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HTA-Report | Summary

DAHTA@DIMDI
Waisenhausgasse 36-38a
D-50676 Köln

Tel.: +49 221 4724-525
Fax +49 221 4724-444
dahta@dimdi.de
www.dimdi.de

Hormones for therapy of climacteric afflictions

Eberhardt S, Keil T, Kulp W, Greiner W, Willich SN, Schulenburg JM Graf von der

Background

"*Natural*" menopause occurs when a woman has her last period. All over the world this is usually between 45 and 55 years of age, with an average age of 51. What is termed "*induced*" menopause occurs after two ovaries are removed through a bilateral ovarectomy operation or when chemotherapy or radiation therapy shuts down ovarian function. Perimenopause refers to the interval from just before the onset of 'natural' menopause until twelve months later.
The menopausal transition or climacteric period describes the change in a woman's life from the reproductive years to the time of relatively low estrogen. Many women suffer differing levels of psychological and physical complaints when their periods stop, this being the sign of a fall off in the cyclical peaks of estradiol production in the ovaries. While some women have no symptoms between the age of 40 and 60, a large number of women suffer complaints of varying degree. This involves mainly vasomotor symptoms such as hot flushes and night sweats which are usually confined to the upper body. In North America and Europe 45 to 80 % of women are affected. In Asia, the number is 10 to 50 %. A number of further symptoms which can occur singly or together are often considered part of the menopausal or climacteric syndrome. However, unlike the symptoms already mentioned, these are not specifically menopausal but rather the result of the vasomotor symptoms or are caused by something else. They often include depression, headaches, sleep disturbance, mood swings and impaired concentration or memory loss.
The period following menopause is called postmenopause. Here estrogen levels are much lower than during the reproductive years. The menopausal transition, with all these associated health problems, usually stretches from premenopause over several years into the beginning of postmenopause. The vasomotor symptoms and associated problems do taper off or even disappear in the first two years of postmenopause. Many diseases, symptoms and pathological changes are connected beyond the menopausal transition with the lower estrogen levels of postmenopause and are or were seen as medical indications for long-term hormone therapy (HT) at this time of life, especially to prevent fractures due to osteoporosis or a heart attack. Estrogens alone or combined with progestin, based on natural or synthetic hormone preparations, feature most frequently in HT. The combination HT is given to prevent endometrial hyperplasia and endometrial cancer.
The objective of this HTA-report is to assess medically and from an economic point of view, the use of HT to treat hot flushes and night sweats and to prevent osteoporosis and cardiovascular disease in postmenopausal women. Published studies and systematic reviews will be evaluated and summarised according to standardised criteria. The medical assessment will consider the efficacy and the risk factors within the framework of the particular indicators. The economic evaluation will focus on the cost-effectiveness of HT compared with no treatment or between different types of HT.

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Objectives

The medical efficacy and cost-effectiveness of HT will be evaluated in medical and socio-economic terms. This HTA-report will first address the question of whether HT is an effective method as a treatment for vasomotor symptoms (hot flushes and night sweats). Furthermore, it will consider whether HT is an effective medication in postmenopause for primary prevention of osteoporosis and cardiovascular disease.

Medical evaluation

Methods

For the group of women without serious preconditions who received HT either as a therapy for hot flushes and night sweats or to prevent osteoporosis and cardiovascular disease, relevant publications were identified using a structured search of the literature through DIMDI on 23 March 2004. For this purpose MEDLINE, EMBASE, Int. Health Technology Assessment, the Cochrane Library, the databank of the NHS Centre for Reviews and Dissemination at the University of York were consulted as well as 19 other databases. This reference search was also extended by looking up internet sites of national and international scientific societies for gynaecology and menopause.
The search parameters focussed on the indications of HT in the menopausal transition (hot flushes and night sweats) and the use of HT for disease prevention in postmenopause (osteoporosis and cardiovascular disease). There was such an abundance of literature that the present review was limited to publications in English and German between 01 January 1999 and 23 March 2004.
The information was sorted according to certain criteria. The basic requirement for the publications that were selected through a structured search and the ongoing review was that the title and abstract made it clear that the publication was about the use of hormones to treat women with hot flushes and night sweats and to prevent osteoporosis and cardiovascular disease in postmenopause. Studies where it was clear from the title or abstract that authors were looking exclusively at HT for women with serious problems such as carcinoma or post hysterectomy were not included. The selected studies also had to consider clinically relevant endpoints such as death or disease and not just bio-chemical markers as a surrogate parameter, e. g. bone density measurement or laboratory results. The publications identified in this way were categorised according to the quality of their methodology as well as relevance and then evaluated for this HTA-report, if they met the basic quality requirements. The checklist of the ‘Scientific Working Group: Technology Assessment for Health Care’ provided the criteria for medical quality. Studies which did not meet the given criteria were not evaluated. The results are presented below for each individual publication.

