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Title: Differential effects of alternatives to hormone replacement therapy in postmenopausal healthy women.

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Abstract:

This thesis was done in Center for Clinical & Basic Research in Ballerup, Denmark. The aim was to evaluate the effect of tibolone and raloxifene, both estrogen-like alternatives to hormone therapy in the prevention of postmenopausal bone loss and also with regard to the influence on risk markers for cardiovascular disease. As a comparator hormone therapy was chosen.

A total of three randomized, placebo-controlled and double-blinded trials of two to three years duration in 970 healthy postmenopausal women showed that:

1. Tibolone reduces bone turnover and increases bone mass. The efficacies of the two dose levels studied, 1,25 mg and 2,5 mg are comparable and equivalent with the efficacy of therapy with 1-2 mg estradiol.
2. Raloxifene also reduces bone turnover and increases bone mass. The efficacies of the three dose levels studied, 30, 60 and 150 mg, are of a comparable order of magnitude but seem weaker than that of of tibolone and standard regimens of hormone therapy.
3. Tibolone reduces HDL-cholesterol and triglycerides, but does not change LDL-cholesterol. This is in accordance with a predominantly progestogenic influence. In contrast, tibolone has an estrogenic influence on markers of haemostasis, thus inducing changes favouring fibrinolysis.
4. Raloxifene reduces LDL-cholesterol but does not change HDL-cholesterol or triglycerides. This is in accordance with a partial estrogenic effect.

Furthermore, four experiments in 284 female rabbits in the ovariectomized cholesterol-fed rabbit model with duration of three weeks to one year showed that raloxifene reduces aortic atherosclerosis with a partial estrogenic effect.

Evaluation of the safety profile showed that tibolone therapy leads to weak endometrial stimulation. Thus, 20% of exposed women experiences vaginal spotting. Raloxifene does not lead to menstrual-like bleeding and reduces the incidence of breastcancer with 76%. This effect is seen in estrogen-positive cancers only.

It is concluded that although tibolone and raloxifene widen therapeutic options in postmenopausal women, neither of these drugs represent the ideal alternative to hormone therapy. Tibolone may induce at least some of estrogen's safety problems and raloxifene is less effective in the prevention of osteoporosis and does not alleviate climacteric complaints, but can worsen these symptoms. However, the study of the differential aspects of these drugs may increase the understanding of therapeutic effects in estrogen-sensitive tissues and may help in targetting the development of new drugs for postmenopausal women.