



6th IMS Workshop

Menopause and Ageing, Quality of Life and Sexuality

Proceedings

Ultra Low Dose HRT – the evidence.

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Pisa, Italy, 1-4 December 2006



Introduction

We live in an era when the population is ageing; at the time of writing more than 30% of women are aged 50 years of age or over. Maintenance of peri and postmenopausal health is therefore of paramount importance if we are to minimise the economic impact on society in this and future millenia. The recent adverse media on hormone replacement therapy (HRT), still the most effective treatment available for the alleviation of menopausal symptoms, could therefore not have come at a worse time. The controversy surrounding the pros and cons of HRT has left menopausal women, health professionals and society in general, confused as to how best to deal with both the short and long term sequelae of the menopause. The immediate symptoms, often debilitating and the long term sequelae such as osteoporosis, still need to be dealt with, and will take on ever increasing importance because of our ageing society.

Until five years ago, Hormone Replacement Therapy (HRT) was used by over a third of post menopausal women for symptoms and prophylaxis against the long term sequelae of the menopause. However, as a result of adverse publicity on the possible risks of HRT (breast and cardiovascular) arising from publication of the Women's Health Initiative and Million Women studies in 2002/3, there was a significant downturn in HRT usage which dropped by up to 50% in some countries.¹⁻⁴ The last couple of years has seen stabilisation of usage following recent favourable data on cardiovascular and breast cancer risks and life expectancy.⁵ Encouraged by clinicians and the menopause societies, about a third of women who came off their HRT have now asked to restart because of a return of their symptoms.⁶ Although the regulatory authorities e.g. Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK and the European Agency for the Evaluation of Medicinal Products (EMA) still advocate the use of HRT they stipulate that it should be at the minimum effective dose.⁷

Trend towards lower dose HRT preparations Maintaining benefits – immediate

Although the advice from regulatory authorities to the use the lowest effective dosage came relatively recently, the trend towards low dose HRT actually began in the late 1990s with the introduction of the first low-dose continuous combined preparation of 1 mg 17 β -estradiol plus 0.5mg norethisterone acetate (NETA). Data from the Woman's Health Initiative study demonstrated risks in older age group women (average age 63y) using a relative over-dosage of hormones. This accelerated the interest in lower dose formulations than the relatively high dose HRT regimen of 0.625 mg conjugated equine estrogens (CEE) combined with 2.5 mg medroxyprogesterone acetate (MPA) used in WHI. The Kronos Early Estrogen Prevention study (KEEPS), currently under way, is looking at surrogate markers of cardiovascular risk in younger women using a lower dosage of 0.45mg CEE or 50mcg estradiol together with micronised progesterone.

Data now suggest that the benefits of HRT can be maintained with lower doses than previously used. Trials have already documented the efficacy of not only 1 mg 17 β -estradiol but also 0.3mg and 0.45 mg CEE.⁸⁻¹³ These lower doses have been shown to be therapeutic not only for vasomotor symptoms, but they also produce urogenital and mood benefits and improve overall quality of life.^{14,15} A 12-week dose ranging study by Notelovitz et al¹⁶ evaluated the efficacy of unopposed 17 β -estradiol on moderate to severe vasomotor symptoms. The doses of unopposed estradiol studied were 0.25 mg, 0.5mg, 1.0mg to 2.0 mg. By Week 4, the 1 mg and 2 mg 17 β -estradiol groups showed a statistically significant effect compared to placebo while the 0.5 mg dose achieved statistical significance at Week 8. The lowest investigated dose of 0.25 mg 17 β -estradiol was not statistically different from placebo. At this stage, there was speculation whether the addition of progestogen would have had an additive effect on the benefits of the lower dose regimens.

