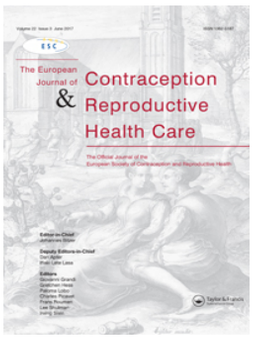

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REVIEW

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The use of cyproterone acetate/ethinyl estradiol in hyperandrogenic skin symptoms – a review

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ABSTRACT

Introduction: Hyperandrogenism affects approximately 10–20% of women of reproductive age. Hyperandrogenic skin symptoms such as hirsutism, acne, seborrhea and alopecia are associated with significant quality of life and psychological impairment. Women with abnormalities in androgen metabolism may have accompanying anovulation and/or polycystic ovary syndrome (PCOS), both of which have reproductive and metabolic implications if left untreated. Cyproterone acetate (CPA), combined with ethinylestradiol (EE), is indicated for the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhea) and/or hirsutism, in women of reproductive age.

Objective: To review the data on the efficacy and safety of CPA 2 mg/EE 35 μg for the treatment of hyperandrogenic skin symptoms in women.

Methods: A non-systematic narrative review based on a literature search of the PubMed database.

Results: Seventy-eight studies were identified. The majority of sufficiently powered studies show a high efficacy of CPA 2 mg/EE 35 μg in the treatment of severe acne and hirsutism. Studies show that therapeutic response in women with hirsutism requires a long-term approach and that hyperandrogenic skin symptoms in patients with PCOS are efficiently treated. Additional benefits include cycle control and, in some women, improvement in mood and perception of body image. Safety and tolerability data are summarized by the pharmacovigilance risk assessment committee (PRAC) of the European Medicine's Agency's (EMA).

Conclusions: This review provides a comprehensive overview about the efficacy of CPA 2 mg/EE 35 μg in the treatment of hyperandrogenic skin symptoms, thus allowing both health care professionals and women to balance the risks and benefits of treatment based on evidence.

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Introduction

Definition and prevalence of hyperandrogenism and hyperandrogenic skin symptoms

Hyperandrogenism (androgen excess) affects approximately 10–20% of women of reproductive age [1]. It can present as biochemical hyperandrogenism, where there is excessive production and/or secretion of androgens, which may be of ovarian or adrenal origin. It can also present as clinical hyperandrogenism, where the pilosebaceous unit has increased sensitivity to normal serum androgen levels and causes hyperandrogenic skin symptoms [1]. Women with biochemical hyperandrogenism may present solely with clinical symptoms or have accompanying anovulation and/or polycystic ovary syndrome (PCOS).

Hyperandrogenic skin symptoms include acne, hirsutism, seborrhea and alopecia. The majority of data regarding prevalence of these skin symptoms are derived from studies of women with PCOS. Hirsutism is the most sensitive marker for increased levels of androgen (hyperandrogenism), and is present in 70% of women with PCOS [2]. Acne is a less prevalent and less specific marker of elevated androgens (hyperandrogenism) and is present as a symptom in approximately 15% of women with PCOS [3]. Both hirsutism and acne can significantly and negatively impact on quality of life and cause anxiety and depression [4,5]. Female androgenic alopecia affects approximately 35% of women with PCOS and can occur either in isolation (rarely) or in association with other skin symptoms of hyperandrogenism [6]. Seborrhea can also present as a symptom of androgen excess. An accurate figure for prevalence is difficult to determine but it is frequently reported alongside other symptoms of hyperandrogenism. In some cases, women present with all four hyperandrogenic skin symptoms, described as the seborrhea, acne, hirsutism and alopecia (SAHA) syndrome by Orfanos et al. [7]. The SAHA syndrome presents in approximately 20% of women affected by hyperandrogenism and is a useful marker of hormonal disorders of androgen metabolism [8].

Principles of pharmacologic treatment

Pharmacological treatment of hyperandrogenic skin symptoms has two aims: firstly, to reduce the level of circulating androgens and, secondly, to inhibit their effect at tissue level. Unlike the combined oral contraceptives (COCs) commonly used to treat hyperandrogenic symptoms, cyproterone acetate (CPA) 2 mg, combined with ethinylestradiol (EE) 35 μg, is indicated for the treatment of moderate to severe acne related to androgen-sensitivity (with or without

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seborrhea) and/or hirsutism, in women of reproductive age [9]. CPA is a steroidal antiandrogen: it competitively inhibits the binding of both testosterone and its conversion product, 5-α-dihydrotestosterone (DHT) to the androgen receptor; it reduces testosterone and androstenedione production in the ovary; it blocks the conversion of testosterone to DHT by inhibiting the 5-α-reductase [10–16].

The potency of CPA is greater than other antiandrogenic progestogens typically present in COCs [17], resulting in achievement of greater clinical improvement [10]. EE enhances the action of CPA by increasing sex hormone-binding globulin (SHBG) levels, which leads to a reduction in free testosterone and thus adds to the antiandrogenic action of CPA. There is data available regarding the use of CPA/EE in the treatment of hyperandrogenism in women, all of which is underpinned by long-term clinical experience.

The need for an update of evidence and knowledge

Cochrane database reviews describing the efficacy of CPA/EE in hirsutism and acne highlight the heterogeneity of studies and challenges in pooling data to generate robust conclusions about the efficacy of therapeutic interventions in the management of hyperandrogenic skin symptoms [18–20]. Yet, evidence supporting the efficacy of interventions such as CPA/EE remains important. Women with skin symptoms of hyperandrogenism may also have abnormalities in androgen metabolism (biochemical hyperandrogenism) and accompanying anovulation and/or PCOS, both of which have reproductive and metabolic implications [2]. There is growing awareness of the effect of androgen excess on metabolic risk factors and a need to measure the impact of treatment on haemostasis, lipid metabolism and liver function. At the same time, concerns regarding the safety and the risks of antiandrogenic progestogens should be weighed against the benefit for patients. In the wake of these concerns about safety, it seems appropriate to look in detail at the risks and benefits of this important treatment.

