

## Dienogest-The Millennium Molecule!!

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### Mini Review

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### Introduction

Dienogest (DNG) is a fourth generation progestin, being extensively used in a wide variety of clinical settings in gynecology. In order to write this comprehensive review, a literature search was performed to identify systematic reviews and randomised trials involving DNG. Databases searched included MEDLINE, PUBMED, Embase and the Cochrane library. The term 'dienogest' was associated with the following search terms: 'endometriosis', 'contraception', 'hormone replacement therapy', 'safety', 'efficacy'

### Pharmacology

Dienogest (DNG) is a 19-nortestosterone derivative (a C-19 progestogen) with a cyanomethyl instead of an ethinyl group at the C-17 position. Properties derived from its C-19 derivative structure include its short plasma half life, of about 10h (which means the drug is not accumulated), and its high oral bioavailability, of more than 90%. DNG also has some properties typical of other progesterone derivatives, including a lack of effect on the metabolic and cardiovascular systems, and considerable antiandrogenic activity [1,2]. DNG has no antiestrogenic activity, which is explained in its role in the treatment of endometriosis [3]. It is exclusively protein bound (albumin-90%, free-10%). The lack of DNG binding to sex hormone binding globulin means it does not displace testosterone, resulting in the androgenic effects observed with other progestins. It is metabolized by hydroxylation and conjugation, predominantly in the liver [4]. DNG is available in the dose of 2mg/day (Figure 1, Table 1).

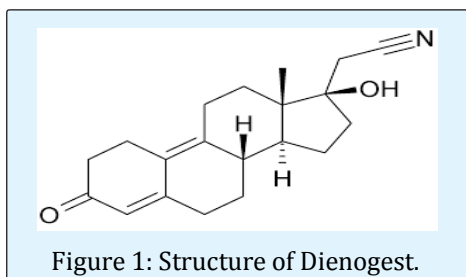


Figure 1: Structure of Dienogest.

Typical of other progesterone derivatives	Attributed to its C19 Derivative Structure
Lack of CVS and metabolic effects	Short plasma half life
Anti-androgenic activity	High endometrial efficacy High oral bioavailability

Table 1: Properties of Dienogest.

### Adverse Effects

In a safety cohort of 727 women [5], the most frequently reported adverse effect with DNG was headache (9%), acne (5.1%), nausea (4.2%), and weight gain (3.6%). Changes in menstrual bleeding patterns were also common in these trials. After 9-12 months of use, bleeding was regularized in 22%, but 28% reported amenorrhoea, oligomenorrhoea in 24% and polymenorrhoea in 2.7%.

Clinical settings in which dienogest is currently used

- Endometriosis
- In contraception
- Hormone replacement therapy (HRT)

### Dienogest in Endometriosis

Mechanism of action: DNG reduces endometriotic lesions through a number of biological mechanisms. It is associated with relatively moderate inhibition of gonadotrophin secretion, leading to a modest reduction in the endogenous production of estradiol [5]. When given continuously, dienogest induces a hypoestrogenic, hypergestagenic local endocrine environment, causing a decidualization of endometrial tissue followed by atrophy of the endometriotic lesions [6]. In exploratory models of

endometriosis, dienogest also demonstrates antiproliferative, anti-inflammatory, and anti-angiogenic effects [7,8].

### Dienogest versus GnRh Agonists

**Pain relief:** A large RCT(N=252) was carried out, in which 124 women were randomised to receive DNG and 128 women received leuprolide acetate( LA) [9]. The VAS (Visual analog scale) score was selected as the primary efficacy variable in this study because the VAS is an appropriate and well established tool for the measurement of pelvic pain associated with endometriosis [10]. Absolute reductions in VAS score from baseline to week 24 were 47.5 mm with DNG and 46.0 mm with LA. This finding was of high clinical relevance, as pelvic pain is one of the most important symptoms of endometriosis and because agents in the GnRh agonist class are widely considered a reference standard treatment for improving these symptoms [11].

**Hypoestrogenic effects:** It is a known fact that GnRH agonists produce hypogonadotropic hypogonadism. An interesting hypothesis was proposed by Barbieri [12], way back in 1992. It stated that, 'a concentration of estradiol that will partially prevent bone loss may not stimulate endometrial growth'. DNG maintains estrogen levels within the therapeutic window for endometriosis that is 30-50 pg/ml. Hence, the incidence of hypoestrogenic effects is less with DNG when compared to LA [9].

**Bone mineral density (BMD) reduction:** GnRH agonists cause significant loss in trabecular and cortical bone, particularly lumbar spine and femoral neck. This may even exceed 1% per month [13]. On the other hand, DNG showed no change in the mean lumbar BMD during the treatment period [9], demonstrating minimal changes in bone turnover/bone resorption markers.

### Dienogest versus Other Progestins (Norethindrone Acetate)

Dienogest as the first-choice progestin for the medical therapy of symptomatic endometriosis does not confer additional benefits compared with norethindrone acetate in terms of pain relief, health-related quality of life, or sexual functioning [14]. Effectiveness of either of the progestins is greatly affected by economic aspects.