In view of the Notelovitz data¹⁶, it was decided to carry out a randomised placebo controlled prospective multicentre study (CHOICE)¹⁷ using the 0.5mg dose of estradiol with added progestogen. CHOICE revealed similar positive results with ultra low dose cHRT combinations of 0.5 mg 17 β -estradiol + 0.1 mg NETA or 0.5 mg 17 β -estradiol +0.25 mg NETA in the reduc-



tion of moderate to severe hot flushes and number of responders, but with a more rapid effect. In CHOICE statistical significance compared to placebo was reached by Week 3 for all primary endpoints (figure 1). Other investigated parameters also showed rapid significant reduction in the active treatment groups compared to placebo including the hot flush weekly weighted score.

The Greene Climacteric Scale scores, particularly “difficulty in sleeping,” also achieved rapid statistically significant improvement (figure 2). There were also significant improvements in vaginal maturation values and vaginal pH even in this relatively young population who did not necessarily complain of urogenital symptoms at trial entry. Once again, improvements in these outcome measures with these ultra low dose combinations were comparable to the benefits previously achieved with higher dose preparations.

The difference in reaching statistical significance of the ultra low dose treatment in the CHOICE trial (by week 3) compared to the Notalovitz study¹⁶ (by week 8) can be explained by a larger sample size, but also can be attributed to the addition of NETA. Work presented by Notalovitz et al at the 1998 North American Menopause Society (NAMS) meeting in Toronto showed that the addition of low dose NETA (0.5 mg) to low dose 1 mg 17 β -estradiol enhanced vasomotor symptom relief, compared to 1 mg of 17 β -estradiol alone or placebo. The positive additive effect of NETA on vasomotor symptom relief was seen as early as Week 4 and has also been noted in previous studies.¹⁸⁻¹⁹

Maintaining benefits – long term

Low dose and ultra low dose regimens have been shown to prevent osteoporosis.²⁰⁻²¹ In a recently published two year study of low and ultra dose combinations of oral estradiol alone or with norethisterone doses as low as 0.25mg estradiol produced significant increases in bone mineral density (BMD).²¹ The study showed that the addition of norethisterone had an additive effect on BMD and that there was a dose response effect of estradiol on BMD (figure 3). Reduction of bone turnover has also been demonstrated with ultra low dose transdermal estradiol (14mcg patches).²² The 14mcg transdermal

estradiol negated the need for progestogenic opposition with only one case of hyperplasia reported in endometrial biopsies taken after two years of estrogen therapy. However, both the 0.25mg oral estradiol and 14mcg transdermal estradiol doses appear to be ineffective in controlling vasomotor symptoms.

Maintaining benefits – bleeding

It is likely that there are intrinsic differences in what effect different progestogens have on endometrial transformation and bleeding.²³ Data also show that lower-dose ccHRT regimens produce higher amenorrhoea rates compared to higher-dose ccHRT²⁴. Table 1a shows the varying amenorrhoea rates with standard, low and ultra low dose estradiol/NETA continuous combined (cc) HRT and tibolone. Table 1b shows the cumulative amenorrhoea for low dose combinations or CEE/MPA and ultra low dose estradiol/NETA. The data from the CHOICE study indicate that treatment with the ultra low dose ccHRT resulted in extremely favourable amenorrhoea rates of 89% from the very outset of the treatment (figure 4). These amenorrhoea rates are higher than those achieved with commonly used standard or low dose ccHRT. This favourable bleeding profile of the ultra low dose ccHRT resulted in a drop out rate of only 1% for both ultra low dose combinations due to bleeding. The same drop out rate due to bleeding was observed in the placebo group. There was no significant difference with placebo either in bleeding rates or endometrial thickness by transvaginal ultrasound measurement. At a time that there is concern about the role of progestogen in breast cancer genesis, it behoves us to use the minimum effective dose for endometrial transformation and maintenance of amenorrhoea.