Results

For the evaluation of HT in the treatment of hot flushes and night sweats during the menopausal transition, out of the total of 272 identified published papers, 16 publications reporting the results from 18 studies fulfilled the given medical inclusion criteria and the requirements in terms of high quality methodology and transparency. The evaluated studies all showed that HT can be regarded as an effective method for treating these complaints during

the menopausal transition. The hormonal preparations that were studied in these papers showed a significantly higher efficacy of 75 to 95 % compared with placebos for postmenopausal women. For women who were still perimenopausal, the few results available suggest a much smaller or no difference between HT and placebos. There were differences in the efficacy of the same medication depending on the dose but no significant differences between differing hormonal preparations by intra-nasal versus oral or transdermal application. Other forms of medication were not examined in the selected studies.
For the evaluation of HT to prevent osteoporosis and cardiovascular disease in postmenopause, only ten publications out of the total 272 identified sources met the set medical inclusion criteria and the requirements in terms of high quality methodology and transparency. The studies gave the following results.
Postmenopausal women using HT as compared to a placebo showed:

- a 24 to 27 % lower risk of any fractures (47 to 59 less fractures per 10000 women per year);
- a 33 % lower risk of hip fractures (five fractures less per 10000 women per year);
- a 22 % higher risk of cardiovascular disease (including heart attack, stroke and thromboembolic events) (27 more per 10000 women per year);
- a 41 % higher risk of stroke (eight strokes more per 10000 women per year);
- a 111 % higher risk of thromboembolic events (18 more cases per 10000 women per year);
- a 24 % higher risk of breast cancer (ten more breast cancer cases per 10000 women per year);
- a higher risk of ovarian cancer and a slightly lower risk of endometrial cancer (neither of which were statistically significant);
- no change in risk for total mortality.

Overall, it was shown that HT containing equine estrogens plus medroxyprogesterone acetate does not prevent osteoporosis and cardiovascular disease in healthy postmenopausal women.
For other medication or combinations of HT, there is only information from good randomised studies for the risk of fractures and thromboembolic diseases, but not for the other outcomes.

Discussion

The authors of the studies see HT as an effective method for treating vasomotor symptoms (hot flushes and night sweats). However, since the majority of the studies under scrutiny were sponsored by the producers of the medications in question, the critical discussion of the results and the methods used in the study are rather superficial. The women in the study populations were mostly postmenopausal and thus only partly representative for women who are often still perimenopausal and are receiving HT in everyday clinical practice for hot flushes and night sweats. Overall the relatively short observation periods of these studies, mainly for three and seldom for more than six months is not usual practice where the women affected are often treated over a much longer time scale.
In the assessment concerning the prevention of osteoporosis and cardiovascular disease among healthy women in postmenopause, after careful consideration, the positive effects don’t seem to outweigh the negative ef-

fects. Thus HT cannot be regarded as a suitable primary preventative measure for healthy postmenopausal women. Strictly speaking, definitive claims cannot be made for forms of HT other than the estrogen-progestin combination, which has been investigated the most. The effects on women in other age groups may also differ from those found here.

Economical evaluation

Methods

The proceeding of information retrieval and economic assessment correspond to the stated medical assessment. The relevant criteria in this context are screened on the basis of the checklist for assessment of health economic studies by the 'German Scientific Working Group: Technology Assessment for Health Care'.

