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New products and regimens (since 2003)

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TRENDS IN HRT USAGE AND DEVELOPMENT

As a result of adverse publicity on the purported risks of hormone replacement therapy (HRT) arising from publication of the Women's Health Initiative (WHI) study and the Million Women Study (MWS) in 2002/2003, there was a significant downturn in HRT usage which dropped by up to 50% in some countries. The last couple of years have seen stabilization of usage, following recent favorable data on cardiovascular and breast cancer risks and life expectancy. Menopause remains a serious issue which most women feel should be treated¹. Consequently, both clinicians and scientists have started to look at ways in which the benefits of HRT can be maintained whilst side-effects and risks can be minimized. However, in view of the decline in the HRT market, some pharmaceutical companies have been reluctant to invest time and money in the development and promotion of new HRT products. Some less profitable products, e.g. nasal estrogen, have recently been withdrawn from the market, thus denying some individuals the only HRT which suits them. This paper will examine the different ways in which some formulations have evolved over the last few years in an attempt to achieve the holy grail of symptom relief without compromise.

NEW DOSING OF ORAL FORMULATIONS

New data suggest that the benefits of HRT can be maintained with lower doses than previously used whilst minimizing risks and possibly side-effects. HRT has evolved from standard-dose through to low-dose regimens, e.g. conjugated equine estrogens 0.3 mg (Wyeth Pharmaceuticals)². After initial dose-ranging studies of estradiol confirming efficacy at lower doses than previously thought possible³, ultra-low-dose regimens of 0.5 mg estradiol in combination with 0.25 and 0.1 mg norethisterone acetate have been studied. Data from a recent study, The Clinical Study on Hormone Dose Optimization in Climacteric Symptoms Evaluation (CHOICE)⁴, showed maintenance of efficacy of symptom relief with high amenorrhea rates, minimal adverse events and neutrality to the breast and metabolism. CHOICE was a randomized, placebo-controlled, prospective, multicenter study of 0.5 mg 17 β -estradiol + 0.1 mg norethisterone acetate (NETA) or 0.5 mg 17 β -estradiol + 0.25 mg NETA (Novo Nordisk FemCare). Statistical significance compared to placebo was reached by week 3 for all primary endpoints, e.g. the reduction in number and severity of moderate to severe hot flushes (Figure 1). Other investigated parameters also showed rapid significant reduction in the active treatment groups compared to placebo, including

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the hot flush weekly weighted score. The Greene Climacteric Scale scores, particularly ‘difficulty in sleeping’, also achieved rapid statistically significant improvement. Improvements in these outcome measures with these ultra-low-dose combinations were comparable to the benefits previously achieved with higher-dose preparations.

Safety data from the CHOICE study indicate that treatment with the ultra-low-dose continuous combined HRT (ccHRT) resulted in extremely favorable amenorrhea rates of 89% from the very outset of the treatment. These amenorrhea rates are higher than those achieved with commonly used standard- or low-dose ccHRT. This favorable 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. 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 2)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. Minimizing the dose of estrogen and progestogen whilst maintaining benefits could have significant benefits in encouraging continuation of therapy^{6,7}. Osteoporosis protection

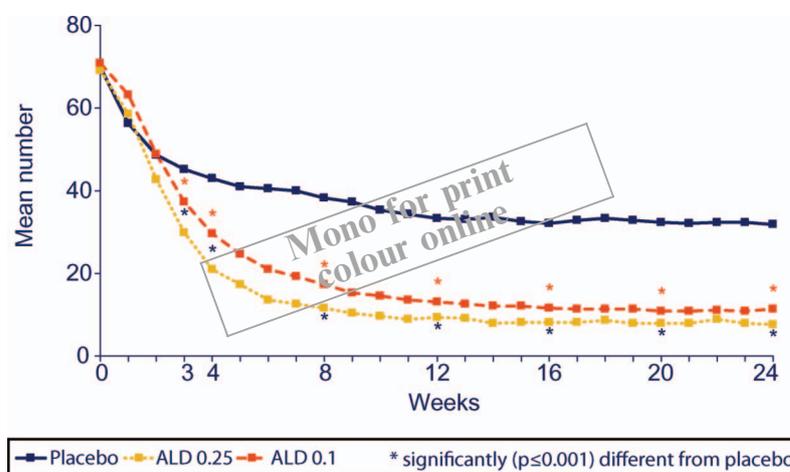


Figure 1 Number of moderate to severe hot flushes per week in the CHOICE trial⁴. ALD 0.1, 0.5 mg 17β-estradiol +0.1 mg norethisterone acetate (NETA); ALD 0.25, 0.5 mg 17β-estradiol +0.25 mg NETA