This review, developed on behalf of the global appropriate care for women with androgen excess (AWARE) group, sets out to summarize the evidence supporting the efficacy and safety of CPA/EE in the treatment of hyperandrogenic skin symptoms. In addition, it summarizes the effects of CPA/EE on metabolic parameters.

Methods

A limited number of studies involving large study populations, variable time frames and lack of clearly defined assessment of both long- and short-term treatment outcomes in hyperandrogenic skin symptoms [18–20] limits the possibility of systematic review or meta-analysis [21]. As a result, a narrative review (non-systematic approach that borrows from systematic methodologies and employs a bibliographic research strategy) was undertaken by the authors [22,23].

An electronic literature search of the PubMed database was performed. Keywords included (but were not limited to): CPA 2 mg/EE 35 μg; Diane-35; Diane(tte); cyproterone; EE; acne; hirsutism; seborrhea; safety; efficacy; risks/benefits. Inclusion criteria were defined as studies comparing CPA/EE with placebo or other comparator in the treatment of acne, hirsutism, seborrhea, SAHA, hyperandrogenic skin symptoms of PCOS. The search was restricted to English-language abstracts and human studies.

Study abstracts were collated and grouped according to hyperandrogenic skin symptom (acne, hirsutism, seborrhea, SAHA, hyperandrogenic skin symptoms of PCOS). Authors reviewed the search findings and agreed further groupings as follows:

- CPA/EE vs placebo and comparator
- Large and small studies, where large is defined as ≥100 participants
- Treatment duration, where the study period is either ≤ or ≥6 months for acne; ≤ or ≥12 months for hirsutism and seborrhea

Where possible, studies involving validated assessment of improvement in dermatological endpoint were prioritized for review. For acne, outcomes described by the cochrane review were prioritized [19]: facial lesion counts (both total and specific); acne severity grades; global assessment (clinician or participant). For hirsutism, studies using Ferriman–Gallwey (F–G) or modified (m)F–G Clinical Score were prioritized [24,25]. For seborrhea, studies using the seborrhea area and severity index-face were prioritized for review. Safety evaluations included the number and type of adverse drug reactions (ADRs) reported and treatment discontinuation due to ADRs.

Results

A total of 78 studies were identified as part of the search process (see Figure 1). Twenty-five were excluded because the dose of either CPA or EE used in the study was outside of routine clinical practice in the management of hyperandrogenic skin symptoms or the abstract described a review or commentary article rather than a clinical study. A total of 52 abstracts were screened for efficacy and safety findings. Final analysis of the full publications prompted exclusion of a further nine studies due to use of high doses of CPA, either in combination with EE or as part of a higher dose sequential regimen, not disclosed in the abstract. Forty-three studies are therefore included in this narrative review.

CPA/EE in the treatment of acne

Ten studies evaluated the efficacy and safety of CPA/EE in the treatment of acne (see Appendix 1). They dated from 1985 to 2008 and included one placebo-controlled study, five comparator studies, two dosing studies and two combination studies. All of the studies had improvement in acne as a primary outcome measure and assessed changes in the number and severity of acne lesions and/or the number of inflammatory lesions (see Appendix 1). Description of formal evaluation methods was limited to Cook score [26,27] and investigator global assessment (IGA) (1 = clear, 2 = excellent improvement, 3 = good, 4 = moderate, 5 = no and 6 = deterioration) [28]. Secondary outcome measures

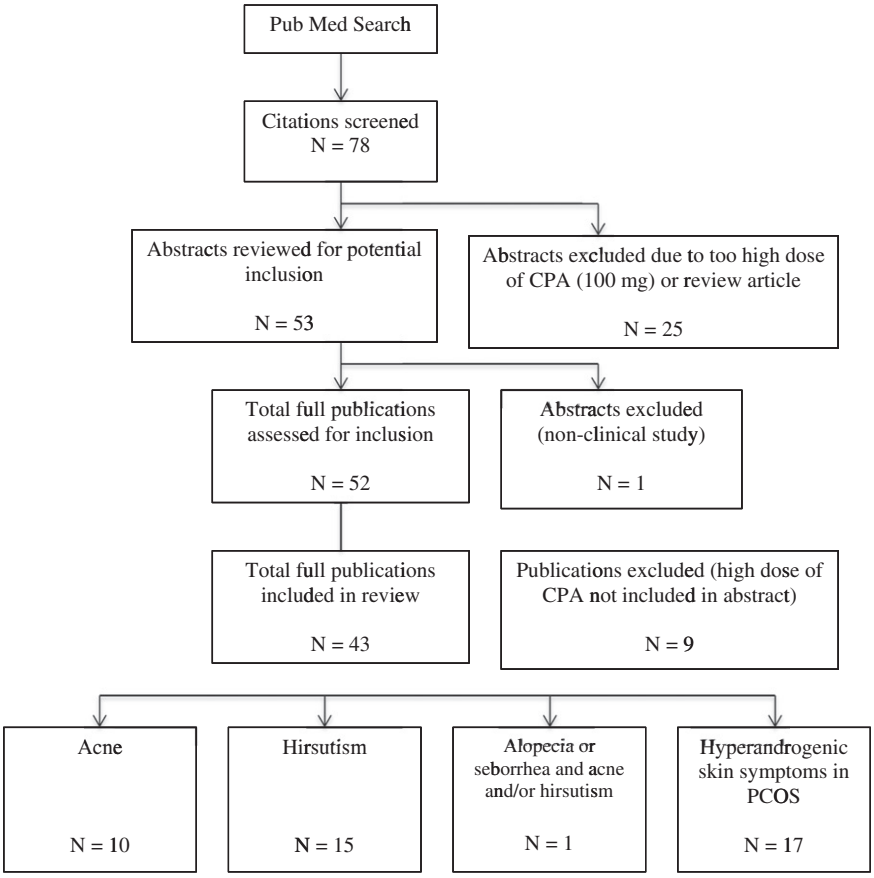

Figure 1. Literature selection process for review.

included laboratory assessment of changes in hormone and lipid levels, bacterial colonization and sebum excretion rate.

