it as a clinical controlled study only.
Goodfellow 1984	Of the original 36 patients, 13 were female and twelve were receiving spironolactone, thus only 1 patient was receiving a placebo.
Pittaway 1985	36 women were treated with either spironolactone and oral contraceptives or spironolactone and dexamethasone. Single drug therapy was individualised according to the major source of the androgens, menstrual dysfunction, and desire for contraception. Thus this was not a randomised trial.
Siegberg 1987	The study included women with hyperandrogenism but only 15 were hirsute women. There was no mention of how many hirsute women were in the treatment and placebo group. The author informed us that the original data was no longer available. Therefore this trial was excluded.
Unluhizarci 2002	Women with randomised according to an alternating sequences.

(*Continued*)

Wild 1991	Patients were selected for treatment based on their contraceptive needs. Those requiring contraception were randomised to two types of oral contraceptives. Those not requiring contraception were placed on spironolactone .Thus treatment allocation was not random.

DATA AND ANALYSES

Comparison 1. 100mg spironolactone versus placebo for hirsutism

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Subjective improvement in hair growth	2	42	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.18 [1.96, 26.28]
2 Ferriman-Galwey score	1	20	Mean Difference (IV, Fixed, 95% CI)	-7.20 [-10.98, -3.42]
3 Hair diameter at 6 months (mean of 6 and 9 months)	2	42	Mean Difference (IV, Fixed, 95% CI)	-9.94 [-22.48, 2.60]
4 Free testosterone level at 6 months (mean of 6 and 9 months)	2	42	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.50, 0.54]
5 Androstenedione level at 6 months (mean of 6 and 9 months)	2	42	Mean Difference (IV, Fixed, 95% CI)	0.55 [-0.93, 2.04]
6 Dehydroepiandrosterone level at 6 months (mean of 6 and 9 months)	1	22	Mean Difference (IV, Fixed, 95% CI)	0.30 [-2.19, 2.79]

Comparison 2. 5% spironolactone versus 3% spironolactone for acne vulgaris

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sebum secretion rate at 2 months	1	8	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.12, 0.32]

Comparison 3. 3%topical spironolactone versus 3% topical carenoate for acne vulgaris

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sebum excretion at 2 months	1	11	Mean Difference (IV, Fixed, 95% CI)	0.20 [0.08, 0.32]

Comparison 4. Dexamethasone and spironolactone versus spironolactone for hirsutism

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ferriman and Gallwey score at 6 months	1	23	Mean Difference (IV, Fixed, 95% CI)	1.20 [-2.20, 4.60]
2 Androstenedione level at 6 months	1	23	Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 Dehydroepiandrosterone level at 6 months	1	23	Mean Difference (IV, Fixed, 95% CI)	-3.09 [-6.78, -0.82]
4 Testosterone level at 6 months	1	23	Mean Difference (IV, Fixed, 95% CI)	-0.30 [1.00, 0.40]
5 Side effects - Polymenorrhea	1	23	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.17, 4.33]
6 Side effects - induction of cycle regularity	1	23	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.23, 5.82]

Comparison 5. 100mg versus 200mg spironolactone dosage trial for hirsutism

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Androstenedione level after 3 months of treatment	1	30	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.00, 1.40]
2 Dehydroepiandrosterone level after 3 months of treatment	1	30	Mean Difference (IV, Fixed, 95% CI)	0.24 [-0.46, 0.94]

Comparison 6. 100 mg spironolactone versus 12.5 mg/d cyproterone acetate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ferriman-Galwey Score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 6 months of treatment	1	28	Mean Difference (IV, Fixed, 95% CI)	0.72 [-0.12, 1.56]
1.2 12 months of treatment	1	28	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-1.04, 0.92]
1.3 12 months after treatment	1	28	Mean Difference (IV, Fixed, 95% CI)	-1.18 [-2.10, -0.26]
2 Free Testosterone	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 12 months of treatment	1	28	Mean Difference (IV, Fixed, 95% CI)	-1.06 [-4.74, 1.74]
2.2 12 months after end of treatment	1	2	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 7. 100 mg spironolactone versus 5 mg/day of finasteride

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ferriman-Galwey score	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 6 months of treatment	1	28	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.94, 0.56]
1.2 12 months of treatment	1	28	Mean Difference (IV, Fixed, 95% CI)	-0.53 [-1.61, 0.55]
1.3 12 months after the end of treatment	1	28	Mean Difference (IV, Fixed, 95% CI)	-2.35 [-3.23, -1.45]
1.4 Decrease in score after 3 months treatment	1	14	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.5 Decrease in score after 6 months treatment	1	14	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.07, 0.27]
2 Free Testosterone level	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 12 months of treatment	1	28	Mean Difference (IV, Fixed, 95% CI)	-2.01 [-4.62, 0.62]
3 Anagen hair diameter at 3 months			Other data	No numeric data
4 Anagen hair diameter at 6 months			Other data	No numeric data
5 Self reported improvement in hirsuitism at 3 months	1	14	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.02, 4.02]
6 Self reported improvement in hirsuitsm at 6 months	1	14	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.02, 2.06]

Comparison 8. Spironolactone 50 mg versus metformin 1000mg for hirsuitsm

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ferriman- Gallwey score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Score at 3 months	1	69	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-3.01, 0.41]
1.2 Score at 6 months	1	69	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-2.57, -0.03]
2 Serum testosterone	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 3 months	1	69	Mean Difference (IV, Fixed, 95% CI)	-0.59 [-1.30, 0.12]
2.2 6 months	1	69	Mean Difference (IV, Fixed, 95% CI)	0.25 [-0.20, 0.68]
3 DHEAS	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 3 months	1	69	Mean Difference (IV, Fixed, 95% CI)	0.31 [-1.31, 1.93]
3.2 6 months	1	69	Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.99, 1.25]
4 Side effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Polyuria	1	69	Odds Ratio (M-H, Fixed, 95% CI)	10.48 [0.54, 202.47]
4.2 Abdominal pain	1	69	Odds Ratio (M-H, Fixed, 95% CI)	3.18 [0.13, 80.79]
4.3 Menstrual irregularity	1	69	Odds Ratio (M-H, Fixed, 95% CI)	26.45 [1.47, 475.45]
4.4 hyperuricemia	1	69	Odds Ratio (M-H, Fixed, 95% CI)	3.18 [0.13, 80.79]
4.5 Nausea and vomiting	1	69	Odds Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 1.96]
4.6 Diarrhoea	1	69	Odds Ratio (M-H, Fixed, 95% CI)	0.05 [0.00, 0.85]
4.7 Hyperadrenergic symptoms (not hypoglycaema)	1	69	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 4.20]

4.8 Drug withdrawal	1	69	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.08, 2.84]

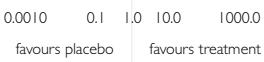
Analysis 1.1. Comparison 1 100mg spironolactone versus placebo for hirsutism, Outcome 1 Subjective improvement in hair growth.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 1 100mg spironolactone versus placebo for hirsutism

Outcome: 1 Subjective improvement in hair growth

Study or subgroup	100mg oral SPL n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
McLellan 1989	8/11	3/11		63.1 %	5.67 [1.11, 29.04]
Moghetti 2000	4/10	0/10		36.9 %	10.75 [1.27, 91.00]
Total (95% CI)	**21**	**21**		**100.0 %**	**7.18 [1.96, 26.28]**
Total events: 12 (100mg oral SPL), 3 (placebo)					
Heterogeneity: Chi^2 = 0.22, df = 1 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 2.98 (P = 0.0029)					



Analysis 1.2. Comparison 1 100mg spironolactone versus placebo for hirsutism, Outcome 2 Ferriman-Galwey score.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 1 100mg spironolactone versus placebo for hirsutism

Outcome: 2 Ferriman-Galwey score

Study or subgroup	Spironolactone N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Moghetti 2000	10	10 (3.5)	10	17.2 (5)		100.0 %	-7.20 [-10.98, -3.42]
Total (95% CI)	**10**		**10**			**100.0 %**	**-7.20 [-10.98, -3.42]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.73 (P = 0.00019)							

Analysis 1.3. Comparison 1 100mg spironolactone versus placebo for hirsutism, Outcome 3 Hair diameter at 6 months (mean of 6 and 9 months).

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

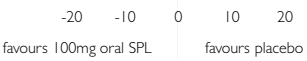
Comparison: 1 100mg spironolactone versus placebo for hirsutism

Outcome: 3 Hair diameter at 6 months (mean of 6 and 9 months)

Study or subgroup	100mg oral SPL N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
McLellan 1989	11	81 (13.27)	11	92 (19.9)		78.7 %	-11.00 [-25.13, 3.13]
Moghetti 2000	10	144 (37.9)	10	150 (22.05)		21.3 %	-6.00 [-33.18, 21.18]
Total (95% CI)	**21**		**21**			**100.0 %**	**-9.94 [-22.48, 2.60]**

Heterogeneity: $Chi^2 = 0.10$, df = 1 (P = 0.75); $I^2 = 0.0\%$

Test for overall effect: Z = 1.55 (P = 0.12)



Analysis 1.4. Comparison 1 100mg spironolactone versus placebo for hirsutism, Outcome 4 Free testosterone level at 6 months (mean of 6 and 9 months).