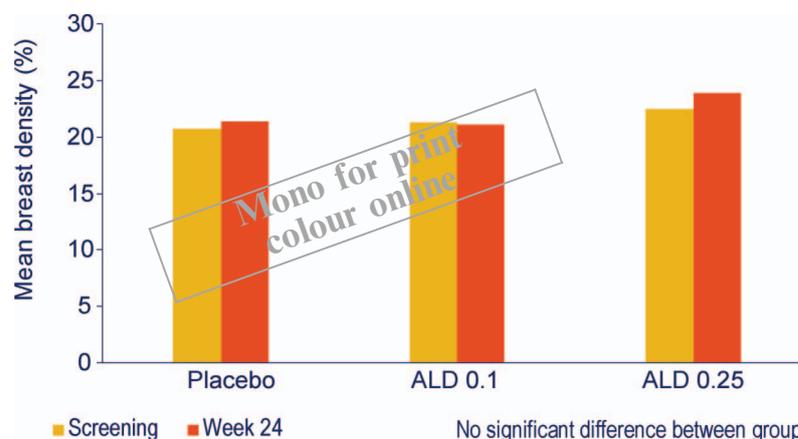


Figure 2 Mammographic density (digitized quantification) in the CHOICE trial at screening and at week 24⁴. ALD 0.1, 0.5 mg 17β-estradiol +0.1 mg norethisterone acetate (NETA); ALD 0.25, 0.5 mg 17β-estradiol +0.25 mg NETA

appears to be maintained even at these ultra-low doses⁸.

NEW DOSING OF TRANSDERMAL FORMULATIONS

Data from the WHI study suggest that estrogen increases the risk of breast cancer only when combined with progestogen. In an attempt to minimize the effect of estrogen on the endometrium and thus negate the need for endometrial protection from progestogen, a 14 µg transdermal system (Menostar[®], Bayer Schering Pharma) has been developed. In a randomized, prospective, placebo-controlled study of 417 women aged 60–80 years, the 14 µg transdermal estradiol negated the need for progestogenic opposition, with only one case of hyperplasia reported in endometrial biopsies taken after 2 years of estrogen therapy⁹. This dosage was effective in reducing bone turnover in asymptomatic women. However, it is probably too low a dose to effectively relieve symptoms.

RECEPTOR SPECIFIC PROGESTOGENS AND PROGESTERONE

Progesterone receptor-specific progestins, e.g. trimegestone, and natural progesterone have less side-effects due to avoidance of the mineralocorticoid and androgen receptors. Micronized progesterone (Utrogestan[®], Besins/Ferring) is finally being launched in the UK. Available for a long

time in mainland Europe and the USA, it appears to be metabolically neutral and is being studied in the Kronos Early Estrogen Prevention Study (KEEPS)¹⁰. Recent data from the EPIC cohort (France) suggest no excess risk of breast cancer when micronized progesterone is combined with estrogen (relative risk (RR) 0.9; 95% confidence interval (CI) 0.7–1.2), whereas risk was found to be slightly increased with standard doses of estrogen and synthetic progestogen (RR 1.4; 95% CI 1.2–1.7) after 5.8 years' observation¹¹. These data require confirmation from large, randomized, prospective studies.

REGIMENS CONTAINING NEW PROGESTOGENS

The relatively new progestin, drospirenone, a spironolactone analog, is now being used in HRT (Angeliq[®], Bayer Schering Pharma), where it has been combined with 1.0 mg estradiol¹². It is not only progesterone receptor-specific but has antiandrogenic and antimineralocorticoid properties; the former makes it useful for avoiding hirsutism and the latter for fluid retention and hypertension. Recent data have confirmed the antihypertensive effect of this regimen. A total of 750 women with Stage I/II hypertension were randomized to 17β-estradiol 1.0 mg with 1.0/2.0/3.0 mg drospirenone over an 8-week study period. In the drospirenone 2.0 mg group, systolic blood pressure was reduced by 3.4 mmHg and diastolic blood pressure by 4 mmHg when measured by office cuff (Figure 3). These small reductions in

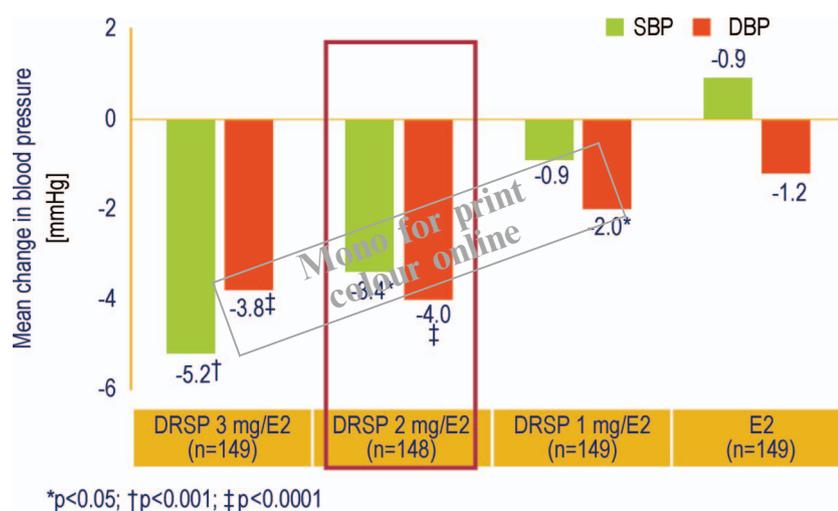


Figure 3 Results of a dose-ranging study in 750 women with Stage I/II hypertension who were randomized to 1.0 mg 17β-estradiol (E2) with 1.0/2.0/3.0 mg drospirenone (DRSP) over an 8-week study period¹². Adjusted mean change in clinic systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared with placebo

blood pressure could have significant health benefits in the reduction in incidence of coronary heart disease and stroke.

its use would be difficult to regulate and that longer-term safety data were required.