Efficacy in acne

The studies reported CPA/EE to be highly effective in improving acne as early as three months, when used alone or in combination, and in some women refractory to other types of treatment [27–30]. Percentage changes in total lesion count with CPA/EE ranged from 53.6 ± 27.5% ($n = 528$) to 72 ± 27% ($n = 44$) [28,30]. Greenwood et al. [31] reported an 80% reduction in non-inflammatory and inflammatory lesion counts with CPA/EE ($n = 14$) at six months. When looking more specifically at types of lesion (comedones, papules, pustules and nodules), statistically significant changes were noted at three months and final numbers of each lesion were reported as 24%, 36%, 17% and 1%, respectively relative to pretreatment (=100%) at six months in the CPA/EE group ($n = 88$) by Vartiainen et al. [29]. An improvement in acne in 90.2% of patients ($n = 480/532$), as assessed by IGA, was reported by Palombo-Kinne et al. [28], Dieben et al. [32] reported a reduction in acne grade 4 (nodules present) and 5 (pustules, no nodules) of 50% and 36%, respectively with CPA/EE at six months.

Improvements in acne were seen within two cycles but greatest improvements are seen at six months; two studies evaluated the efficacy of CPA/EE after 12 months and showed a continued improvement [27,33]. In the former study, treatment with CPA/EE improved specific acne lesions (comedones, papules and macules) and overall severity compared to baseline after six months ($p < .01$). Further significant improvement was achieved in the number of macules and papules after 12 months at which point, over two-thirds of the patients were either free of facial acne or exhibited just a few small, scattered lesions [27]. Efficacy of CPA/EE in acne was consistent, irrespective of whether assessed objectively (by the investigator) or subjectively (by the patient) [29,30].

CPA/EE in the treatment of hirsutism

We identified 15 studies evaluating the efficacy of CPA/EE in women with hirsutism (either idiopathic [IH] or as a skin symptom of PCOS), dating from 1982 to 2012 (see Appendix 2). They included four comparator studies, two dosing studies, nine combination studies and one reverse sequential regimen study.

All of the studies used improvement in hirsutism (the majority assessed by F–G or mF–G) as a primary outcome. Some studies also assessed changes in hair diameter and growth rate; hair distribution (facial, bust and abdomen); and frequency of shaving or hot wax treatment. Secondary outcome measures included laboratory assessment of changes in hormone and lipid levels.

Efficacy in hirsutism

In general, the studies reported CPA/EE to be highly effective in reducing hirsutism scores (either F–G or mF–G), and frequency of shaving or hot wax treatment as early as three months. Statistically significant changes are generally seen between 6 and 12 months after initiation of treatment. Greatest improvements in hirsutism scores with CPA/EE were generally seen at 12 months with mean reductions (±SD) ranging from 24.6 (±1.91)% to 54.31 (±22.1)% [34–37].

One study showed the benefit of continuing treatment with CPA/EE to 24 months, with F–G scores declining from 11.8 ± 0.6 SE to 4.7 ± 0.6, a score almost equal to control (3.6 ± 0.3) [38]. There was some evidence to show that hair in different areas of the body may respond to CPA/EE treatment differently: facial hair appears to respond more quickly [34]. Sert et al. [35] reported a 59% decrease in the need to shave or use hot wax treatment after receiving CPA/EE for 12 months. In studies where CPA/EE was combined with other treatment options, for example, flutamide, finasteride or spironolactone, reductions in hirsutism scores were generally greater with combination treatment than with CPA/EE alone. Ibanez et al. [39] looked at the efficacy of CPA/EE in the treatment of hirsutism and acne in adolescent women and reported a 23.2% reduction in hirsutism score (mF–G) and 36.3% reduction in acne score at six months.

CPA/EE in the treatment of seborrhea or alopecia and/or acne or hirsutism

One study evaluated the efficacy and safety of CPA/EE in the treatment of seborrhea (with or without accompanying symptoms of acne or hirsutism), dated 2002 (see Appendix 3). The study compared drospirenone/EE with CPA/EE. The primary outcomes included sebum production (as measured by photometry), number/diameter of hairs and acne. The study also assessed hormone and lipid profiles. The only study evaluating the efficacy and safety of CPA/EE in alopecia identified as during the search involved use of CPA/EE in combination with CPA and was therefore excluded. CPA/EE is not indicated for the treatment of androgenic alopecia.

Efficacy in seborrhea

In the study looking at the effect of CPA/EE on seborrhea and acne, Van Vloten et al. [40] reported a 39.3% reduction in median sebum production and 58.8% reduction in median acne lesion count at nine months.

CPA/EE in the treatment of hyperandrogenic skin symptoms of PCOS

Seventeen studies evaluated the efficacy and safety of CPA/EE in the treatment of hyperandrogenic symptoms of PCOS, dating from 1986 to 2014 (see Appendix 4). They included 13 comparator studies (of which five involved an insulin sensitizer as the comparator), two combination studies and one open-label study. All studies assessed the clinical and biochemical features of hyperandrogenism. Improvement in hirsutism score featured as an outcome measure in 12 studies, hirsutism and acne in three studies and hirsutism and seborrhea in one study.

Efficacy in hyperandrogenic skin symptoms of PCOS

In general, the studies described significant improvements in serum androgen levels and hyperandrogenic skin symptoms of PCOS with CPA/EE as early as six months. The significant reductions in hirsutism scores (F–G and mF–G) at six months ranged from 17.7% to 38.2% [41–43]. When treatment effect was assessed at 9 or 12 months, changes in hirsutism score ranged from 5% to 35% [44,45].