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 1 100mg spironolactone versus placebo for hirsutism

Outcome: 4 Free testosterone level at 6 months (mean of 6 and 9 months)

Study or subgroup	100mg oral SPL N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
McLellan 1989	11	2.5 (0.66)	11	2.6 (0.99)		55.2 %	-0.10 [-0.80, 0.60]
Moghetti 2000	10	3.42 (0.75)	10	3.25 (1.01)		44.8 %	0.17 [-0.61, 0.95]
Total (95% CI)	**21**		**21**			**100.0 %**	**0.02 [-0.50, 0.54]**

Heterogeneity: $Chi^2 = 0.25$, df = 1 (P = 0.61); $I^2 = 0.0\%$

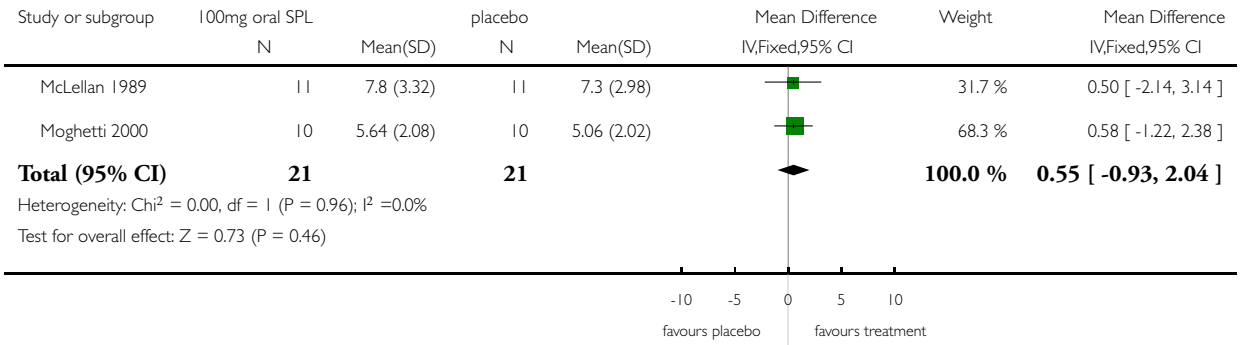
Test for overall effect: Z = 0.08 (P = 0.94)

Analysis 1.5. Comparison 1 100mg spironolactone versus placebo for hirsutism, Outcome 5 Androstenedione level at 6 months (mean of 6 and 9 months).

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 1 100mg spironolactone versus placebo for hirsutism

Outcome: 5 Androstenedione level at 6 months (mean of 6 and 9 months)

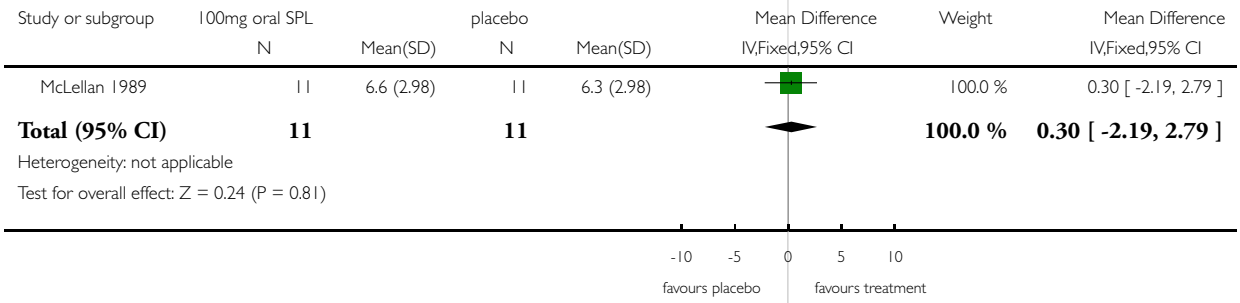


Analysis 1.6. Comparison 1 100mg spironolactone versus placebo for hirsutism, Outcome 6 Dehydroepiandrosterone level at 6 months (mean of 6 and 9 months).

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 1 100mg spironolactone versus placebo for hirsutism

Outcome: 6 Dehydroepiandrosterone level at 6 months (mean of 6 and 9 months)



Analysis 2.1. Comparison 2 5% spironolactone versus 3% spironolactone for acne vulgaris, Outcome 1 Sebum secretion rate at 2 months.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

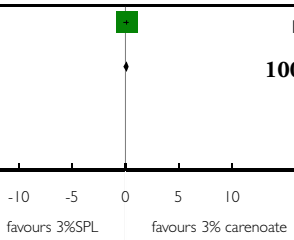
Comparison: 2 5% spironolactone versus 3% spironolactone for acne vulgaris

Outcome: 1 Sebum secretion rate at 2 months

Study or subgroup	3%SPL N	Mean(SD)	3% carenoate N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Walton 1986	4	1.25 (0.2)	4	1.15 (0.1)		100.0 %	0.10 [-0.12, 0.32]
Total (95% CI)	**4**		**4**			**100.0 %**	**0.10 [-0.12, 0.32]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.89 (P = 0.37)



Analysis 3.1. Comparison 3 3%topical spironolactone versus 3% topical carenoate for acne vulgaris, Outcome 1 Sebum excretion at 2 months.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

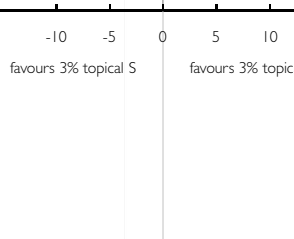
Comparison: 3 3%topical spironolactone versus 3% topical carenoate for acne vulgaris

Outcome: 1 Sebum excretion at 2 months

Study or subgroup	3% topical SPL N	Mean(SD)	3% topical carenoate N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Walton 1986	7	1.35 (0.1)	4	1.15 (0.1)		100.0 %	0.20 [0.08, 0.32]
Total (95% CI)	**7**		**4**			**100.0 %**	**0.20 [0.08, 0.32]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.19 (P = 0.0014)



Analysis 4.1. Comparison 4 Dexamethasone and spironolactone versus spironolactone for hirsutism, Outcome 1 Ferriman and Gallwey score at 6 months.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

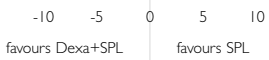
Comparison: 4 Dexamethasone and spironolactone versus spironolactone for hirsutism

Outcome: 1 Ferriman and Gallwey score at 6 months

Study or subgroup	Dexa+SPL N	Mean(SD)	SPL N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Prezelj 1989	13	10.2 (4.9)	10	9 (3.4)		100.0 %	1.20 [-2.20, 4.60]
Total (95% CI)	**13**		**10**			**100.0 %**	**1.20 [-2.20, 4.60]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.69 (P = 0.49)



Analysis 4.2. Comparison 4 Dexamethasone and spironolactone versus spironolactone for hirsutism, Outcome 2 Androstenedione level at 6 months.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

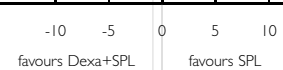
Comparison: 4 Dexamethasone and spironolactone versus spironolactone for hirsutism

Outcome: 2 Androstenedione level at 6 months

Study or subgroup	Dexa+SPL N	Mean(SD)	SPL N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Prezelj 1989	13	7.2 (2.2)	10	7.2 (3.1)		100.0 %	0.0 [-2.26, 2.26]
Total (95% CI)	**13**		**10**			**100.0 %**	**0.0 [-2.26, 2.26]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)



Analysis 4.3. Comparison 4 Dexamethasone and spironolactone versus spironolactone for hirsutism, Outcome 3 Dehydroepiandrosterone level at 6 months.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 4 Dexamethasone and spironolactone versus spironolactone for hirsutism

Outcome: 3 Dehydroepiandrosterone level at 6 months

Study or subgroup	Dexa+SPL N	Mean(SD)	SPL N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Prezelj 1989	13	4.3 (4.2)	10	8.1 (3.1)		100.0 %	-3.80 [-6.78, -0.82]
Total (95% CI)	**13**		**10**			**100.0 %**	**-3.80 [-6.78, -0.82]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.50 (P = 0.013)

Analysis 4.4. Comparison 4 Dexamethasone and spironolactone versus spironolactone for hirsutism, Outcome 4 Testosterone level at 6 months.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

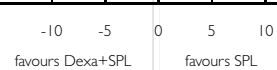
Comparison: 4 Dexamethasone and spironolactone versus spironolactone for hirsutism

Outcome: 4 Testosterone level at 6 months

Study or subgroup	Dexa+SPL N	Mean(SD)	SPL N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Prezelj 1989	13	1.8 (0.9)	10	2.1 (0.8)		100.0 %	-0.30 [-1.00, 0.40]
Total (95% CI)	**13**		**10**			**100.0 %**	**-0.30 [-1.00, 0.40]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.84 (P = 0.40)

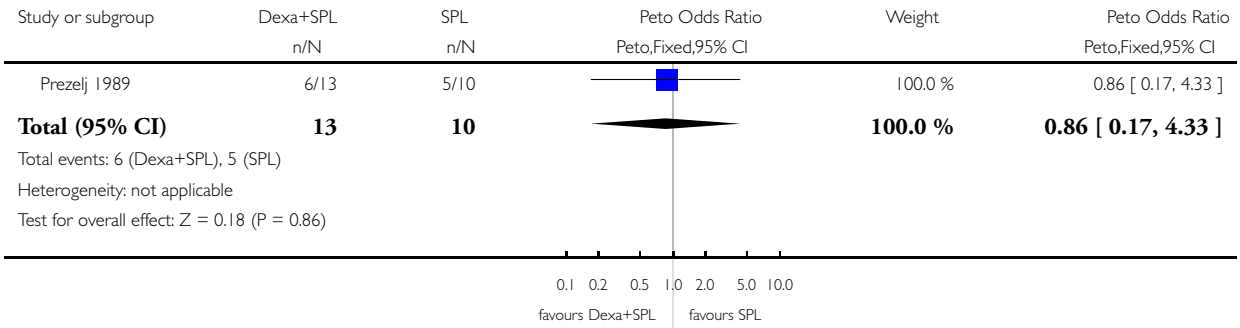


Analysis 4.5. Comparison 4 Dexamethasone and spironolactone versus spironolactone for hirsutism, Outcome 5 Side effects - Polymenorrhea.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 4 Dexamethasone and spironolactone versus spironolactone for hirsutism