Results

Out of the identified 42 citations that were implemented into the evaluation, merely six publications conformed to the inclusion criteria. One more article was identified through hand search. Therefore to address the study questions two publications were evaluated regarding 'Treatment of vasomotor symptoms (hot flashes and night sweats)' and five studies regarding 'Primary prevention of osteoporosis and cardiovascular disease in postmenopausal women'.
For the use of HT as a treatment for hot flushes and night sweats the results of one study showed HT as a cost-effective alternative to the 'no therapy'-strategy. One further study evaluated costs and consequences of two alternative supplements for HT, but none of these alternatives proved to be significantly beneficial. However, these studies varied vastly in terms of study groups, study drugs with regard to type and dose as well as to choice of study perspective. Thus the question of whether HT for this medical indication (hot flushes and night sweats) could be economically efficient cannot be answered based on available information.
Two of the economic evaluations for the use of HT in primary prevention of osteoporosis and cardiovascular disease showed the HT not as a cost-effective alternative to the 'no therapy'-strategy under almost all scenarios. One further study, which explicitly included the results of the WHI-study regarding estrogen + progestin therapy, accounted for a net harm associated with HT, consequently the consideration of cost-effectiveness was not relevant. By contrast a further study indeed arrived to a positive conclusion regarding the cost effectiveness of HT for primary prevention of osteoporosis and cardiovascular disease, but given that a pivotal assumption of this study from a contemporary point of view proved false, this result should be regarded under reserve. Equally a fifth study with a positive result regarding the cost-effectiveness of HT could not be included, because it only selectively considered the effects of HT on fracture incidence but no other with HT associated events like breast cancer or cardiovascular disease were taken into consideration. This does respectively did not reflect the state of scientific findings – neither currently nor at the time of the study implementation.

Discussion

The included studies assessing the questions of cost-effectiveness of HT as a treatment for vasomotor symptoms (hot flushes and night sweats) and for primary prevention of osteoporosis and cardiovascular disease in post-menopausal women were mostly cost-benefit-analyses based on Markov modelling. This methodological approach measures up to the object of research, since quality of life is a crucial outcome parameter in the assessment of both medical indications. Furthermore, Markov models allow for simplified pictures of complex structures and especially they enable the consideration of long-term effects in the economic evaluation, as required for showing the antidromic effects associated with HT over a longer time horizon.
Since the included economic publications assessing HT as a treatment of hot flushes and night sweats varied vastly in terms of study groups, studied drugs, choice of study perspective and in addition they were not carried out with respect to the German health care system, for Germany a considerable demand of health economic evaluations can be stated.
Further economic evaluations particularly should consider the following aspects. The study groups should be differentiated more clearly in respect to peri- and postmenopausal women. Furthermore dose and type of HT under evaluation should be specified in more detail. The validity of model results would be enhanced by usage of empirical data of the considered setting. The implementation of further evaluations with consistently confined subgroups which will consider certain combinations of agents from the same perspective and which in addition will use a standardized methodology to deduct aggregated measures of benefits would be desirable.
Of particular interest are - beyond a mere comparison with the alternative 'no therapy' - evaluations of the cost-effectiveness relation of several agents respectively doses with each other given that with the varying impact on bleeding patterns also the compliance with the therapy likely will vary.
To address the question of economical effects in the primary prevention of postmenopausal osteoporosis and cardiovascular disease only one health economic study considered the latest scientific findings about positive and negative effects of long-term HT. Because from the medical point of view the results of the Women's Health Initiative (WHI) showed that the benefits of combined HT do not outweigh the risks, it can be assumed, that further evaluations regarding the cost-effectiveness of the HT for primary prevention are not useful.

Ethical evaluation and sociological aspects

The current ethical discussion about the menopausal transition and HT has become controversial; Lyerly et. al.[1] mention the feminist approach which on the one hand criticizes the attitude of the medical profession, namely that problems experienced by women during the menopausal transition are categorised as 'psychological' and therefore 'not real'. On the other hand, a large part of the literature classified as feminist criticises gynecologists and society for the predominant medical approach to the menopausal transition, a universal experience of women. By giving the menopausal transition a pathological image they have turned a natural process into a medical condition. This is emphasized in the choice of the term 'estrogen deficit disease' which led to HT being prescribed for life. Since the relative lack of estrogen is part of a natural process and is not a disease as such, the more neutral term, 'hormone therapy' should be used rather than 'hormone replacement therapy', as the former does not imply a pathological condition.

Regarding further research, the question of ethical implications needs to be addressed: it would be worthwhile to have more accurate estimates of the frequency of hot flushes and night sweats and also additional symptoms associated with the menopausal transition in the general female population. There is also a lack of good quality population based studies on how it affects the quality of life of the woman affected. There is also a need for research in order to be better able to estimate the benefit and risk of treating hot flushes and night sweats with HT over a long period. There are very few studies of women with premature menopause or of cured cancer patients (urogenital or breast cancer) who suffer from hot flushes after their ovaries have been removed.