Creatsas et al. [46], Luque-Ramierz et al. [47], Lemay et al. [48], Falsetti et al. [49] described consistent reduction in hirsutism scores (F–G and mF–G) in all areas of the body. Kahraman et al. [46] describe more prominent changes in specific body areas, for example, the abdomen. In an open-label study, Golland and Elstein [50] reported a healing/improvement rate of 54.6% (reduction in mean F–G score from 14.3 to 5.7) at 12 months with CPA/EE in 22 women with severe facial hirsutism. Seven women experienced complete resolution of symptoms and a further six women experienced significant symptom improvement with CPA/EE after 12 months. Two studies described the return of hyperandrogenic skin symptoms following cessation of treatment with CPA/EE treatment by six months [33,51].

When looking at other parameters, CPA/EE showed significant reduction in hair diameter in all areas evaluated (chin, abdomen, mid-thigh, forearm and combined arms) at 12 months [45]. Greatest changes were seen in the abdomen (25%) and mid-thigh (20%) and objective results correlated with patients' own qualitative assessment of improvement in hirsutism at 12 months [45]. Golland and Elstein [51] also reported correlation between objective and patient assessment.

Cyproterone acetate/ethinylestradiol was shown to improve coexisting acne and seborrhea in women with PCOS. In the study by Erkkola et al. [52], CPA/EE normalised seborrhea in 59.2% of patients within nine months and also led to an improvement of facial acne in 80.7% and complete healing of acne in 59.7% of women. Golland and Elstein [51] also described improvements in coexisting acne and seborrhea with CPA/EE.

Four of the studies compared the effects of CPA/EE on the hyperandrogenic skin symptoms of PCOS with COCs [10,46,47,53]. Kahraman et al. [45] compared CPA/EE with drosperinone (DRSP)/EE and reported a significant difference in reduction in hirsutism score between the two, changes in mF–G score of −35% (−71 to 10) and −18% (−18 to 30) in women treated with CPA/EE and DRSP/EE, respectively.

Mastorakos et al. [54] and Creatsas et al. [46] compared the effects of CPA/EE with desogestrel (DSG)/EE and described similar and significant declines in F–G score for both formulations (compared to baseline) at six months and a continued, but not significant decline until 12 months. Bhattarcharya and Jha [10] compared the effects of CPA/EE on hirsutism score with both DSG/EE and DRSP/EE over 12 months. There was a significant decrease in mF–G score with CPA/EE (−5.29) when compared with DSG (−1.69) and DRSP (−2.12) [10].

CPA/EE as combination treatment

Studies involving CPA/EE combined with other agents showed mixed results. For example, when combined with antibiotics (tetracycline) in the treatment of acne, or with antiandrogens (finasteride or spironolactone) in the treatment of hirsutism, the potential for enhanced efficacy was suggested [31,36,37,55]. Studies where CPA/EE was added to gonadotropin releasing hormone agonist (GnRHa) to evaluate potential for amplification of treatment response

in hyperandrogenic symptoms of PCOS described significant improvement in hirsutism symptoms overall (reductions in hirsutism score were between 24% and 47.4%) but no significant difference between the two groups [50,52,56]. Sequential use of CPA/EE with rosiglitazone did not generate any greater symptom improvement than use of CPA/EE alone in women with PCOS [49].

Additional benefits of CPA/EE

Cyproterone acetate/ethinylestradiol offers additional benefits when used in the treatment of hyperandrogenic skin symptoms: improvements in menstrual cycle regularity, potential quality of life and psychological benefit and effective contraception in those women wishing to avoid pregnancy. CPA/EE induced regular withdrawal bleeds and reduced ovary size during treatment in women with hyperandrogenic skin symptoms associated with PCOS [47,54,62]. There was a trend towards improvements in quality of life with CPA/EE in adolescents [57]. CPA/EE demonstrated improvement in subjective perception of psychiatric status in women with hyperandrogenic skin symptoms associated with PCOS [57].

Safety of CPA/EE

Concerns have been raised recently about the safety of CPA/EE, particularly the risk of thromboembolic events. A review conducted by the European Medicine's Agency's (EMA) pharmacovigilance risk assessment committee (PRAC) concluded that the benefits of CPA/EE outweighed the risks when used to treat moderate to severe acne related to androgen excess and/or hirsutism in women of reproductive age provided that several measures were undertaken to minimize the risk of thromboembolism [58]. The PRAC review confirmed the rare and known risk of thromboembolism with CPA/EE and highlighted the importance of discussing with patients the increase in risk associated with age, smoking, obesity and prolonged immobility [59]. The studies included within this review show CPA/EE to be generally well tolerated with a side effect profile similar to that seen with EE-containing COCs. Reported side effects include headaches, nausea, weight gain, breast tenderness, loss of libido and, rarely, hepatotoxicity effects, with low rates of discontinuation. Breast tension persisted through six months of treatment in one study [59]. No thromboembolic events are reported in any of the 46 reviewed studies involving treatment for up to 24 months.

Metabolic effects of CPA/EE

The metabolic effects of CPA/EE and their implications are not discussed in detail. Observations were mainly limited to lipid metabolism when CPA/EE use was evaluated in the treatment of hyperandrogenic skin symptoms. The conflicting findings regarding metabolic effects of CPA/EE in the treatment of skin symptoms in women with PCOS are discussed in Ruan et al. [60].

Lipid metabolism

In the studies involving CPA/EE in the treatment of acne, generally, any changes in liver function or lipid levels were reported to be within normal limits [60]. Some changes in lipid metabolism (elevated triglycerides and changes in high-density lipoprotein (HDL) cholesterol/low-density lipoprotein (LDL) cholesterol were seen but these remained within normal limits and declined in clinical relevance beyond six months [60].