Minimising Side Effects

Moderate doses of estrogen can produce breast discomfort and bleeding problems at initiation of therapy which can affect continuation of therapy. Higher doses of estrogen also require higher doses of progestogenic opposition which can also lead to side effects due to competition with the mineralocorticoid and androgen receptors and due to central nervous system



effects. Lower doses can minimise these side effects; for example estrogenic side effects such as nausea, bleeding, bloating, breast pain, headache and progestogenic side effects such as migraine, bleeding problems and PMS-like side effects e.g. mood disturbance, bloating, acne, greasy skin.²⁵⁻²⁸ Data from the CHOICE trial showed no statistical difference in adverse effects between active treatment and placebo and a metabolically neutral effect on parameters such as cholesterol and blood glucose. Body weight, a particular concern for women which influences continuation of therapy, was also unaffected by both ultra low dose combinations. This reduction of side effects and maintenance of benefits encourages uptake and continuation of therapy.²⁹⁻³²

Mammographic density

Standard dose HRT preparations appear to increase mammographic density more than their low dose counterparts. A standard dose continuous combined preparation (Premique CEE 0.625mg / MPA 5mg) produced an increase in mammographic density in significantly more women than tibolone, the latter of which is thought to have a minimal effect on breast tissue [45% v 2%].³³ A recent study demonstrated an increase in mammographic density in more than double the number of Kliofem (E2 2mg/NETA 1mg) users compared to Kliovance (E2 1mg/NETA 0.5mg) users [31.8% v 12.2% respectively].³⁴ Data in a subset of women from the CHOICE study (154 subjects) showed that the ultra low dose preparations produced no significant difference in mammographic density (visual and digitized) compared to placebo after 24 weeks of therapy (figure 5). There was also no significant difference between the groups in terms of breast discomfort, pain and tenderness. It is hoped that this dose response effect could translate to neutrality on the breast with the ultra low dose preparations.

Minimising other risks

Currently available estrogen efficacy data on vasomotor symptom relief indicate that there is a positive dose response effect i.e. a higher estrogen dose results in a greater reduction of symptoms. However, data also show that higher es-

trogen doses also result in increased risks such as venous thrombo-embolism and stroke.³⁵⁻³⁶ There may even be a dose response effect of estrogen and progestogen for breast cancer risk though this has never been confirmed. These risks are significant concerns for both patients and prescribers. The potential reduction of risks with lower dose preparations should facilitate return to HRT, uptake by new users and continuation of therapy. Unfortunately, it is unlikely that prospective randomised trials of sufficient duration or magnitude will be funded in the near future to confirm that lower dose preparations minimise or avoid these risks.

What is low and ultra low dose HRT?

There has been some controversy as to what constitutes low and ultra low dose HRT. For 17 β estradiol and estradiol valerate containing preparations the general consensus appears to be that 2mg is standard dose, 1mg is low dose and 0.5mg is ultra low dose. For conjugated equine estrogen preparations, 0.625mg is standard dose and 0.3mg low dose (table 2).³⁷ Dose ranging studies suggest that preparations containing less than 0.5mg of estradiol (unopposed) appear to be ineffective for vasomotor symptom relief.¹⁶ It is therefore unlikely that a nomenclature will have to be found to define the 0.25mg dosage (e.g. super ultra low dose)!

Clinical application of low and ultra low dose combinations

Over the last decade there has been a trend towards reducing the starting dose of HRT to 1 mg of estradiol; this has been accelerated by the WHI study. In view of the efficacy and safety of the ultra low dose preparations studied in CHOICE, it is now proposed that 0.5mg should become the new starting dose for the majority of women seeking relief from vasomotor and other symptoms associated with the menopause. However, women who have been through an early menopause (i.e. below the age of 45y) should continue to be treated with higher doses of estrogen as this is more physiological for them. Other exceptions to the ultra low dose starting dose should include women with severe osteoporosis and severe psychological symp-



toms as these women benefit from the dose response effect of higher levels of estrogen.