### Fertility Considerations with DNG Use

Based on the current evidence, dienogest causes complete inhibition of ovulation at a daily dose of 2 mg

[15,16]. However, dienogest monotherapy was not developed as a contraceptive, and women taking dienogest as a treatment for endometriosis are advised to use non-hormonal methods of contraception [17]. The ovarian activity resumes rapidly (range 1-43 days) after cessation of dienogest [15]. Successful pregnancy has been reported in women with endometriosis following the cessation of dienogest treatment 2 mg daily for duration of up to 1 year [18,19].

### Long Term Safety Profile of DNG in Endometriosis:

Two large trials have been performed in Europe and Japan, to investigate the role of DNG in the long term treatment of endometriosis. The European trial offered DNG for an overall treatment period of 65 weeks [19]. The intensity of pain showed significant, sustained improvement during this long term study. In addition, during the 24 week treatment free period following the long term study, visual analog scores increased only moderately, suggesting that DNG induces a beneficial effect that may persist even after treatment cessation.

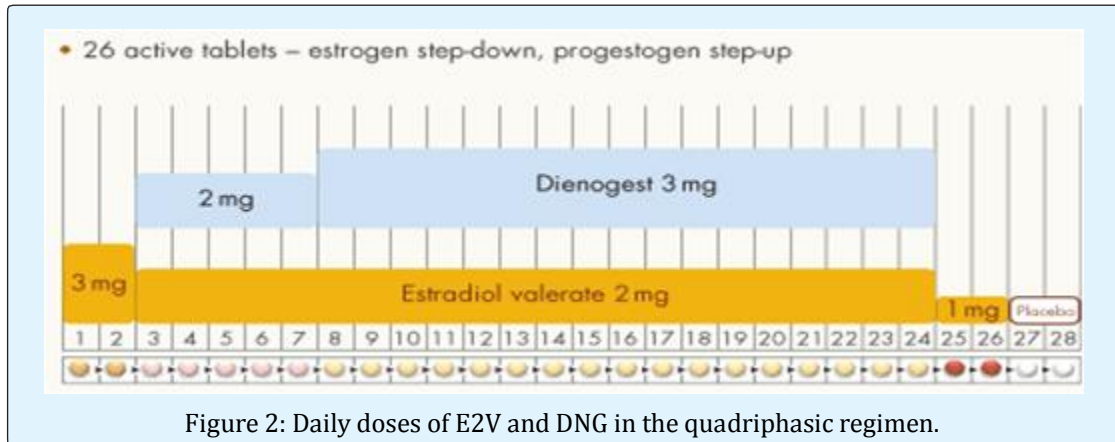
The results of the European study were supported by a 52 week, non-randomized trial of DNG conducted in Japan on 135 women with confirmed endometriosis [20]. Patient satisfaction with DNG at the end of treatment was high, with 88.9% of women responding that they were "certainly willing" or "would prefer" to use DNG again.

### Dienogest as a Contraceptive

Estradiol valerate/dienogest (E2V/DNG) is a 4-phasic oral contraceptive approved for the prevention of pregnancy. The 4-phasic design allows for acceptable cycle control and in efficacy trials of estradiol valerate/dienogest in women aged 18-35 years, the Pearl Index ranged from 0.40 to 1.64, a range comparable to that of other combination oral contraceptives [21].

In most combination oral contraceptives, the estrogen component is responsible for providing cycle control and stabilizing the endometrium for an acceptable bleeding pattern. E2V, unlike ethinyl estradiol, did not provide an adequate level of endometrial stability, as evidenced by breakthrough bleeding rates in preliminary studies [22]. Hence, E2V containing combination oral contraceptives did not reach the market until this novel combination of E2V and DNG was evaluated.

This combination integrates an estrogen step-down and a progestin step-up approach in a quadri-phasic regimen (Figure 2).



The American College of Obstetrics and Gynecology recommends that patients with anovulatory or ovulatory bleeding be treated with a combination oral contraceptive if they require contraception [23,24]. E2V/DNG is an appropriate first choice in heavy menstrual bleeding, for most premenopausal women who have a need for contraception, do not have contraindications to estrogen therapy, and do not desire LNG-IUD insertion. Use of E2V/DNG for six months has led to significant reduction in heavy menstrual bleeding with an average 65% reduction in mean blood loss [23].

### Dienogest in HRT

A combination of 2 mg estradiol valerate with 2 mg dienogest (E2V/DNG) is the first continuous combined postmenopausal hormone replacement therapy (HRT) preparation to contain a progestogen with substantial anti-androgenic activity. A study of its clinical efficacy and safety in a comparative study versus a combination of 2 mg estradiol with 1 mg norethisterone acetate (E2/NETA) has shown both preparations to be highly effective in achieving a rapid response in women with postmenopausal symptoms [25]. E2V/DNG is a novel HRT preparation that has a highly favorable bleeding profile.

### Conclusion

Dienogest is a novel drug in the treatment of endometriosis, with an efficacy comparable to GnRh agonists. It is orally administered (unlike GnRh agonists) and more reasonably priced. Its role in contraception and HRT seems promising.

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