Weight and other vital signs

When studied in the treatment of acne, no effect was seen on BMI or vital signs with CPA/EE [28]. There were no significant changes in clinical markers of obesity and blood pressure reported with 12-month treatment of acne in women with PCOS [10,61]. BMI and waist to height ratio (WHR) remained stable with CPA/EE throughout six months treatment [62]. However, CPA/EE was shown to increase arterial stiffness as a predictor of CV risk [62].

Discussion

Findings and interpretation

Critical analysis of efficacy and safety findings in the studies included in the review confirms the role of CPA/EE in the treatment of hyperandrogenic skin symptoms. Although some improvement in both hirsutism and acne is seen within six months, maximum effect is generally achieved over a longer period. However, the return of hyperandrogenic skin symptoms within six months of cessation of treatment indicates the need for long-term therapy. In general, improvement is described as a quantifiable reduction of symptom scores (either objective or subjective). It does not indicate 'healing of the disease' but amelioration of symptoms with a positive effect on quality of life.

Published clinical trials show that CPA/EE is generally well tolerated with a side effect profile similar to that seen with COCs. No thromboembolic events were reported in any of the 46 studies included in this review, some of which involved treatment for up to 24 months. However, the number of patients included does not allow the authors to make a general statement on cardiovascular safety.

Cyproterone acetate/ethinylestradiol offers some additional benefits when used in the treatment of hyperandrogenic skin symptoms: improvements in menstrual cycle regularity, potential quality of life and psychological benefit and effective contraception in those women wishing to avoid pregnancy.

Strength and weaknesses of the review and comparison with previous reviews

Data describing the efficacy of CPA/EE in hirsutism and acne has been included in three cochrane database reviews [18–20]. Conclusions from these reviews highlight the heterogeneity of studies and challenges in pooling data to generate robust conclusions about the efficacy of therapeutic interventions in the management of hyperandrogenic skin symptoms as clinical entity.

Based on the cochrane reviews, we have performed a narrative review focusing on clinically relevant studies and using transparent selection criteria. The conclusions and themes drawn here are limited to the studies included in the review and are influenced by a number of factors.

Efficacy benefits	Risks of treatment	Additional benefits
Effective treatment of hyperandrogenic skin symptoms: Acne (6 months) – improvements in all types of lesion, lesion count, and acne severity. Hirsutism (6 and 12 months) – significant reductions in hirsutism score (F-G and mF-G) and the need to use cosmetic treatments Seborrhea (9 months) – significant reduction in sebum production Symptoms and androgen levels in PCOS (6 months) – significant reduction in hirsutism score (F-G and mF-G) in all body areas	Treatment is well tolerated with a side effect profile similar to that seen with combined oral contraceptives (COCs) Increased triglyceride levels (but within normal limits) Caution is advised in women who are obese and/or have type II diabetes (or a family history of the disease)	Potential for additional benefits e.g. contraception, menstrual cycle regulation; potential improvement in quality of life /psychological effects generated by skin symptoms Can be used in combination e.g. with GnHR agonists, spironolactone, finasteride or oral antibiotics

Figure 2. Use of CPA/EE in the treatment of hyperandrogenic skin symptoms.

These include small patient populations, lack of validated tools to assess changes in skin symptoms (with the exception of hirsutism), inconsistencies in the reporting of results leading to difficulties when comparing study outcomes and summarising overall effects, and the limited long-term safety assessment due to the short-term duration of studies. We believe, however, that the overarching results are clinically meaningful, especially given that these conditions are chronic in nature and, although symptoms can be improved, they rarely disappear completely. Compared to what has been shown in the Cochrane reviews, the present narrative review, which included newer studies, confirms and strengthens the evidence supporting the efficacy of the combination of CPA 2 mg and EE 35 μcg, not only in acne but also in hirsutism and it underlines the importance of long term treatment of these chronic skin diseases.

Unanswered questions and future research

The findings of this review highlight a number of areas where further study would be useful. Clinical studies confirmed an effect of CPA/EE on lipid metabolism but generally regarded changes to be within normal limits and of little clinical relevance. Effects of CPA/EE on insulin resistance remain inconsistent and prompt the need for more research into metabolic changes in women affected by hyperandrogenism. There is potential for the efficacy of CPA/EE in the treatment of hyperandrogenic skin symptoms to be enhanced by using it in combination with other treatments but further research is needed.

The specific role of CPA/EE in the management of hyperandrogenic symptoms in women with PCOS is discussed in an accompanying review by Mueck et al. [61].

Implications for clinical practice

Hyperandrogenic skin symptoms such as acne and hirsutism are associated with considerable impairment of quality of life and adverse psychological impact [4,5]. Pharmacological treatment of these symptoms aims to reduce the level of circulating androgens and inhibit their effect at tissue level. CPA/EE has been available as a treatment option for hyperandrogenic skin symptoms for approximately three decades. It is indicated for the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhea) and/or hirsutism, in women of reproductive age and has been described as the treatment of choice for hyperandrogenism [62,63].

Critical analysis of the role of CPA/EE in the treatment of hyperandrogenic skin symptoms identified five key themes relevant to best practice (see Figure 2):

- A high efficacy in the treatment of moderate to severe acne;
- A high efficacy in the treatment of hirsutism;
- Treatment is well tolerated with a side effect profile similar to that seen with COCs;
- A definite effect on lipid metabolism but within normal limits and of little clinical relevance; however, caution is advised when considering women who are obese and/or have type II diabetes;
- Potential for the efficacy of CPA/EE in the treatment of hyperandrogenic skin symptoms to be enhanced by using it in combination;
- Potential for additional benefits when used in the treatment of hyperandrogenic skin symptoms.

