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Review

Oral estradiol and dydrogesterone combination therapy in postmenopausal women: Review of efficacy and safety

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ABSTRACT

HRT is known to be effective for the relief of menopausal symptoms and prevention of osteoporosis. HRT should be tailored to the woman, enhancing the beneficial effects of the treatment while minimizing the risks. It is difficult to evaluate data on particular preparations of HRT and the different dosages in isolation. The purpose of this review is to highlight the efficacy and safety specific to oral estradiol and dydrogesterone combinations of four different dose strengths. A systematic literature search using Medline was carried out to identify studies containing efficacy or safety data. The findings of the retrieved publications confirm that estradiol and dydrogesterone combinations give very effective menopausal symptom relief and prevention of osteoporosis whilst maintaining a good safety profile. Data also show that these combinations of HRT give additional benefit to certain metabolic parameters including lipids, insulin, glucose and body fat distribution. By selecting the treatment and dose most suitable for each individual woman at her particular stage of menopause, the benefits can be optimized whilst mitigating the risks. HRT plays an important role in improving and maintaining women's health when used appropriately.

Contents

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1. Introduction

Hormone replacement therapy (HRT) is the use of exogenous hormones to relieve menopause symptoms [1] and improve the quality of life (QoL) of women [2,3]. As women live longer than previously, preservation of bone mass becomes increasingly important. HRT is currently used for osteoporosis prevention in postmenopausal women.

Multiple HRT combinations are available. However, many studies report on HRT as a group. The constituent drugs and their combination in HRT are important in determining their safety and efficacy. In addition, HRT has metabolic effects which in some patients may be beneficial in maintaining and possibly improving women's health. It is recognized that different progestogens [4,5] and estrogens have distinct properties.

The purpose of this review is to examine the efficacy and the safety literature on the unique profile of oral estradiol and dydrogesterone combinations (E/D).

Four dose strengths of the E/D combination are available. Two are sequential combined preparations (E/D 2/10 mg and E/D 1/10 mg) and two are continuous combined preparations (E/D 1/5 mg and E/D 0.5/2.5 mg).

2. Methods

A systematic search was carried out using the Medline database on the 12 November 2012. The search terms were (estradiol or oestradiol) and (dydrogesterone or dydrogesteron or retroprogesterone). Filters used in the search were: human, 1988–2012, English, French, and German.

The studies from the literature search are summarized in Section 3. Publications were excluded from this review if they were: a review, case report, comment, meta-analysis, in vitro or animal study; did not study E/D in combination; did not study efficacy, safety or metabolic parameters; did not use treatment as HRT; did not study oral treatment; or used previously published data. Three additional publications which met the search criteria, and with which the authors were familiar, were also included. The studies are contextualized in Section 4.

3. Results

The selection of publications is detailed in Fig. 1. With the three added publications, 45 publications were included in this review. The publications were divided as 12 efficacy, 16 metabolic parameters and 17 safety.

3.1. Summary of patient characteristics and outcome measures

3.1.1. Patient characteristics

Subjects in all studies of the included publications were described as healthy and post- or peri-menopausal. Women with a history of neoplasia, premalignant disease, abnormal vaginal bleeding, an abnormal endometrial ultrasound scan, or significant medical, psychiatric or neurological illnesses were excluded. The women tended to be non-hysterectomized and had undergone natural menopause. Women taking concomitant medication to relieve the symptoms of estrogen deficiency, liver-enzyme-inducing drugs, anticoagulants, bisphosphonates, fluoride, recent steroids or high-dose vitamin D were excluded. Women with previous use of hormone treatment were included in some studies after a wash-out period. The subjects in the randomized trials tended to be aged between 40 and 75 years. The five observational studies also included women in the age group ≥75 years.

3.1.2. Assessment of efficacy

Efficacy of HRT was mainly assessed by subjective measures for patients' symptom relief (vasomotor, vaginal atrophy, loss of libido, fatigue, incontinence) and objective measures for osteoporosis and metabolic parameters. Treatment of menopausal symptoms was mostly measured by rating scales and patient diaries completed before and during treatment. The scales used were different between studies. Changes from baseline within the study or efficacy compared to control were measured. To assess the efficacy of osteoporosis prevention and treatment, bone mineral density (BMD) was measured by dual energy X-ray absorptiometry (DXA) of the lumbar spine and of the femoral neck, Ward's triangle and trochanteric regions of the hip. One study measured serum and urine bone turnover markers. Various metabolic parameters were assessed and body composition and fat distribution were measured using DXA scanning.

3.1.3. Assessment of safety

Endometrial safety was measured by biopsies to assess endometrial proliferation at different treatment doses. Bleeding patterns were recorded in patient diaries. Cardiovascular and breast cancer incidence were assessed retrospectively by observational and nested case-control studies on database and registry data.

3.2. Efficacy

Twelve of the 45 publications presented efficacy data for the licensed indications of E/D (Table 1). The majority of studies were randomized controlled trials of at least 12 weeks' duration.

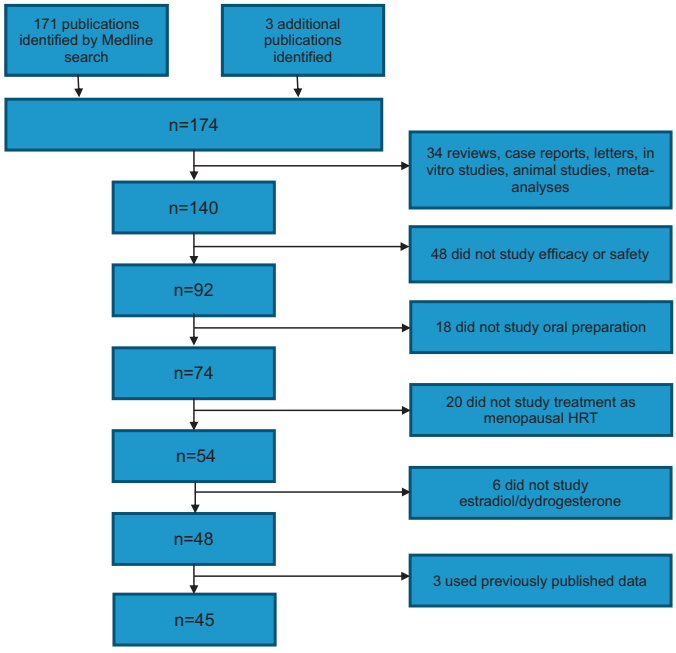

Fig. 1. Flowchart showing study selection.