LOCAL DELIVERY SYSTEMS

The 20 µg/day levonorgestrel intrauterine system (Bayer Schering Pharma) reduces systemic progestin side-effects by releasing the progestogen directly into the endometrium, with low systemic levels. However, in severely progestogen-intolerant women, even the low systemic levels of the 20 µg levonorgestrel intrauterine system can produce side-effects. The lower-dose, 10 µg system appears to be better tolerated by these women. In a recent study, 294 postmenopausal women with a median age of 53 years were treated with transdermal 17β-estradiol 50 µg and a 10 µg levonorgestrel intrauterine system. The 10 µg intrauterine system was easily inserted at the first attempt in 297/294 (94%) women. At 11 months, 67% of the subjects were amenorrheic and 87% had no bleeding. The adverse event rate was low, with headaches occurring only in 13.3% and mastalgia in 7.8%¹³. However, due to profitability issues, there has been a decision not to market this system yet despite these favorable data.

ANDROGENS

For many years, implanted pellets of testosterone have been the only licensed form of androgen therapy for women complaining of low libido. Some specialists have used, off label, titrated doses of the male testosterone patch and gel. However, work over the last years has led to the development of the new female androgen patch (Intrinsa[®], Procter & Gamble). Having received a European license in July 2006, the patch has recently been launched in Europe for the treatment of hypoactive sexual desire disorder (HSDD). It is indicated for use in hysterectomized women using estrogen who are distressed by low libido, following the results of two large studies in over 1000 women which showed statistically significant benefits compared to placebo¹⁴. These benefits included a significant increase in number of satisfying sexual episodes, an increase in sexual desire and a reduction of distress due to low libido. Additionally, following recent encouraging data¹⁵, it is hoped that a license might also be sought and granted in naturally menopausal women with HSDD. The FDA has yet to grant Intrinsa a license in the USA, on the premise that

NON-HORMONAL REGIMENS

Selective serotonin and noradrenaline reuptake inhibitors (SSRIs/SNRIs) have been used off label for a number of years as an alternative to HRT for the treatment of vasomotor symptoms. Laboratory data in the ovariectomized rodent model have shown a dose-dependent improvement in thermoregulation with desvenlafaxine succinate (DVS, Wyeth Pharmaceuticals)¹⁶. Data from three phase-III clinical trials (yet to be published) show an approximately 60% symptom reduction with this selective noradrenaline and serotonin reuptake inhibitor. It is expected that a non-hormonal treatment for vasomotor symptoms based on this compound will be launched this year. This will be the first licensed alternative to HRT for the treatment of vasomotor symptoms.

NEW PRODUCTS IN THE PIPELINE

In the future, advances in the tissue-selective agents, the use of selective estrogen receptor modulators (SERMs) and the new progesterone receptor antagonists and modulators should also facilitate the specific targeting of the estrogen and progesterone receptors. One SERM (bazedoxifene, Wyeth Pharmaceuticals) has been combined with Premarin[®] (Wyeth Pharmaceuticals). This SERM/estrogen combination has been named 'tissue-selective estrogen complex'. The aim is to maintain the benefits of symptom relief whilst minimizing effects on the endometrium and breast. Encouraging data were presented recently at the 6th International Menopause Society Workshop on varying bazedoxifene/conjugated equine estrogen dosage regimens¹⁷. The combinations were all effective in relieving vasomotor symptoms and one regimen maintained very good endometrial suppression and amenorrhea rates. There were bone-sparing effects and an apparently neutrality on the breast. Further data are awaited from phase-III clinical trials.

SUMMARY

The downturn in the HRT market (since WHI/MWS) has now stabilized. New products are being developed which maintain benefits and minimize risks. However, some useful products have already been withdrawn by pharma

companies through profitability decisions, e.g. Aerodiol[®]; some other products will regrettably not be launched despite favorable data (MLS, or 10 µg Mirena[®]). The new ultra-low-dose oral preparations (0.5 mg estradiol/0.1 mg and 0.25 mg NETA) appear to maintain benefits for symptom relief and osteoporosis whilst minimizing side-effects and risks. A 14 µg transdermal system appears to maintain bone protection without the need for endometrial protection. New progestogens can minimize progestogenic side-effects through antiandrogenic and anti-mineralocorticoid effects, e.g. drospirenone,

bioidentical progesterone and selective progesterone receptor modulators. A new female androgen patch (Intrinsa[®]) has been licensed this year in Europe for treatment of female androgen deficiency causing distressing low libido. A non-hormonal option (SNRI) for vasomotor symptom management is currently in phase-III clinical trial stage and should be launched later this year. A SERM/estrogen replacement therapy (bazedoxifene/Premarin) combination, currently in phase-III clinical trials, is showing encouraging data for efficacy/risks and should provide a further option for hormone therapy in the future.

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