Given the characteristics of the combination treatment of CPA/EE and the fact that hyperandrogenic skin disorders such as acne and hirsutism are chronic diseases, the implications for clinical practice are:

- Treatment success depends on long term adherence of the patients;
- Repetitive treatment episodes may be necessary;
- Chronic treatment needs a continuous re-evaluation of the benefit/risk ratio, especially in patients in whom additional risk factors for cardiovascular complications may occur over time, such as obesity or smoking;
- Age itself is an independent risk factor and should always be considered.

Conclusions

Clinical trials included in this review show a high efficacy of CPA/EE in the treatment of hyperandrogenic skin symptoms, irrespective of whether they occur independently of or secondary to PCOS. Resolution is gradual and governed by symptom severity and duration of treatment. The review also shows that CPA/EE is generally well tolerated with a side effect profile similar to that seen with COCs.

This review does not set out to compare the effects of CPA/EE across the different studies or effect comparisons with other hormonal treatments; it focuses on summarizing the main effects of treatment in order to inform clinical practice to provide evidence-based information to assist in balancing the benefits and risks of this treatment. It also highlights areas to consider when individualizing treatment and where further study would add to that knowledge. These include the safety of long-term use of CPA/EE and the associated metabolic implications, given the complex interaction between hyperandrogenism and insulin sensitivity, particularly in PCOS.

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Johannes Bitzer has worked as an Advisor for and received honoraria by Bayer Health Care, Merck, Teva, Exeltis, Lilly, Boehringer-Ingelheim, Vifor, Gedeon Richter. He has also given invited lectures and received honoraria by Bayer AG, Merck, Johnson and Johnson, Teva, Mylan, Allergan, Abbott, Lilly, Pfizer, Gedeon Richter.

Thomas Römer has received honorarium and travel cost for lectures and advisory boards from Bayer AG, MSD and Gedeon Richter.

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Appendix 1. Summary of studies of CPA/EE in acne.

Author (date)	*n*	Outcome measures (inc. assessment tools used where available)
Large, placebo-controlled studies (n≥ 100)		
Palombo-Kinne et al. [28]	1326	Change (%) from baseline in inflammatory and total lesion count at cycle 6 in women receiving EE/DNG ($n = 525$); EE/CPA ($n = 537$); or placebo ($n = 264$). Proportion (%) of patients with acne improvement according to the Investigator Global Assessment
Large (n ≥ 100) comparator studies (t ≥ 3 months)		
Vartiainen et al. [29]	172	Clinical assessment of improvement in the number of comedones, papules, pustules and nodules at six months in women receiving either combiphasic EE/DSG (25 μg DSG and 40 μg EE for 7 days followed by 125 μg DSG and 30 μg EE for 15 days) or EE35/CPA (2 mg CPA and 35 μg EE for 21 days)
Carlborg [30]	133	Clinical assessment of change in number of acne lesions at six months in women receiving CPA 2 mg/EE 50 μg (Diane); CPA 2 mg/EE 35 μg (Diane mite); or LNG 50 μg/EE 30 μg (Neovletta)
Dieben et al. [32]	183	Clinical and photographic evaluation of change in number of acne lesions and severity at end of cycle 4 in women receiving CTR-24 and Diane-35. Laboratory assessment of changes in testosterone, 3 alpha-17 beta-androstanediol glucuronide and SHBG at baseline and end of cycle 4
Small (n ≤ 100) comparator studies (t ≥ 3 months)		
Charoenvisal et al. [64]	34	Change in mean objective acne score at six months in women receiving low-dose oral contraceptive containing DSG (Marvelon) or an antiandrogenic preparation containing CPA (Diane)
Miller et al. [65]	90	Clinical and photographic assessment of change in acne severity (visual analogue scale) and lesion count bimonthly at six months in women receiving with Diane; high-dose CPA regimen with EE; or Minovlar. Bacteriological sampling and sebum excretion rate (SER) measurements were also carried out
Small (n ≤ 100) dosing studies (t ≥ 3 months)		
Fugere et al. [59]	40	Improvement in acne lesions (Cook score) at 3, 6 9 and 12 months in women receiving 2 mg CPA in combination with either 35 μg or 50 μg EE2 (Diane-35 versus Diane-50). Changes in lipid levels were also assessed
Colver et al. [66]	96	Assessment of improvement in acne (visual analogue scale) at nine months in women receiving CPA 2 mg in combination with either 35 μg or 50 μg EE
Small (n ≤ 100) combination studies (t ≥ 3 months)		
Carmina and Lobo [33]	48	Change in Cook scores at 12 months in women receiving CPA 2 mg with 35 μg EE; CPA 50 mg with 25 μg EE (reverse sequential regimen); flutamide 250 mg daily; or finasteride 5 mg daily
Greenwood et al. [31]	62	Clinical assessment of improvement in acne lesions (severity and number) at six months in women receiving tetracycline alone; oestrogen-CPA; or a combination of these agents. Sebum excretion rates and bacterial counts were also assessed at six months

CPA: cyproterone acetate; EE: ethinylestradiol; SHBG: sex hormone-binding globulin; DHEAS: dihydroepiandrosterone sulphate; HDL: high density lipoprotein; LDL: low density lipoprotein.

Appendix 2. Summary of studies of CPA/EE in hirsutism.