Outcome: 5 Side effects - Polymenorrhea

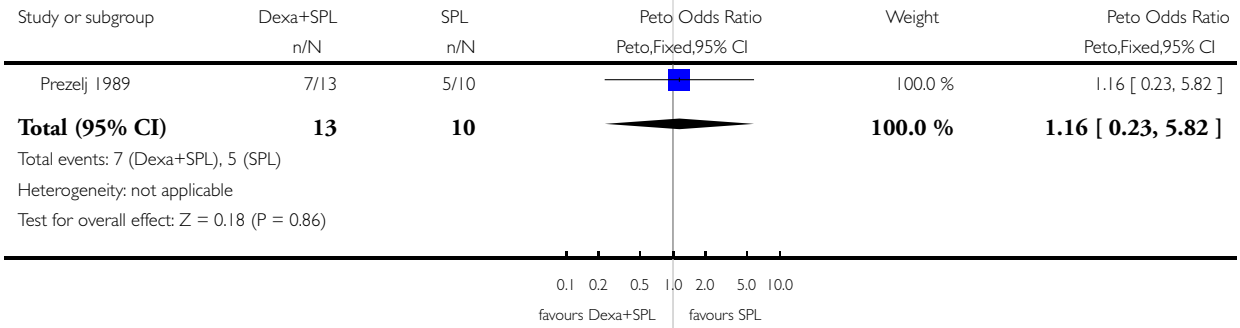


Analysis 4.6. Comparison 4 Dexamethasone and spironolactone versus spironolactone for hirsutism, Outcome 6 Side effects - induction of cycle regularity.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 4 Dexamethasone and spironolactone versus spironolactone for hirsutism

Outcome: 6 Side effects - induction of cycle regularity

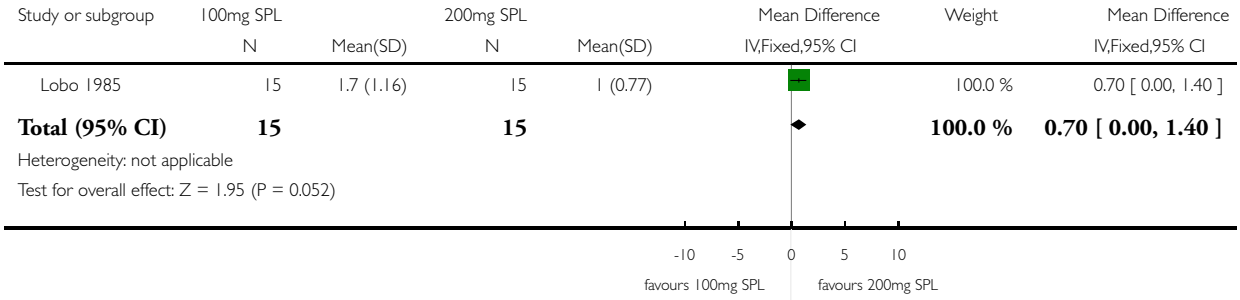


Analysis 5.1. Comparison 5 100mg versus 200mg spironolactone dosage trial for hirsutism, Outcome 1 Androstenedione level after 3 months of treatment.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 5 100mg versus 200mg spironolactone dosage trial for hirsutism

Outcome: 1 Androstenedione level after 3 months of treatment

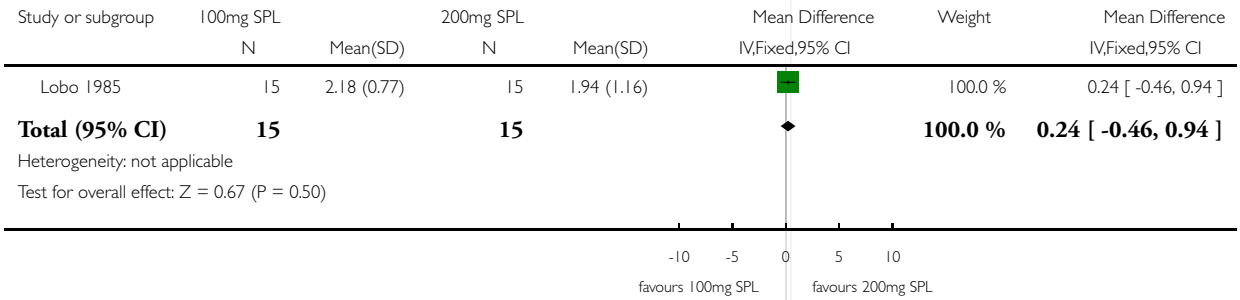


Analysis 5.2. Comparison 5 100mg versus 200mg spironolactone dosage trial for hirsutism, Outcome 2 Dehydroepiandrosterone level after 3 months of treatment.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 5 100mg versus 200mg spironolactone dosage trial for hirsutism

Outcome: 2 Dehydroepiandrosterone level after 3 months of treatment

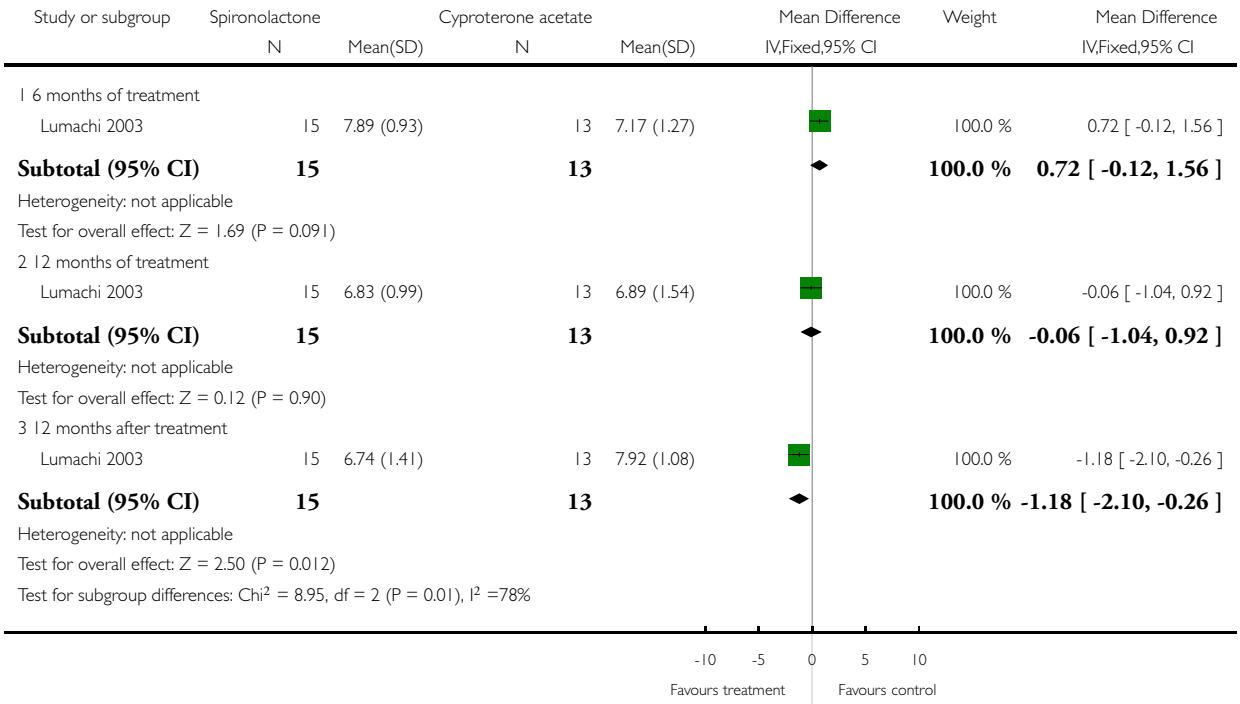


Analysis 6.1. Comparison 6 100 mg spironolactone versus 12.5 mg/d cyproterone acetate, Outcome 1 Ferriman-Galwey Score.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 6 100 mg spironolactone versus 12.5 mg/d cyproterone acetate

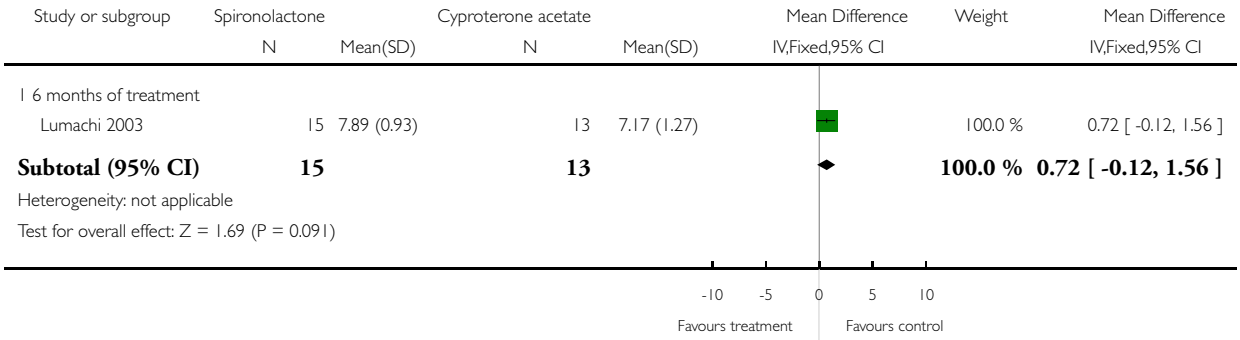
Outcome: 1 Ferriman-Galwey Score



Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 6 100 mg spironolactone versus 12.5 mg/d cyproterone acetate

