



## EDITORIAL

# Best practice for HRT: unpicking the evidence

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Menopause is a normal life event for women and so it is not an illness or a medical condition. As our life expectancy has increased hugely this now means that on average, women spend nearly one-third of their lives being postmenopausal. This has resulted in more women being adversely affected by symptoms of their menopause often to the detriment of their families, work, and life in general. Many women suffer in silence and do not realise how effective hormone replacement therapy (HRT) can be at dramatically improving both their symptoms and also their quality of life.

Around 80% of women going through their menopause experience symptoms but only a small proportion of menopausal women take HRT; in some parts of the UK only around 10% of menopausal women take HRT.<sup>1</sup>

Symptoms of the menopause last far longer than most women anticipate, the average length of time is 4 years and many women still have symptoms after 10 years.

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## NICE GUIDELINES

The National Institute for Health and Care Excellence (NICE) guidelines on menopause were published in November 2015 and should be encouraging for clinicians.<sup>2</sup> These are the first clinical guidelines on menopause and provide clear recommendations on the diagnosis and treatment of women with menopausal symptoms.

The negative publicity which followed the flawed Women's Health Initiative (WHI) study over a decade ago led to many women and also numerous doctors being concerned and anxious about the potential risks of HRT. This has resulted in many women needlessly suffering from menopause symptoms and also increasing their risk of osteoporosis and cardiovascular disease by not taking HRT.

The WHI study was undertaken to look at the risks and benefits of older women taking HRT. The women in this study were, on average, 63 years old, so their results cannot be used to determine the risks with HRT for women who are <60 years. They were using a type of HRT that we do not prescribe now, many of the women in this study were overweight or obese (so had other risk factors for cardiovascular disease and cancer), and there was a 75% drop out rate in this study. However, the media hype around this study over a decade ago failed to inform women of this.

Interestingly, two of the authors of the WHI study have recently published an apology for this misinterpretation of the study in the *New England Journal of Medicine*.<sup>3</sup> They have admitted that this misunderstanding has been the cause for many women not taking HRT and thereby not benefiting from it.

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## **BENEFITS OF HRT**

Numerous studies have been published since the WHI study which have confirmed many benefits of taking HRT. Symptoms of the menopause such as hot flushes, mood swings, night sweats, and reduced libido all improve.

Age and years since menopause are now known to be important variables affecting the benefit–risk profile of HRT.<sup>4</sup> It is also associated with less progression of subclinical atherosclerosis compared to placebo.<sup>5</sup>

Even sub-analysis of the WHI study has shown that there is no increased risk of cardiovascular disease in women starting HRT within 10 years of the menopause.

There is a substantial increase in quality-adjusted life-years, even over a 30-year period, in women who initiate HRT in close proximity to menopause, which supports HRT as a highly cost-effective strategy for improving quality-adjusted life.<sup>6</sup> Indeed, there are very few potential therapies with such consistent data for reducing coronary heart disease and overall mortality as postmenopausal HRT.

It is not just the timing of HRT that is important. The type of HRT also affects a woman's risks and benefits. Some observational studies have shown that HRT containing micronised progesterone or dydrogesterone may be associated with a lower risk of breast cancer, cardiovascular disease, and thromboembolic events compared with androgenic progestogens.<sup>7</sup> Women who have had a hysterectomy and only require oestrogen have a lower risk of breast cancer compared to women taking combined HRT.

In addition, the mode of delivery of oestrogen is also important because, in contrast with oral oestrogen, low-dose transdermal oestrogen appears to be linked to a lower risk of cholecystitis, stroke, and deep venous thromboembolism.<sup>8</sup> This is because the factors of coagulation are not activated and neither is the renin angiotensin aldosterone cascade.

HRT benefits and risks vary by dosage, regimen, and timing of initiation. It is therefore very important to be

mindful that broad sweeping conclusions concerning HRT are not possible. It is essential that healthcare professionals, women, and also the media realise that the different HRT products available do not have a single class effect.

NICE, very sensibly, states that we should have an individualised approach at all stages of diagnosis, investigation, and management of the menopause. This is clearly reiterated in the recently published International Menopause Society Recommendations on women's midlife health and menopause hormone therapy.<sup>9</sup> Ideally women should receive appropriate information, which will enable them to make informed choices regarding treatment they receive.

Clearly HRT is only one part of the management of perimenopausal and menopausal women. Lifestyle recommendations regarding diet, exercise, smoking cessation, and safe levels of alcohol consumption should be encouraged.

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## **OTHER SYMPTOMS OF THE MENOPAUSE**

Symptoms of depression and low mood can be very common and often respond well to HRT. There is no clear evidence that antidepressants improve the low mood in menopausal women.

A large proportion of women present during or after their menopause with symptoms of urogenital atrophy; the commonest symptoms are those of recurrent urinary tract infections with negative midstream specimens of urine. These symptoms are often very effectively managed by topical vaginal oestrogen. Vaginal oestrogen should be offered to these women (including those on systemic HRT) and then continued for as long as needed to relieve symptoms. This means that vaginal oestrogen can safely be given to women on their repeat prescription, which is still not happening routinely in many practices. The only real contraindication to these preparations is active breast cancer. After all, a year's supply of topical oestrogen is equivalent to having one tablet of HRT.

When women are asked about reasons not to take HRT, the most common answer is their concern about the increased risk of breast cancer.

A recent observational study has shown that there is an increased risk of breast cancer (or preinvasive ductal carcinoma in situ) for women using combined HRT after >5 years of treatment and also that this risk increases with prolonged treatment.<sup>10</sup> As shown with other studies, there was no increased risk of breast cancer seen for users of oestrogen-only therapy.

However, this study has not differentiated between the various combined HRT products nor between different progestogens used. This is a shame as there is considerable evidence to suggest that certain synthetic progestogens, such as medroxyprogesterone acetate, may increase breast cancer risk when used in combined HRT when compared to using micronised progesterone.

A very important learning point is that taking HRT does not affect the risk of dying from breast cancer. Women need to be made aware that this increased risk is less than being overweight or having a glass or two of wine each night. Telling them this often really helps to put it into perspective.

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## PREMATURE OVARIAN INSUFFICIENCY

Finally, the NICE guidance is really clear regarding the need for women who have premature ovarian insufficiency to receive HRT at least until the average age of the menopause. Any risks of HRT are not applicable to these young women: risks are only relevant to those women >51 years of age.

Without receiving oestrogen this not only means their lives have often been miserable but these women have a far greater risk of osteoporosis, cardiovascular disease, depression, and cognitive problems.<sup>11</sup> We all should have a lower threshold for asking women when their last period was and then acting appropriately.

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## SUMMARY

These NICE guidelines should enable clinicians to feel more confident about offering HRT to eligible women. They should also be able to help women to make a more informed choice regarding their treatment, which can now be based on a more balanced review of the evidence. HRT is generally a safe, effective treatment of the menopause and as such should be considered for many more women than it has been in the recent past.

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## Notes

### Provenance

Commissioned; externally peer reviewed.

### Competing interests

Louise R Newson runs a weekly private menopause clinic at Spire Parkway Hospital in Solihull. She has received money from Meda to develop non-promotional patient information leaflets on the menopause for distribution to GPs across the country for their patients. She has received money from Mylan to attend the 15th World Congress on Menopause in Prague in September.

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