Author (date)	*n*	Outcome measures (inc. assessment tools used where available)
Comparator studies (t ≥ 6 months)		
Porcile and Gallardo [38]	26	Change in hirsutism score, plasma testosterone, and lipids at 24 months in women with IH and/or PCOS receiving DSG 150 μg/30 μg EE; DSG 150 μg/50 μg EE; or CPA 2 mg/35 μg EE
Batukan et al. [67]	91	Change in hirsutism score (mF–G) and serum total testosterone, free testosterone, androstenedione, dehydroepiandrosterone sulfate and SHBG levels at 6 and 12 months in women receiving either 3 mg DRSP/30 μg EE or 2 mg CPA/35 μg EE
Carmina and Lobo [33]	60	Decrease in hirsutism score (Ferriman–Gallwey–Lorenzo [FGL] index), anagen hair shaft diameters, serum LH and testosterone in hirsute hyperandrogenic women receiving CPA 2 mg/35 μg EE for 21 days each month (Diane group); CPA 50 mg (days 5–15) and EE 50 μg (days 5–25 each month) (CPA group); or decapeptyl 3.75 mg im every 28 days plus conjugated oestrogen 0.625 mg (days 1–21) and MPA 10 mg (days 12–21) (GnRHa group) at 3, 6, 9 and 12 months
Ibanez et al. [39]	34	Changes in hirsutism and acne scores; androgen excess; fasting insulin, lipid profile, C-reactive protein, high molecular-weight adiponectin, leptin, follistatin; carotid intima-media thickness; body composition (absorptiometry); and abdominal fat partitioning (magnetic resonance imaging) at six months in adolescent women receiving EE–CPA or a low-dose combination of pioglitazone, flutamide and metformin (PioFluMet)
Small dosing (n ≤ 100) studies (t ≥ 6 months)		
Belisle and Love [34]	158	Change in mean hirsutism total index and distribution (facial, bust or abdomen) of hair in women with severe hirsutism receiving either low dose CPA (Diane, 2 mg) or a high dose (Androcur, 100 mg)
Small (n ≤ 100) studies (t ≥ 6 months)		
Barth et al. [68]	21	Decrease in hair growth, as measured by F–G scores, direct measurement of hair shaft diameter and linear growth of hair on the face, forearm, abdomen and thigh at 12 months in women receiving Dianette (35 μg EE/2 mg CPA); Dianette plus 20 mg CPA; or Dianette plus 100 mg CPA administered on days 1–10 of the birth control pill cycle (as described by Hammerstein)

(*continued*)

Continued

Author (date)	*n*	Outcome measures (inc. assessment tools used where available)
Small ($n \leq 100$) combination studies ($t \geq 6$ months)		
Sert et al. [35]	79	Change in serum FSH, LH, testosterone and DHEAS levels; decrease in hirsutism score (F–G), and frequency of shaving/hot wax treatment at 6 and 12 months in women receiving Diane 35 plus CPA; Diane 35 plus spironolactone (100 mg); or spironolactone (100 mg) alone
Keleştimur et al. [37]	50	Change in hirsutism score (mF–G) and hormone levels (total and free T, androstenedione, DHEAS, SHBG and prolactin (PRL) at six-month intervals in women receiving either Diane 35 alone or Diane 35 plus spironolactone
Sahin et al. [36]	40	Change in hirsutism score (F–G) and total and free testosterone (T), androstenedione, DHEAS, and SHBG at 6 and 12 months in women receiving either Diane-35 alone or Diane-35 plus finasteride
Inal et al. [65]	80	Change in hirsutism score (mF–G) and hormonal profile at nine months in women receiving flutamide (250 mg/d for the first 10 days of the cycle) or spironolactone (100 mg/d) plus Diane 35
Taner et al. [69]	84	Change in hirsutism score (F–G) and serum hormones at 1, 3 and 6 months in women receiving either 250 mg flutamide per day or 250 mg flutamide plus 35 μg EE and 2 mg CPA per day
Tartagni et al. [55]	50	Change in hirsutism score (mF–G) and serum hormone levels (LH, FSH, free testosterone, DHT, DHEAS, androstenedione and SHBG at 3 and 6 months in women with either IH or hirsutism in PCOS receiving either Diane 35 or Diane 35 plus finasteride at six months
Vegetti et al. [70]	41	Decrease in mean diameter of hair from three different areas and one control area and subjective evaluation of improvement by physician and patient in women with severe hirsutism receiving GnRH analogue (goserelin) plus an OC containing EE and CPA and the same OC alone
Karakurt et al. [71]	29	Change in hirsutism score (mF–G), hormonal and lipid profiles at six months in women receiving either 250 mg/day flutamide alone or 100 mg/day spironolactone plus a combination tablet of 2 mg CPA/35 μg EE
Falsetti et al. [49]	25	Changes in androgen plasma levels, hair diameter and hirsutism score in women with moderate-severe PCOS-dependent hirsutism receiving either GnRH-A (group A) or combined pill and GnRH (group B) for six months

IH: idiopathic hirsutism; PCOS: polycystic ovary syndrome; CPA: cyproterone acetate; EE: ethinylestradiol; F–G: Ferriman–Gallwey; mF–G: modified Ferriman–Gallwey; SHBG: sex hormone-binding globulin; DHT: dihydrotestosterone; DHEAS: dihydroepiandrosterone sulphate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; GnRH: gonadotrophin releasing hormone.

Appendix 3. Summary of studies of CPA/EE in alopecia and seborrhea.

Author (date)	*n*	Outcome measures (inc. assessment tools used where available)
Large ($n \geq 100$) comparator studies ($t \geq 6$ months)		
Van Vloten et al. [40]	128	Changes in median total acne lesion count, sebum production, and hair growth on the upper lip, chin, and chest, levels of SHBG, androgens and LH over nine treatment cycles in women with mild-to-moderate facial acne, with or without seborrhea and/or hirsutism receiving 30 EE/3 mg DRSP or 35 μg EE/2 mg CPA

CPA: cyproterone acetate; EE: ethinylestradiol; DRSP: drosperinone; SHBG: sex hormone-binding globulin; LH: luteinising hormone.

Appendix 4. Summary of studies of CPA/EE in hyperandrogenic skin symptoms of PCOS.