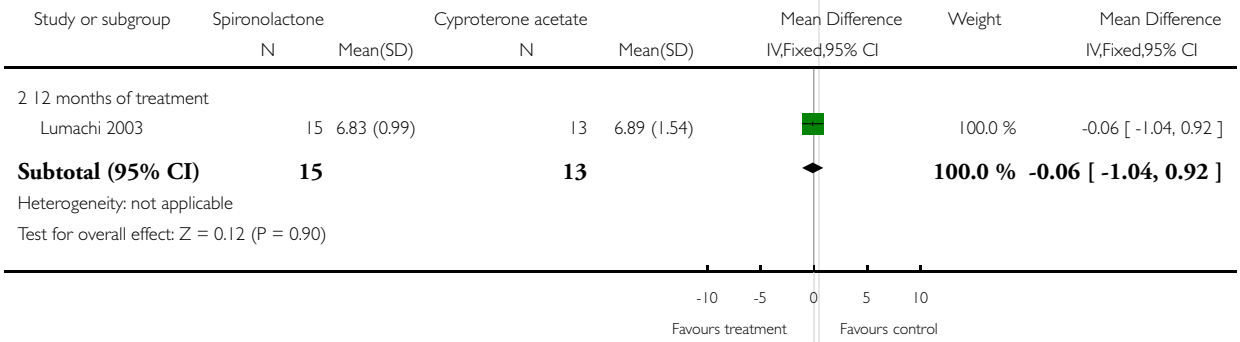
Outcome: 1 Ferriman-Galwey Score



Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 6 100 mg spironolactone versus 12.5 mg/d cyproterone acetate

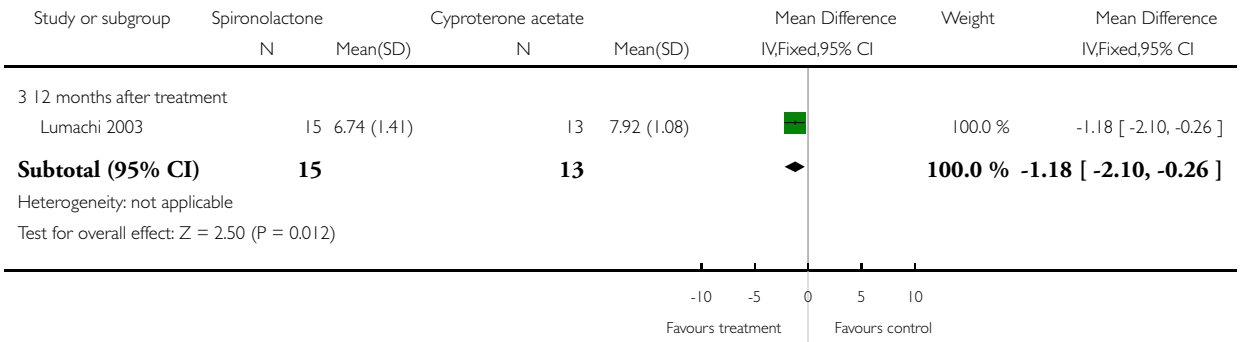
Outcome: 1 Ferriman-Galwey Score



Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 6 100 mg spironolactone versus 12.5 mg/d cyproterone acetate

Outcome: 1 Ferriman-Galwey Score

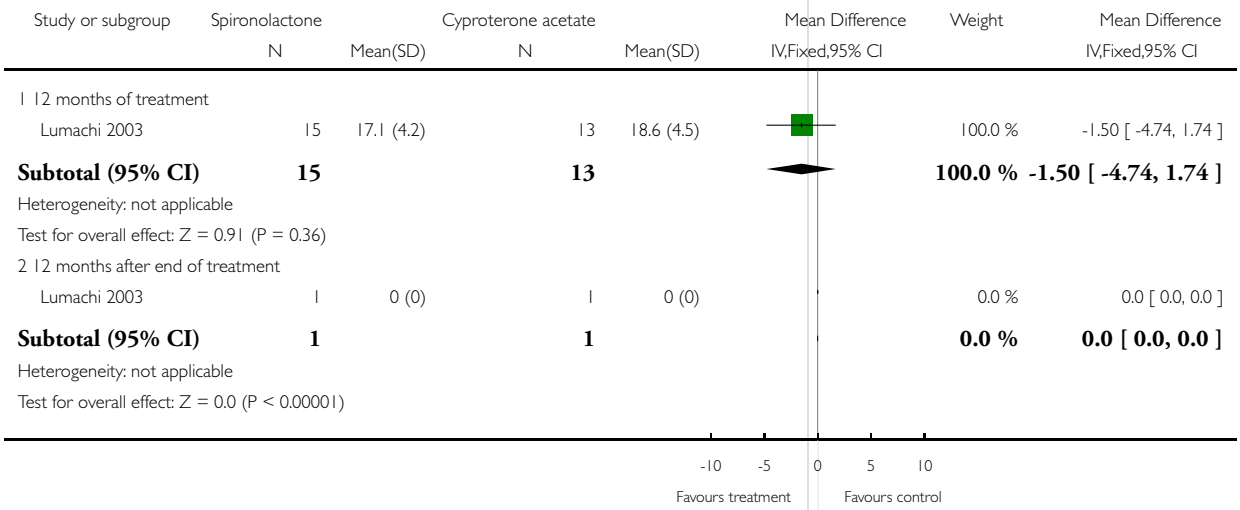


Analysis 6.2. Comparison 6 100 mg spironolactone versus 12.5 mg/d cyproterone acetate, Outcome 2 Free Testosterone.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 6 100 mg spironolactone versus 12.5 mg/d cyproterone acetate

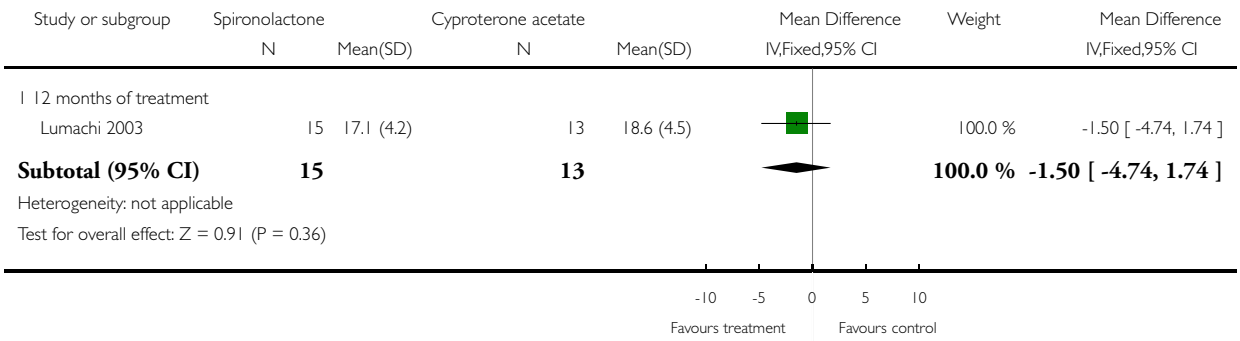
Outcome: 2 Free Testosterone



Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 6 100 mg spironolactone versus 12.5 mg/d cyproterone acetate

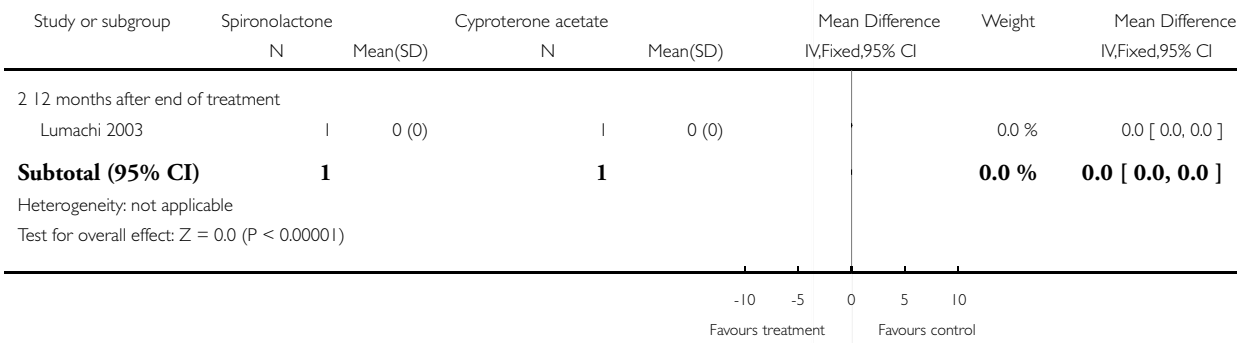
Outcome: 2 Free Testosterone



Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 6 100 mg spironolactone versus 12.5 mg/d cyproterone acetate