Conclusion

In the quest to find the minimum effective dose of HRT, initially low dose (1mg estradiol) and more recently ultra low dose (0.5mg estradiol) combinations have been studied. Both the low, and more recently the ultra low combinations appear to maintain the benefits on menopause symptoms whilst minimising side effects and some risks. In the CHOICE trial both the 0.5 mg 17 β -estradiol + 0.1 mg NETA and 0.5 mg 17 β -estradiol + 0.25 NETA preparations were superior to placebo in efficacy, achieving statistically significant differences in hot flush occurrence and severity by Week 3. This is comparable to the efficacy achieved with higher dose preparations currently available on the market. Significant improvements were also reported in the Greene Climacteric Scale. A high incidence of amenorrhoea was consistent from the initiation of treatment in CHOICE and maintained over the whole study period. The benefits to the skeleton appear to be maintained by ultra low doses of estradiol with an additive effect afforded by norethisterone. Unlike standard and low dose combinations, the ultra low dose combinations in CHOICE had very little, or even a neutral effect on the breast. Considering current concerns with the risk/benefit profile of HRT and the regulatory authority requirement to use the lowest effective dose, it is proposed that the ultra low dose preparations of 0.5 mg 17 β -estradiol + 0.1 mg NETA or 0.5 mg 17 β -estradiol + 0.25 NETA should be considered as the new starting dose for the relief of menopausal symptoms in most menopausal women.



Figure 1

Number of moderate to severe hot flushes by week:

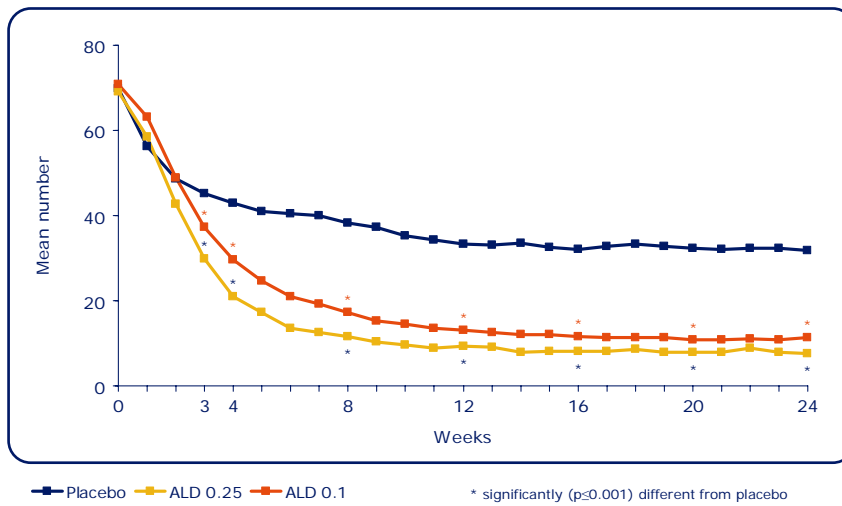


Figure 2

Greene Climacteric Scale – Total symptoms score by week:

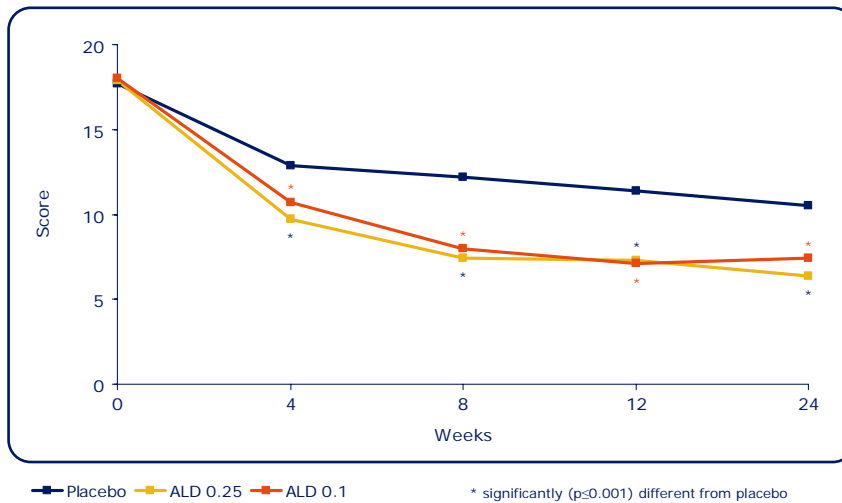




Figure 3

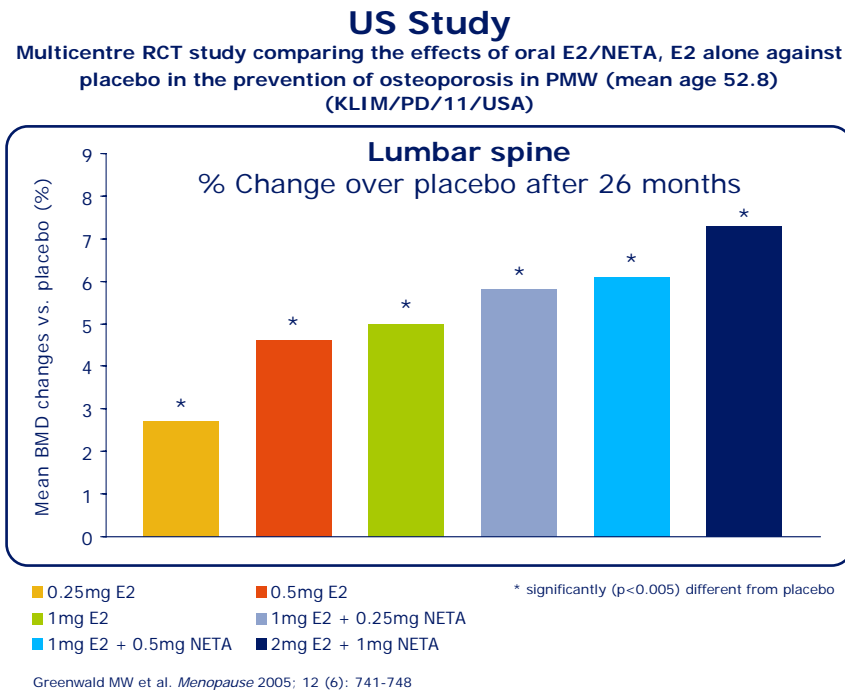


Figure 4

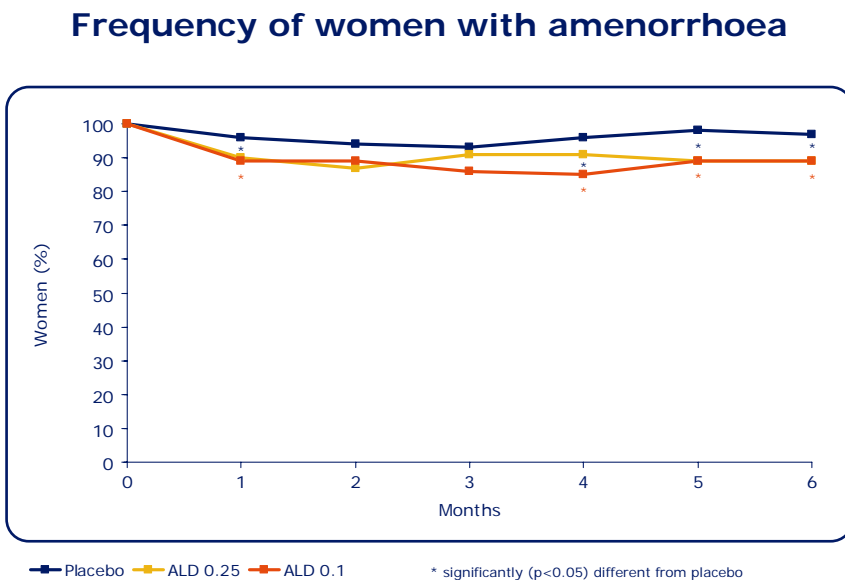




Figure 5

Mammographic density – Digitized quantification

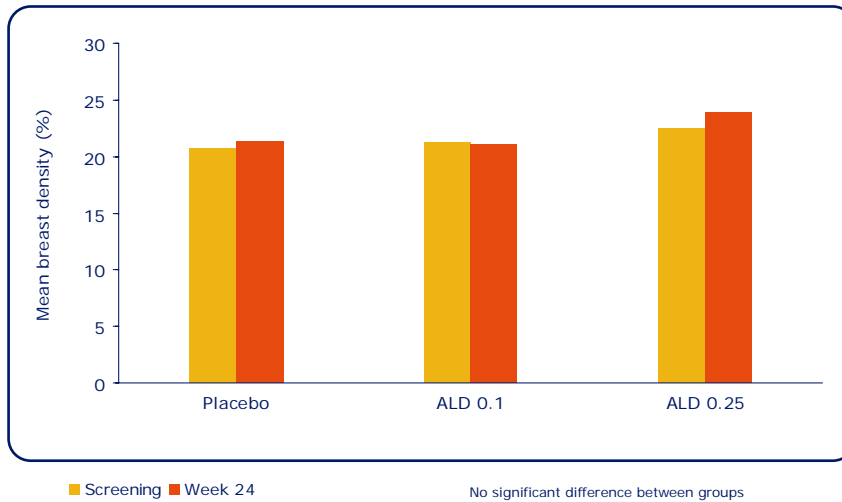


Table 1a

Amenorrhoea rates with standard, low dose and ultra low dose ccHRT's, and tibolone

HRT preparation	1 month	6 months
Kliogest/Kliofem ³⁸ (standard dose ccHRT) E2 2mg NETA 1 mg	67% <i>Hammar 1998</i>	79% <i>Hammar 1998</i>
Activelle/Kliovance ²⁸ (low dose ccHRT) E2 1mg NETA 0.5 mg	73% <i>Archer 1999</i>	83% <i>Archer 1999</i>
Ultra low dose (CHOICE) E2 0.5mg / NETA 0.1mg	89% <i>Sturdee, EMAS 2006</i>	89% <i>Sturdee, EMAS 2006</i>
Ultra low dose (CHOICE) E2 0.5mg / NETA 0.25mg	90% <i>Sturdee, EMAS 2006</i>	89% <i>Sturdee, EMAS 2006</i>
Livial ³⁸ Tibolone 2.5mg	85% <i>Hammar 1998</i>	89% <i>Hammar 1998</i>



Table 1b

Cumulative amenorrhoea rates with low dose
CEE/MPA and ultra low dose estradiol / NETA
ccHRT's

HRT preparation	1 month	6 months
Ultra low dose (CHOICE) E2 0.5mg / NETA 0.1mg	71% <i>Sturdee, IMS 2005</i>	89% <i>Sturdee, EMAS 2006</i>
Ultra low dose (CHOICE) E2 0.5mg / NETA 0.25mg	78% <i>Sturdee, IMS 2005</i>	89% <i>Sturdee, EMAS 2006</i>
Prempro Low dose ²⁴ CEE 0.3mg / MPA 1.5mg	45% <i>Archer 2001</i>	60% <i>Archer 2001</i>
Prempro Low dose ²⁴ CEE 0.45mg / MPA 1.5mg	43% <i>Archer 2001</i>	54% <i>Archer 2001</i>

Table 2

	Low	Standard	High
Conjugated equine estrogens (mg)	0.3	0.625	1.25
Micronised 17 β -estradiol (mg)	1	2	4
Estradiol valerate (mg)	1	2	
Transdermal 17 β -estradiol (mcg)	25	50	100

Gambacciani M, Genazzani AR. Maturitas 40 (2001): 40: 195–201



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