Author (date)	*n*	Outcome measures (inc. assessment tools used where available)
Large ($n \geq 100$) comparator studies ($t \geq 6$ months)		
Bhattacharya and Jha [10]	171	Change in the free androgen index score and clinical, hormonal and biochemical parameters at 6 and 12 months in women receiving pills containing DSG (Novelon; 30/0.15 mg); CPA (Krimson 35; 35/2 mg); or DRSP (Yasmin; 30/3 mg)
Gokmen et al. [43]	141	Changes in hirsutism score (F–G) and lipid and hormonal levels in women receiving low-dose combined oral contraceptive, CPA 100 mg daily for the first 10 days of a 21-day cycle with an oral contraceptive containing 2 mg CPA; spironolactone (100–200 mg daily); or ketoconazole (400 mg daily)
Meyer et al. [61]	100	Decrease in hirsutism score (F–G) at 12 months in women receiving metformin (starting dose 500 g bd titrated upwards to 1 g bd over 4 weeks); high-dose OCP (35 μg EE/2 mg CPA); or low-dose OCP (20 μg EE/100 μg LNG) combined with an antiandrogen (spironolactone 50 mg bd). Hirsutism was not a primary outcome measure. Insulin resistance and surrogate markers of cardiovascular disease including arterial stiffness (pulse wave velocity [PWV]) and endothelial function were assessed as primary endpoints
Small ($n < 100$) studies ($t \geq 6$ months)		
Kahraman et al. [45]	52	Change in clinical features: mF–G; BMI, WHR and biochemical parameters (androgen profile, carbohydrate metabolism, lipid profile and oxidative stress) at 12 months in women with PCOS receiving 35 μg EE/2 mg CPS; or 30 μg EE/3 mg DRSP-containing OCs
Chung et al. [57]	76	Change in clinical and biochemical features of hyperandrogenism and quality of life in women receiving oral MPA for four months, followed by a washout period of four months and then Diane-35 for another four months (group 1) at 12 months. Group 2 received the same combination but in the reverse order
Harborne et al. [44]	52	Change in hirsutism assessed by patient self-assessment and F–G score in women receiving either metformin (500 mg, three times daily) or Dianette (EE, 35 μg; CPA, 2 mg) treatment for 12 months
Mastorakos et al. [54]	36	Change in hirsutism score, lipid, androgen, and sex hormone-binding globulin (SHBG) levels in women receiving 0.15 mg of DSG/30 μg of EE daily; or 2 mg of CPA/35 μg of EE daily for 21 days followed by a 7-day rest for a period at 12 months. An OGTT and metabolism indices, based on previously studied mathematical formulas, were also assessed
Creatsas et al. [46]	24	Change in hirsutism score (F–G) and blood levels of SHBG, total cholesterol (TC), LDL cholesterol, HDL cholesterol, TGs, apolipoproteins A–I, A–II, B, and lipoprotein (a) (Lp(a)) measurements at 3, 6, 9 and 12 months in women receiving either 2 mg CPA/35 μg EE or 0.150 mg DSG/30 μg EE for 12 months

(*continued*)

Continued

Author (date)	*n*	Outcome measures (inc. assessment tools used where available)
Luque-Ramírez et al. [47]	34	Assessment of hyperandrogenism, lipid profiles, and indexes of glucose tolerance and insulin sensitivity at 12 and 24 weeks in women receiving oral treatment with metformin (850 mg twice daily) or with the Diane(35) Diario pill (35 μg EE/2 mg CPA)
Erkkola et al. [52]	83	Change in severity of hyperandrogenic symptoms at nine months in women with acne, seborrhea and hirsutism receiving 2 mg CPA/35 μg EE (Diane 35) and 0.150 mg DSG/30 μg EE (Marvelon)
Morin-Papunen et al. [41]	32	Change in hirsutism score (F–G) at six months in women receiving metformin (500 mg bd for three months, then 1000 mg bd for three months); or EE (35 μg)/CPA (2 mg) oral contraceptive pills (Diane Nova). WHR, serum testosterone, fasting free fatty acid, and insulin concentrations and improved oxidative glucose utilization and menstrual cyclicity were also assessed
Dahlgren et al. [42]	32	Change in hirsutism score (F–G), insulin sensitivity (estimated by glucose clamp technique), blood lipids and hormones at six months in women receiving either EE/CPA cyclically for six months or GnRH analogue (goserelin)
Lemay et al. [48]	28	Decrease in hirsutism score (F–G), plasma lipids and OGTT at six months in women receiving either rosiglitazone 4 mg/day or EE 35 μg/CPA 2 mg (21/28 days cycle) followed by both medications for another six months
Couzinet et al. [72]	10	Changes in severity of acne and seborrhea in women receiving 50 mg/day CPA (orally) and 3 mg DTrp6-LHRH (im), approximately once a month) for three months followed by cross-over treatment after a six-month break
Combination ($t \geq 6$ months) studies		
Acién et al. [56]	12	Change in symptoms (hirsutism [F–G score], weight) and hormonal and biochemical analyses at three and six months in women receiving either GnRH-a plus an OC pill containing EE CPA or EE–CPA alone
De Leo et al. [51]	35	Change in hirsutism score (F–G) in women receiving GnRH agonist; GnRH agonist plus COC; or GnRH agonist plus flutamide for six months. Ovarian and adrenal androgens, gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH), estradiol and oestrone plasma levels were also assessed at six months
Falsetti et al. [49]	25	Changes in androgen plasma levels, hair diameter and hirsutism score in women with moderate-severe PCOS-dependent hirsutism receiving either GnRH-A or combined pill and GnRH-A for six months
Open-label study		
Golland and Elstein [50]	32	Changes in hirsutism score (F–G), hormone serum concentrations, ovarian volume, stromal density, and follicle number and size at 3, 6, 9 and 12 months in women receiving Diane-35

CPA: cyproterone acetate; EE: ethinylestradiol; F–G: Ferriman–Gallwey; mF–G: modified Ferriman–Gallwey; SHBG: sex hormone-binding globulin; DHEAS: dihydroepiandrosterone sulphate; HDL: high-density lipoprotein; LDL: low-density lipoprotein.