Outcome: 2 Free Testosterone



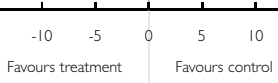
Analysis 7.1. Comparison 7 100 mg spironolactone versus 5 mg/day of finasteride, Outcome 1 Ferriman-Galwey score.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 7 100 mg spironolactone versus 5 mg/day of finasteride

Outcome: 1 Ferriman-Galwey score

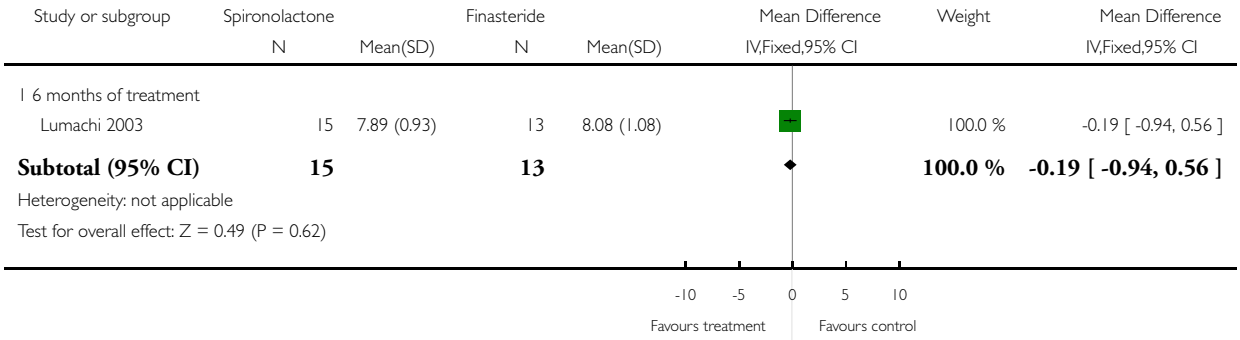
Study or subgroup	Spironolactone N	Mean(SD)	Finasteride N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 6 months of treatment							
Lumachi 2003	15	7.89 (0.93)	13	8.08 (1.08)		100.0 %	-0.19 [-0.94, 0.56]
Subtotal (95% CI)	**15**		**13**			**100.0 %**	**-0.19 [-0.94, 0.56]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.49 (P = 0.62)							
2 12 months of treatment							
Lumachi 2003	15	6.89 (1.54)	13	7.42 (1.38)		100.0 %	-0.53 [-1.61, 0.55]
Subtotal (95% CI)	**15**		**13**			**100.0 %**	**-0.53 [-1.61, 0.55]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.96 (P = 0.34)							
3 12 months after the end of treatment							
Lumachi 2003	15	6.74 (1.41)	13	9.08 (0.99)		100.0 %	-2.34 [-3.23, -1.45]
Subtotal (95% CI)	**15**		**13**			**100.0 %**	**-2.34 [-3.23, -1.45]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.13 (P < 0.00001)							
4 Decrease in score after 3 months treatment							
Wong 1995	5	-1.2 (0.4)	9	-1.2 (0.2)		100.0 %	0.0 [-0.37, 0.37]
Subtotal (95% CI)	**5**		**9**			**100.0 %**	**0.0 [-0.37, 0.37]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
5 Decrease in score after 6 months treatment							
Wong 1995	5	-2.5 (0.7)	9	-2.1 (0.4)		100.0 %	-0.40 [-1.07, 0.27]
Subtotal (95% CI)	**5**		**9**			**100.0 %**	**-0.40 [-1.07, 0.27]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.18 (P = 0.24)							
Test for subgroup differences: Chi^2 = 22.71, df = 4 (P = 0.00), I^2 =82%							



Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 7 100 mg spironolactone versus 5 mg/day of finasteride

Outcome: 1 Ferriman-Galwey score



Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

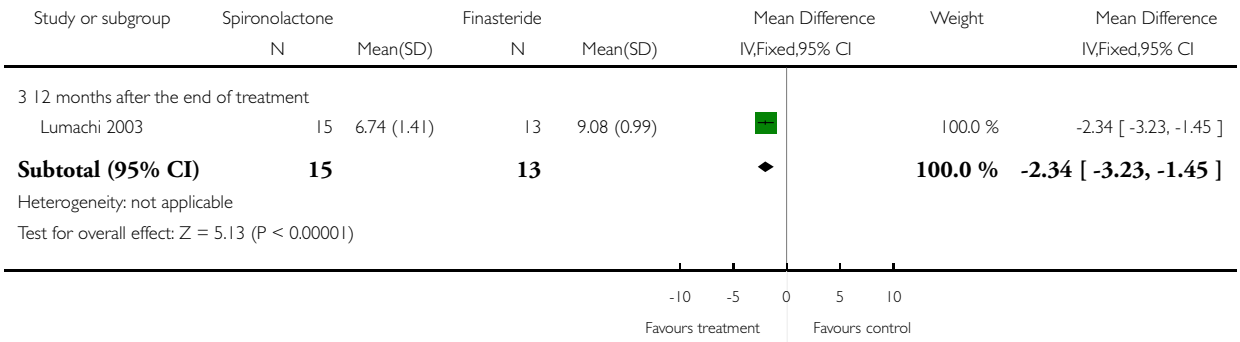
Comparison: 7 100 mg spironolactone versus 5 mg/day of finasteride

Outcome: 1 Ferriman-Galwey score

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 7 100 mg spironolactone versus 5 mg/day of finasteride

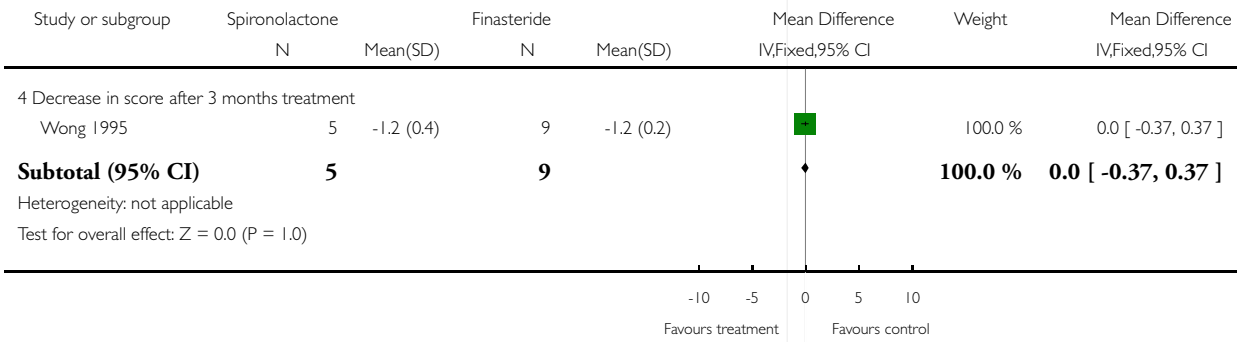
Outcome: 1 Ferriman-Galwey score



Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 7 100 mg spironolactone versus 5 mg/day of finasteride

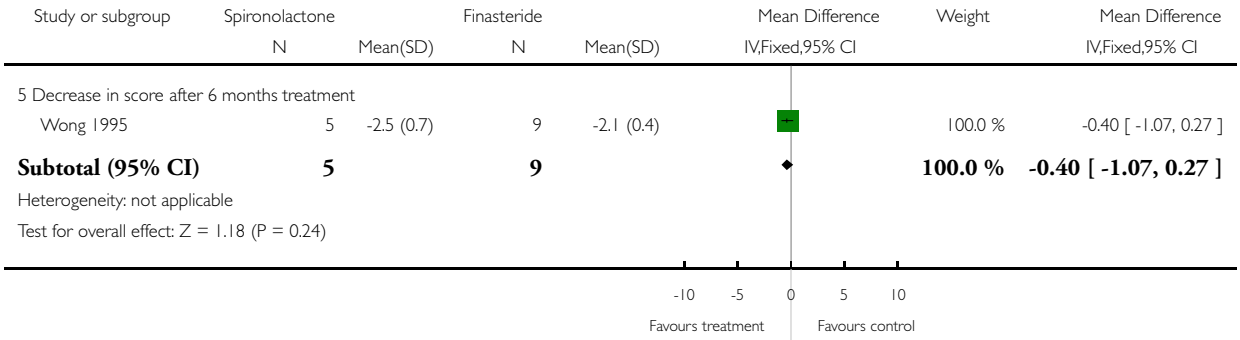
Outcome: 1 Ferriman-Galwey score



Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 7 100 mg spironolactone versus 5 mg/day of finasteride

Outcome: 1 Ferriman-Galwey score

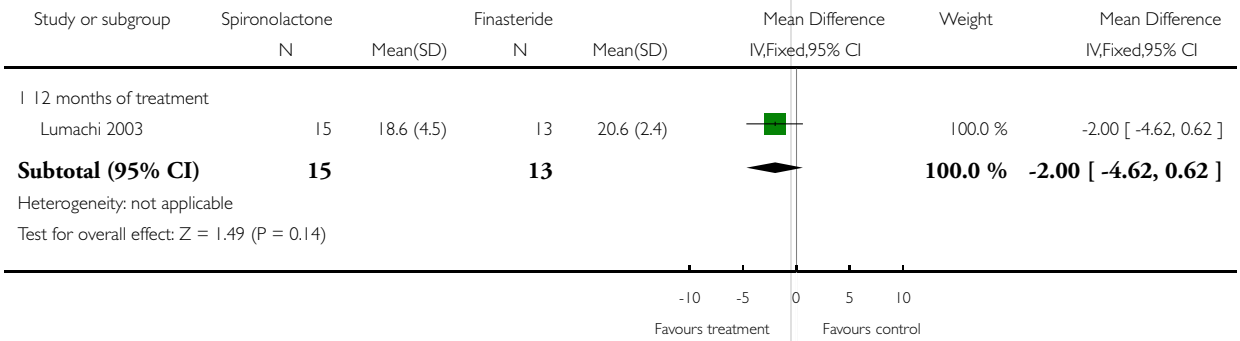


Analysis 7.2. Comparison 7 100 mg spironolactone versus 5 mg/day of finasteride, Outcome 2 Free Testosterone level.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 7 100 mg spironolactone versus 5 mg/day of finasteride

