Dienogest: An effective and safe pharmacotherapy for the long-term management of endometriosis

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Dienogest is an oral progestin with selective 19-nortestosterone and progesterone activity that has been shown to be highly effective in the management of endometriosis.[1] The Visanne Post-approval Observational Study (VIPOS) provided real-world evidence on the absence of serious adverse events with long-term use of dienogest for up to 7 years.[2]

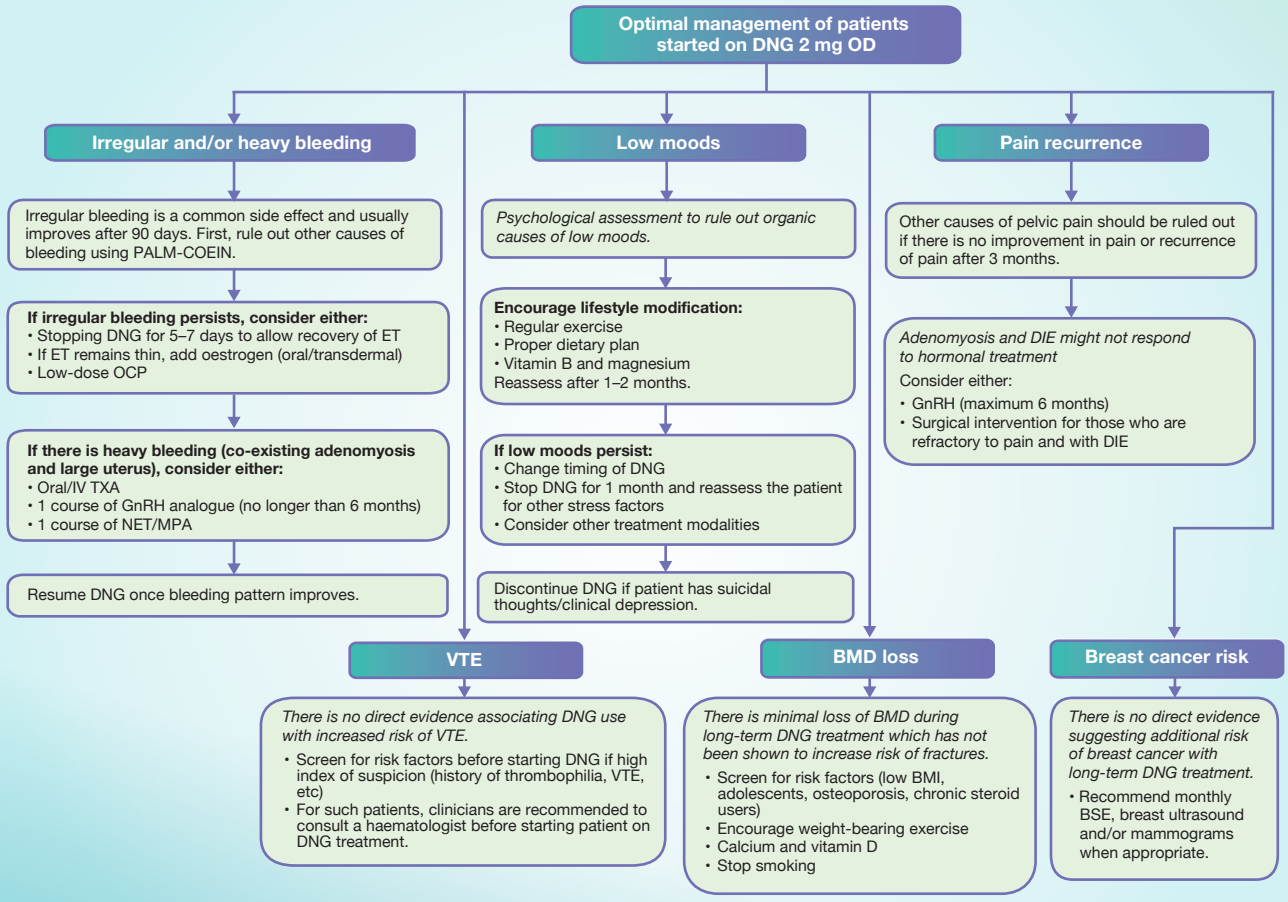
While dienogest is effective and well-tolerated in a majority of women, some may experience issues in the initial phase of treatment. These issues may prevent women from improving their quality of life with long-term dienogest treatment. Proper consultation thus plays a vital role in the successful treatment of endometriosis with dienogest.

We present a treatment algorithm (**Figure**) that summarises our recommendations on how to manage the possible issues during treatment with dienogest. Should any of these issues arise, temporary interruption or modifications in the treatment plan may improve treatment efficacy and patient satisfaction.

