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Original research article

Prescribing of cyproterone acetate/ethinylestradiol in UK general practice: a retrospective descriptive study using The Health Improvement Network☆,☆☆

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Abstract

Objective: To investigate prescribing patterns of cyproterone acetate/ethinylestradiol (CPA/EE) in the United Kingdom before and after the 2013 prescribing guidance.

Study design: We conducted a retrospective descriptive study in UK general practice. The study population included women with a first prescription (index date) for CPA/EE in The Health Improvement Network in 2011 (*N*=2760), 2012 (*N*=2923) and 2014 (*N*=2341).

We evaluated the proportion of new CPA/EE users with (i) a diagnosis of a hyperandrogenic condition, menstrual problem, consultation for contraception management, and other acne treatment, in the year before the index date; and (ii) proportion of new CPA/EE users with concomitant use of another hormonal contraceptive (HC).

Results: The percentage of CPA/EE new users with a record of a hyperandrogenic condition was 61% in 2011, 62% in 2012 and 63% in 2014. Corresponding percentages for acne were 51%, 54% and 55%, respectively. When manually reviewing patient records for a sample of CPA/EE new users (*n*=200), the acne was recorded in 77% of women, hirsutism in 9.5% and polycystic ovary syndrome in 9.5%. Majority of CPA/EE users had a prior acne diagnosis and/or treatment, 76% (*n*=2091) in 2011, 79% (*n*=2296) in 2012 and 78% (*n*=1834) in 2014. Concomitant use of CPA/EE and another HC was rare, 1% of CPA/EE users in 2011 and fewer than 0.5% of CPA/EE users in both 2012 and 2014.

Conclusions: Before and after 2013, the majority of UK women starting treatment with CPA/EE had a condition in line with its approved indication and had received prior acne treatment as per guidance.

Keywords: Cyproterone acetate/ethinylestradiol; Acne; Prescribing; Off-label; Database; Contraception

1. Introduction

In the United Kingdom, cyproterone acetate/ethinylestradiol (CPA/EE; 2 mg/0.035 mg) is indicated for the treatment of moderate to severe acne when topical therapy or systemic antibiotic treatment has failed and for hirsutism in women of reproductive age. Owing to its mode of action, CPA/EE also acts as a contraceptive in women taking it for these conditions, although it is not indicated solely for contraceptive purposes. Other androgen-dependent conditions such as androgenic alopecia, as well as androgen sensitivity-related symptoms of polycystic ovary syndrome (PCOS) — a condition closely related to acne and hirsutism — are also considered potentially treatable with CPA/EE.

In 2013, prescribing advice from the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) restated that CPA/EE should only be used for the treatment of acne after topical therapies and antibiotic treatment have failed, and stated that it should not be used concomitantly with another hormonal contraceptive (HC) in order to minimize

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the chance of a potential increased risk of thromboembolism with exposure to a high estrogen dose. This guidance reiterated the wording on the updated label for CPA/EE at this time as requested by the European Medicines Agency, which had been made in response to a review by the French Medicines Agency that suggested extensive off-label use of CPA/EE as a contraceptive only.

As part of a collaborative European postauthorization safety program (EU PAS register number ENCEPP/SDPP/8412), we carried out a retrospective study, using a validated primary care database in the United Kingdom, which aimed to describe prescribing patterns of CPA/EE in the United Kingdom before and after the 2013 guidance. The objectives of the study were to determine (i) relevant diagnoses recent to first use of CPA/EE and recent prescribing of other acne treatment, and (i) whether CPA/EE is used concomitantly with other HCs, among new users of CPA/EE separately in 2011, 2012 and 2014. The study protocol was reviewed and approved by an independent scientific review committee for The Health Improvement Network (THIN) (reference number 14-080), which ensured that data were to be analyzed and interpreted appropriately. Data collection for THIN was approved by the South East Multicenter Research Ethics Committee in 2003 and individual studies using THIN data do not require separate ethical approval if only anonymized THIN data are used [1].

2. Methods

2.1. Data source

We used data from THIN — a primary care database in the United Kingdom containing administrative, clinical and prescribing information recorded prospectively by general practitioners (GPs) as part of routine patient care. Clinical data are entered using Read codes [2], and a free-text section enables recording of further details. The database is representative of the UK population with regard to age, sex and geographic distribution, and has been validated for use in epidemiological research [3,4]. THIN has also been widely used for drug utilization studies, including those evaluating contraception [5–8].

2.2. Identification of study population

The study population included all women with a first prescription (index date) for CPA/EE in THIN during "one of three calendar years (study years): 2011, 2012 and 2014" (Fig. 1). Women were required to have been registered with their GP for at least 1 year before the index date and to have no prescription for CPA/EE for at least 1 year before the index date or the start of the study year, whichever came first. Cohorts in each study year were mutually exclusive. Users were followed up from the index date until the end of follow-up or censoring (e.g., transfer out of the practice), whichever came first. The end of follow-up was 31st December in each study year, that is, for example December 31, 2011 for new users in 2011. The maximum potential duration of follow-up was therefore 1 year.

2.3. Relevant diagnoses recent to first CPA/EE use

To ascertain relevant diagnoses recent to first use of CPA/EE, we undertook automated computer searches for diagnoses of hyperandrogenic conditions, menstrual problems and GP visits for contraception, either at the index date or in the previous year. Recent acne treatment was ascertained by records of prescriptions for other acne treatment in the year before the index date but excluding the index date. Hyperandrogenic conditions included acne, hirsutism, PCOS, alopecia and seborrhea. For menstrual problems (e.g., oligomenorrhea, amenorrhea) and GP visits for contraception, we only included those that were recorded in the absence of a hyperandrogenic condition. Women could have more than one recent diagnosis prior to starting CPA/EE therapy. Acne treatments were classed as topical agents, systemic preparations and hormonal agents and were assessed separately for users with and without a recent acne diagnosis.

2.3.1. Sensitivity analysis

Among new users of CPA/EE in 2011 and 2012, we randomly selected 100 women in both calendar years and manually reviewed the patients' records including free-text comments to identify recent relevant diagnoses.

2.4. Treatment episodes and switching/concomitant use of CPA/EE with other HCs

For each CPA/EE new user, all CPA/EE prescriptions from the index date until the end of follow-up were concatenated into treatment episodes of uninterrupted use; that is, a prescription for the "same" contraceptive issued before the end of the supply of the previous prescription would be assumed to start the day following the end of the initial prescription and so forth. When there was a gap between the issuing of a prescription and the issuing of the next prescription for the "same" contraceptive, we considered this the start of a new treatment episode (**Supplementary Methods**). This was also undertaken for each other separate HC. We identified CPA/EE and other HC treatment episodes that overlapped and defined concomitant use as when both the start and end date of an HC (non-CPA/EE) treatment episode occurred within the start and end date of a CPA/EE episode or vice versa, or when a switch from CPA/EE to another HC or vice versa preceded the last prescription within a treatment episode. *Switchers* were defined as when a switch from CPA/EE to another HC or vice versa occurred during the last prescription within a treatment episode. We defined *noncon-comitant use* as when both the start and end date of an HC episode (other than CPA/EE) occurred outside a CPA/EE episode. Lastly, when there were no treatment episodes of other HCs within 365 days before the index date and up to the