Outcome: 2 Free Testosterone level



Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 7 100 mg spironolactone versus 5 mg/day of finasteride

Outcome: 2 Free Testosterone level

Study or subgroup	Spironolactone N	Mean(SD)	Finasteride N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 12 months of treatment							
Lumachi 2003	15	18.6 (4.5)	13	20.6 (2.4)		100.0 %	-2.00 [-4.62, 0.62]
Subtotal (95% CI)	**15**		**13**			**100.0 %**	**-2.00 [-4.62, 0.62]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.49 (P = 0.14)							

Anagen hair diameter at 3 months

Wong 1995	5	-10.3 +/- 5.5	9	-9.6+/-3

Anagen hair diameter at 6 months

Wong 1995	5	-13.4+/-3.8	9	-14+/-6.7

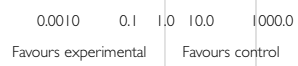
Analysis 7.5. Comparison 7 100 mg spironolactone versus 5 mg/day of finasteride, Outcome 5 Self reported improvement in hirsuitism at 3 months.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 7 100 mg spironolactone versus 5 mg/day of finasteride

Outcome: 5 Self reported improvement in hirsuitism at 3 months

Study or subgroup	Spironolactone n/N	Finasteride n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Wong 1995	1/5	4/9		100.0 %	0.31 [0.02, 4.02]
Total (95% CI)	**5**	**9**		**100.0 %**	**0.31 [0.02, 4.02]**
Total events: 1 (Spironolactone), 4 (Finasteride)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.89 (P = 0.37)					



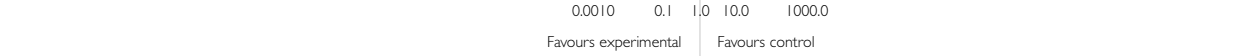
Analysis 7.6. Comparison 7 100 mg spironolactone versus 5 mg/day of finasteride, Outcome 6 Self reported improvement in hirsuitsm at 6 months.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 7 100 mg spironolactone versus 5 mg/day of finasteride

Outcome: 6 Self reported improvement in hirsuitsm at 6 months

Study or subgroup	Spironolactone n/N	Finasteride n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Wong 1995	2/5	7/9		100.0 %	0.19 [0.02, 2.06]
Total (95% CI)	**5**	**9**		**100.0 %**	**0.19 [0.02, 2.06]**
Total events: 2 (Spironolactone), 7 (Finasteride)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.36 (P = 0.17)					



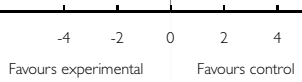
Analysis 8.1. Comparison 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm, Outcome 1 Ferriman- Gallwey score.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm

Outcome: 1 Ferriman- Gallwey score

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Score at 3 months							
Gainie 2004	34	10.1 (3.1)	35	11.4 (4.1)		100.0 %	-1.30 [-3.01, 0.41]
Subtotal (95% CI)	**34**		**35**			**100.0 %**	**-1.30 [-3.01, 0.41]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.49 (P = 0.14)							
2 Score at 6 months							
Gainie 2004	34	8.7 (1.9)	35	10 (3.3)		100.0 %	-1.30 [-2.57, -0.03]
Subtotal (95% CI)	**34**		**35**			**100.0 %**	**-1.30 [-2.57, -0.03]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.01 (P = 0.044)							
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 1.00), I^2 =0.0%							

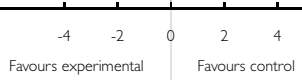


Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm

Outcome: 1 Ferriman- Gallwey score

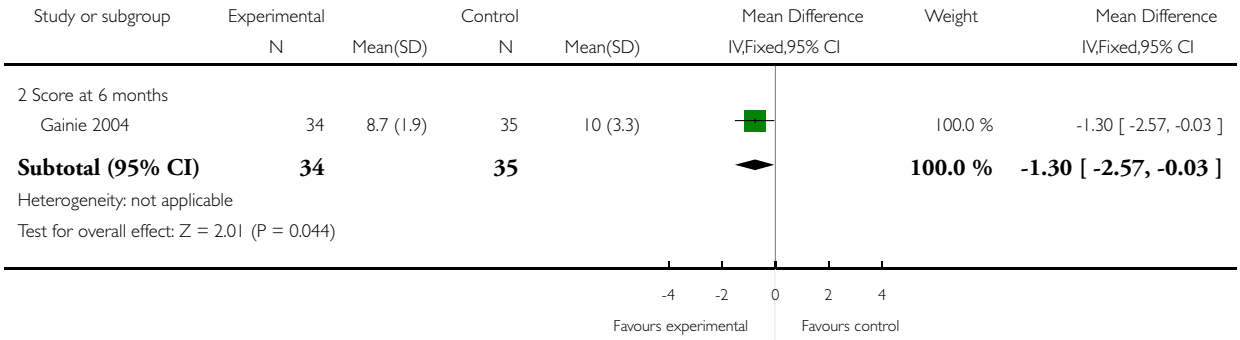
Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Score at 3 months							
Gainie 2004	34	10.1 (3.1)	35	11.4 (4.1)		100.0 %	-1.30 [-3.01, 0.41]
Subtotal (95% CI)	**34**		**35**			**100.0 %**	**-1.30 [-3.01, 0.41]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.49 (P = 0.14)							



Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm

Outcome: 1 Ferriman- Gallwey score

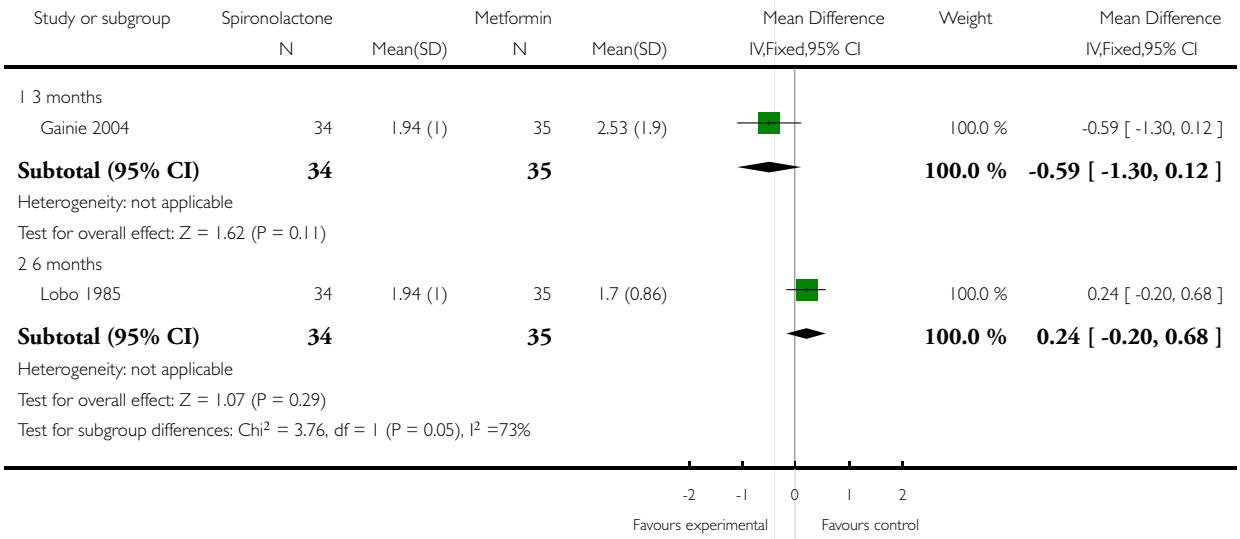


Analysis 8.2. Comparison 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm, Outcome 2 Serum testosterone.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm

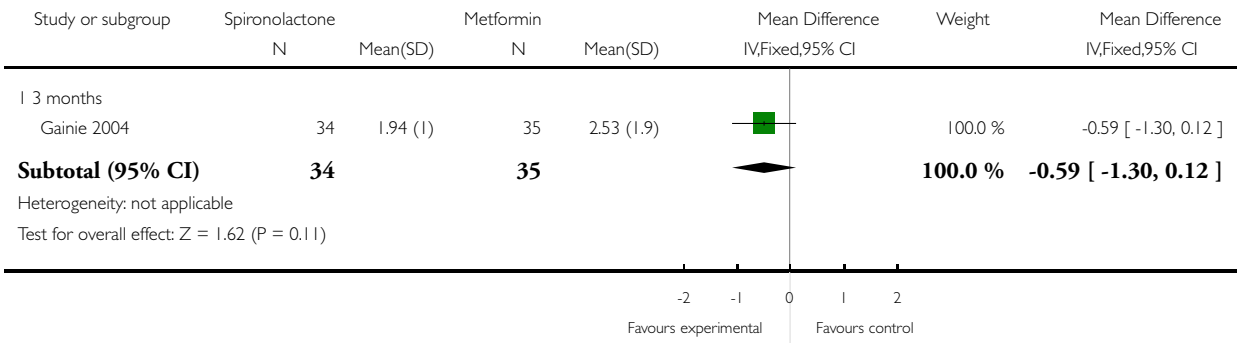
Outcome: 2 Serum testosterone



Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm

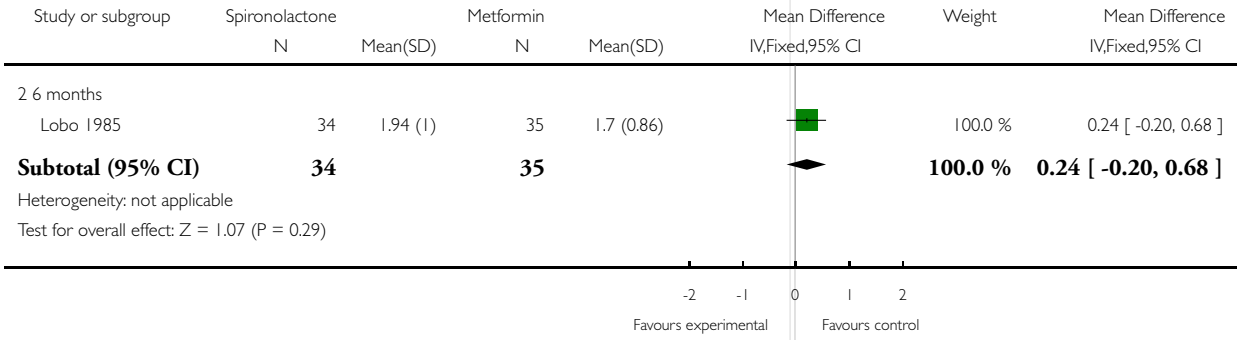
Outcome: 2 Serum testosterone



Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm

Outcome: 2 Serum testosterone

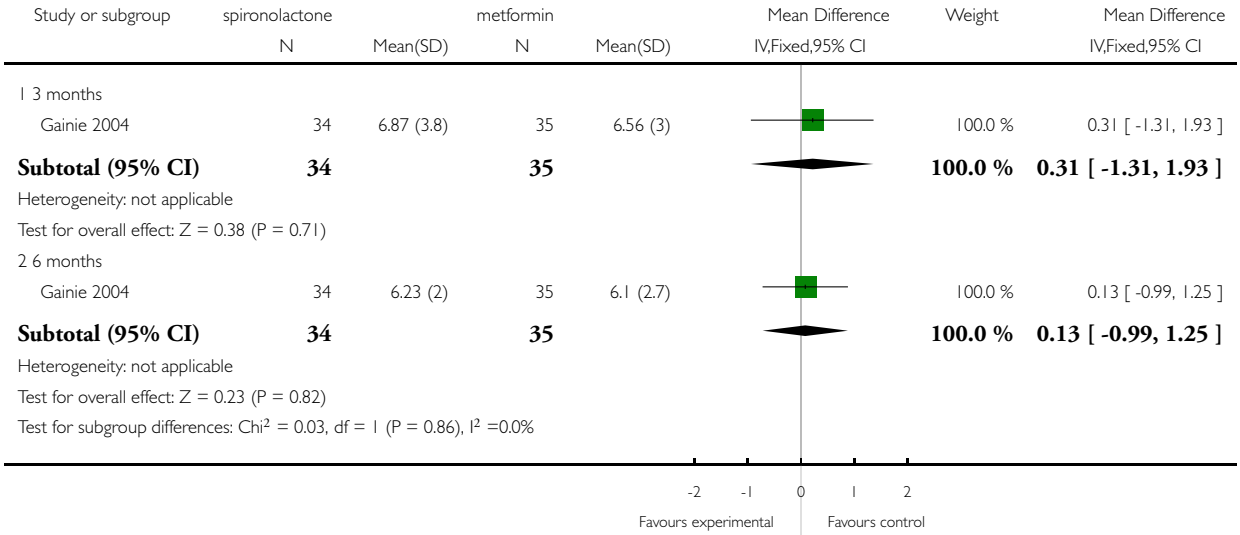


Analysis 8.3. Comparison 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm, Outcome 3 DHEAS.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm

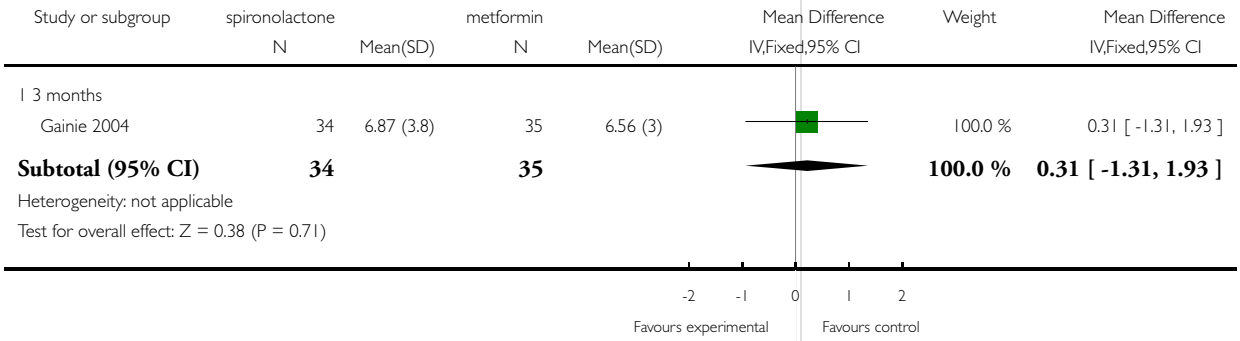
Outcome: 3 DHEAS



Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm

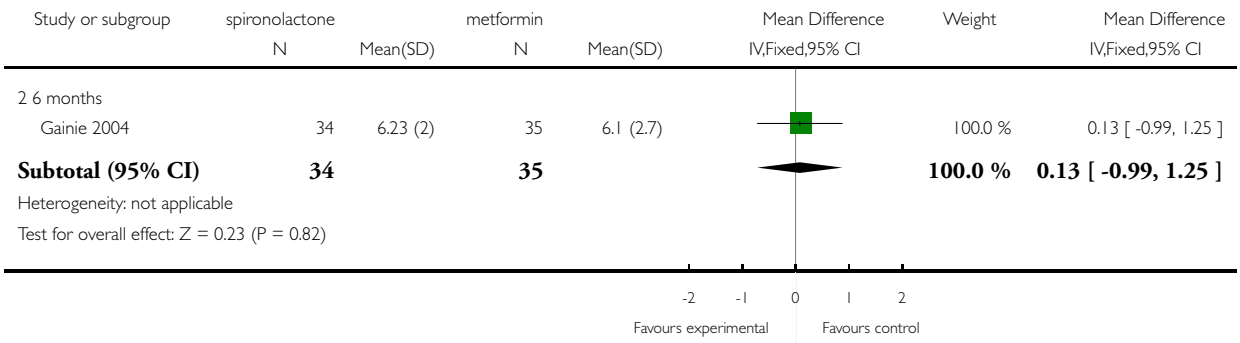
Outcome: 3 DHEAS



Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm

Outcome: 3 DHEAS

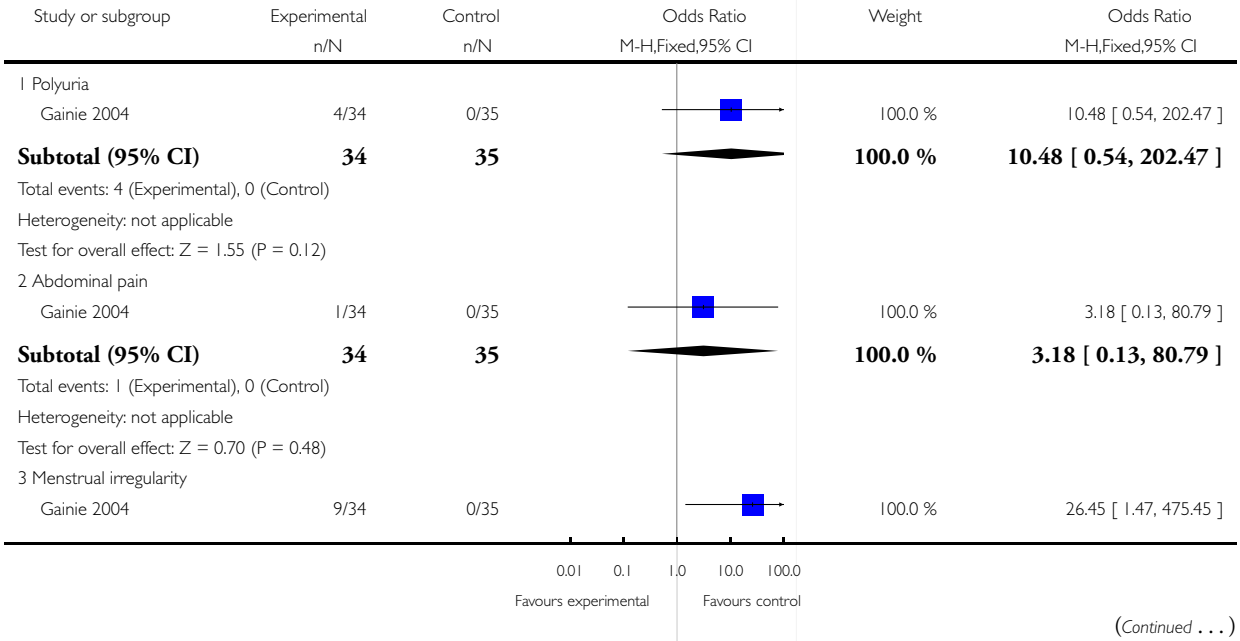


Analysis 8.4. Comparison 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm, Outcome 4 Side effects.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm

Outcome: 4 Side effects



(*Continued . . .*)

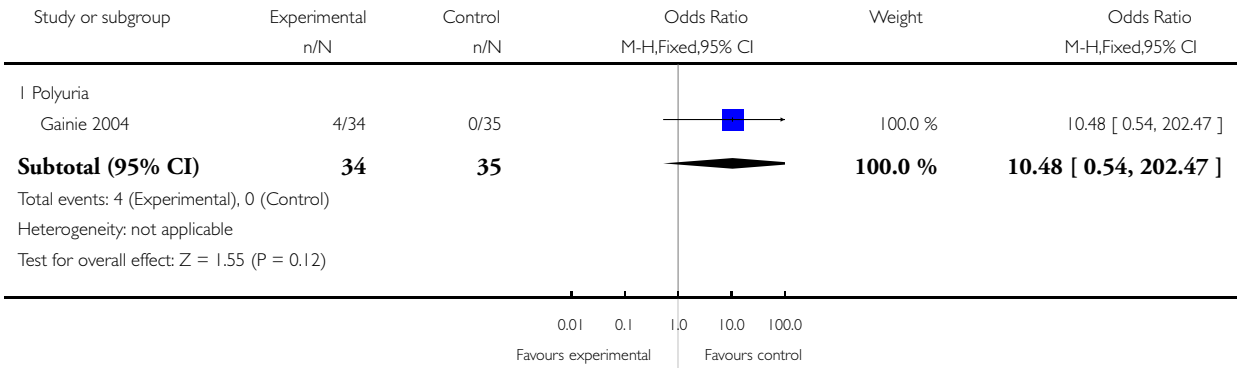
(. . . *Continued*)

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**34**	**35**		**100.0 %**	**26.45 [1.47, 475.45]**
Total events: 9 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.22 (P = 0.026)					
4 hyperuricemia					
Gainie 2004	1/34	0/35		100.0 %	3.18 [0.13, 80.79]
Subtotal (95% CI)	**34**	**35**		**100.0 %**	**3.18 [0.13, 80.79]**
Total events: 1 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.48)					
5 Nausea and vomiting					
Gainie 2004	0/34	4/35		100.0 %	0.10 [0.01, 1.96]
Subtotal (95% CI)	**34**	**35**		**100.0 %**	**0.10 [0.01, 1.96]**
Total events: 0 (Experimental), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.51 (P = 0.13)					
6 Diarrhoea					
Gainie 2004	0/34	8/35		100.0 %	0.05 [0.00, 0.85]
Subtotal (95% CI)	**34**	**35**		**100.0 %**	**0.05 [0.00, 0.85]**
Total events: 0 (Experimental), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.07 (P = 0.038)					
7 Hyperadrenergic symptoms (not hypoglycaema)					
Gainie 2004	0/34	2/35		100.0 %	0.19 [0.01, 4.20]
Subtotal (95% CI)	**34**	**35**		**100.0 %**	**0.19 [0.01, 4.20]**
Total events: 0 (Experimental), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.30)					
8 Drug withdrawal					
Gainie 2004	2/34	4/35		100.0 %	0.48 [0.08, 2.84]
Subtotal (95% CI)	**34**	**35**		**100.0 %**	**0.48 [0.08, 2.84]**
Total events: 2 (Experimental), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm

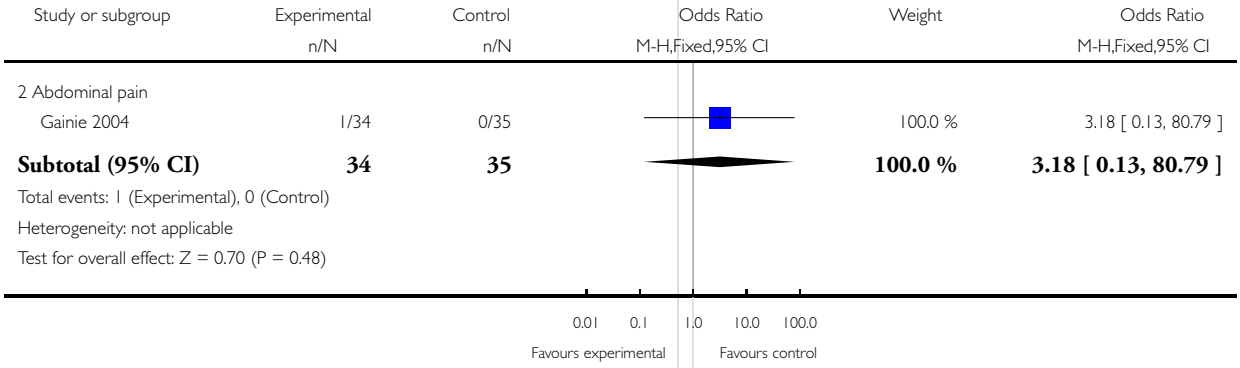
Outcome: 4 Side effects



Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm

Outcome: 4 Side effects



Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm

Outcome: 4 Side effects

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
3 Menstrual irregularity					
Gainie 2004	9/34	0/35		100.0 %	26.45 [1.47, 475.45]
Subtotal (95% CI)	**34**	**35**		**100.0 %**	**26.45 [1.47, 475.45]**
Total events: 9 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.22 (P = 0.026)					

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm

Outcome: 4 Side effects

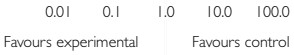
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
4 hyperuricemia					
Gainie 2004	1/34	0/35		100.0 %	3.18 [0.13, 80.79]
Subtotal (95% CI)	**34**	**35**		**100.0 %**	**3.18 [0.13, 80.79]**
Total events: 1 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.48)					

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm

Outcome: 4 Side effects

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
5 Nausea and vomiting					
Gainie 2004	0/34	4/35		100.0 %	0.10 [0.01, 1.96]
Subtotal (95% CI)	**34**	**35**		**100.0 %**	**0.10 [0.01, 1.96]**
Total events: 0 (Experimental), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.51 (P = 0.13)					

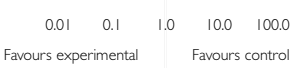


Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm

Outcome: 4 Side effects

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
6 Diarrhoea					
Gainie 2004	0/34	8/35		100.0 %	0.05 [0.00, 0.85]
Subtotal (95% CI)	**34**	**35**		**100.0 %**	**0.05 [0.00, 0.85]**
Total events: 0 (Experimental), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.07 (P = 0.038)					

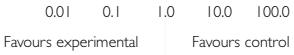


Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm

Outcome: 4 Side effects

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
7 Hyperadrenergic symptoms (not hypoglycaema)					
Gainie 2004	0/34	2/35		100.0 %	0.19 [0.01, 4.20]
Subtotal (95% CI)	**34**	**35**		**100.0 %**	**0.19 [0.01, 4.20]**
Total events: 0 (Experimental), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.30)					

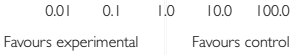


Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 8 Spironolactone 50 mg versus metformin 1000mg for hirsuitsm

Outcome: 4 Side effects

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
8 Drug withdrawal					
Gainie 2004	2/34	4/35		100.0 %	0.48 [0.08, 2.84]
Subtotal (95% CI)	**34**	**35**		**100.0 %**	**0.48 [0.08, 2.84]**
Total events: 2 (Experimental), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					



APPENDICES

Appendix 1. Medline search strategy

hirsutism/
virilism/
hyperandrogenism/
polycystic ovary syndrome/
acne vulgaris/
seborrhoea/
hirsut$.tw.
viril$.tw.
hyperandrog$.tw.
acne.tw.
seborrh$.tw.
hypertrichosis.tw.
polytrich$.tw.
spironolactone/
spironolactone.tw.
aldactone.tw.

WHAT'S NEW

Last assessed as up-to-date: 7 April 2008.

27 April 2008	Amended	Converted to new review format.
27 April 2008	New search has been performed	Two additional studies identified and data added to review Wong 1995 and Ganie 2004.

HISTORY

Protocol first published: Issue 2, 1997

Review first published: Issue 2, 1997

24 July 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Updated in 2008 by Julie Brown and Cindy Farquhar who identified the studies and extracted the data.

Cindy Farquhar, Olivia Lee, Ruth Jepson and Robyn Toomath were involved in the original review.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Dept of Obstetrics and Gynaecology, University of Auckland, NZ, New Zealand.

External sources

- Auckland Medical Research Foundation, NZ, New Zealand.

NOTES

Updated November 2008:with the addition of two trials Wong 1995 and Ganie 2004.

Updated August 2001: with the addition of one trial (Moghetti 2000)

INDEX TERMS

Medical Subject Headings (MeSH)

Acne Vulgaris [*drug therapy]; Aldosterone Antagonists [*therapeutic use]; Drug Therapy, Combination; Glucocorticoids [*therapeutic use]; Hirsutism [*drug therapy]; Randomized Controlled Trials as Topic; Spironolactone [*therapeutic use]

MeSH check words

Female; Humans; Male