Irregular and/or heavy bleeding

Abnormal bleeding should be assessed for other diagnosis using the PALM-COEIN classification. When these conditions have been excluded, dienogest can be stopped for 5–7 days.[3]

Figure. Consensus-based recommendation for the use and possible sequelae of dienogest in the long-term management of patients with endometriosis



Disclaimer: The treatment algorithm summarises recommendations on how to manage the possible issues during long-term treatment of endometriosis with dienogest 2 mg daily based on the consensus of an advisory panel of gynaecologists specialising in endometriosis from Malaysia and Singapore. Treatment (duration and dosage) should be individualised based on patients' need. Counselling is paramount to effective treatment and adherence.

BMD, bone mineral density; **BMI**, body mass index; **BSE**, breast self-examination; **DIE**, deep-infiltrating endometriosis; **DNG**, dienogest; **EAPP**, endometriosis-associated pelvic pain; **EE**, ethinyloestradiol; **ET**, endometrium; **GnRH**, gonadotropin-releasing hormone; **HRT**, hormone replacement therapy; **IV**, intravenous; **MPA**, medroxyprogesterone acetate; **NET**, norethisterone; **OCP**, oral contraceptive pill; **OD**, once daily; **PALM-COEIN**, ***p***olyp; ***a***denomyosis; ***l***eiomyoma; ***m***alignancy and hyperplasia; ***c***oagulopathy; ***o***vulatory dysfunction; ***e***ndometrial; ***i***atrogenic; and ***n***ot yet classified; **SE**, side effects; **TXA**, tranexamic acid; **VTE**, venous thromboembolism

Dienogest can cause abnormal bleeding at the start. Such abnormal bleeding tends to get less with increasing duration of treatment. It can take up to 90 days to resolve.[3,4]

When abnormal bleeding is associated with an endometrial thickness of <4 mm, ethinyloestradiol can be added either orally or via a transferal patch.[5] If heavy bleeding persists, tranexemic acid, norethisterone, medroxyprogesterone and/or GnRH can be added to reduce and stop the bleeding.[6–8] Resume dienogest once bleeding pattern improves.

Low moods

Progestogens have been associated with low or depressive moods. Only a small group of women experience depressive moods with dienogest.[3,7,9,10] Psychological assessment to rule out any organic causes of low moods is recommended. Symptoms of low moods generally appear within the first 6 months of treatment and are usually mild, without requiring any intervention.[7] Moderate symptoms of depressive moods can be resolved by discontinuing dienogest treatment.[10]

To alleviate depressive moods, clinicians should encourage patients to take vitamin B or magnesium supplements and exercise regularly, in addition to involving the patients' partner or family in the management of mood disorders.[11,12] Clinicians should also practise empathy when communicating with patients and provide moral support as needed.

Pain recurrence

If pain recurs whilst on dienogest, a full investigation should be carried out to rule out other causes of pain. GnRH agonist treatment may be administered to help the pain but for no longer than 6 months.[14] Surgery should be considered in cases of abnormal ultrasound findings (e.g. deep-infiltrating endometriosis, concomitant adenomyosis).[13] For long-term management of endometriosis, the resumption of dienogest can be considered after pain symptoms have subsided.

VTE

There is no direct evidence associating dienogest use with increased risk of VTE.[15] Prior to treatment, screening for risk factors such as thrombophilia, low body mass index (BMI), hypertension, previous history of VTE and smoking status should be carried out.[16] In the presence of risk factors, patient counseling on the risk and benefits of dienogest therapy should be carried out and patients should be reviewed regularly while on dienogest. Ideally, clinicians should consult a haematologist before starting a patient with VTE risk factors on dienogest treatment.

BMD loss

Minimal loss of BMD during long-term dienogest treatment does not lead to an increased risk of bone fracture, and changes in BMD should not be a factor deterring the initiation of dienogest for endometriosis treatment.[13] Clinicians should encourage patients to take calcium and vitamin D supplements, perform weight-bearing exercises, as well as cut down on smoking and alcohol consumption to mitigate the risk of BMD loss.[17]

Breast cancer risk

Hormonal treatment-related risk of breast cancer is mainly attributed to oestrogen-progestogen preparations,[18] with limited evidence implicating progestogen-only preparations as a breast cancer causative agent. There is currently no direct evidence indicating increased breast cancer risk in patients receiving dienogest treatment.[19] Clinicans should encourage routine breast screening by conducting monthly BSE, breast ultrasound examination and/or mammograms when appropriate.

Patients requesting for drug holiday

Women on long-term dienogest treatment or those with recurrent side effects can consider a drug holiday of up to 3 months. However, there is a risk of recurrent endometriosis symptoms. Dienogest should then be restarted to treat these symptoms, and can be continued until pregnancy is desired.[20]

Endometriosis should be viewed as a chronic disease that requires life-long management. This consensus was developed as a best practices guide in managing endometriosis, with a focus on addressing common factors that hinder patient adherence to long-term dienogest treatment.

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