In particular, perimenopausal women are given HT to treat hot flushes and night sweats despite insufficient knowledge from good quality studies about its effects for these women. Given the current research findings, peri- and postmenopausal women will probably be less inclined to take part in hormone therapy studies in the future. This gives rise to another relevant aspect, with the continual development of new or different doses of pharmaceutical therapies; there is a danger of perpetuating the concept of “medicalising” peri- and postmenopausal women.

Randomised, controlled studies like those carried out within the framework of the Women’s Health Initiative (WHI) and the Heart and Estrogen / Progestin Replacement Study (HERS) are seen as the ‘gold standard’ in medicine for investigating the efficacy of therapies and preventive measures. Estimates of the positive and negative effects of therapies are usually expressed in relative risks (risk ratio, hazard ratio) which is of little help in choosing a therapy. They should be translated into absolute risks in order to provide an important prerequisite for an informed, responsible and willing participation by the patient in her choice of therapy. This matches the now accepted ideal of the ‘responsible’ patient as it is promoted within the concept of shared decision making.

This model of shared decision making, which is encouraged in the United States and more and more in other health systems, is based on a dialogue of partnership between the medical advisor and the patient, where both take an active part in the decision making process and try through discussion to come to an agreed approach. It is the doctor’s responsibility to give the patient comprehensive, helpfully presented medical information and to support the patient so that she can crystallize her valued judgments, preferences and wishes. The responsibility for the therapy that is decided and agreed upon by both parties is shared. As has been shown, decisions based on consent and sound information about treatment options, including possible risks and side effects, lead to higher patient therapy compliance/adherence. It is thus important within a doctor’s consultation, when the woman concerned is trying to decide on a therapy, to make use of the autonomy principle in the sense of free will.

Within the model of shared decision making, it is most important to include the patient’s psychological and social context, that is the patient’s subjective outlook concerning the existence and the explanation of problems arising in connection with the menopausal symptoms she is experiencing. The patient’s preferences are just as important in evaluating the clinical and economic aspects of HT. In any case, the use of aggregated measures of benefit as are used in considering the outcome parameter quality of life, e. g. with QALY (quality adjusted, additional years of life) hides an underlying problem, which is dealt with by Lyerly et al.[1] aggregated measures of benefit regarding particular health conditions promote generalization about all women and overlook individual differences. The paradox that this approach focuses on the preferences of the women as a group, which may not equate

with the actual preferences of the individuals within the group cannot be resolved. But according to Lyerly et al.[1], for an ethically acceptable version of aggregated measures like QALY, the benefits and limits of its claims should be taken into consideration.
Moreover this report concludes that the fall off in the cycle of ovarian estradiol production in women is not a pathological condition necessarily requiring hormone therapy. If a woman's quality of life is reduced to the extent that HT will relieve the menopausal symptoms, prescribing HT as a long-term treatment, without careful, individually based consideration of the benefits and risks, seems - based on the new information in this HTA-report – to have no ethical justification also considering possible pharmacological and non- pharmacological therapy alternatives.
In order to achieve an optimal set of parameters for a differentiated information exchange during the medical consultation, a number of points need to be considered. On the one hand there are indications that it can take five to 15 years for scientific knowledge to be completely absorbed into medical practice. Some possible ways to shorten this process markedly would be to produce qualifying measures such as therapy guidelines that include current scientific / medical knowledge about HT as well as alternative pharmacological and non-pharmacological therapy options. On the other hand, many patients seek medical and other information around the whole topic of the menopausal transition from sources other than their doctor and often arrive well informed at their doctor's appointment. In this situation also, helpful information should be made available so that the patient has a sound basis on which to make a responsible decision.

Legal considerations

Within the parameters of this HTA-report, the authors did not identify any specific legal concerns about the use of HT.

Summarising discussion of all results

The medical efficacy of HT for hot flushes and night sweats was clearly shown in the present HTA-report. Although the medical studies included considered a large number of different medications and combinations of hormones, only the alternative therapy norethindrone (norethisterone) acetate / ethinyl estradiol (NETA / EE) was investigated in the current economic studies for HT. Therefore future studies should evaluate HT where there is medical evidence for its efficacy in treating hot flushes and night sweats. In doing so, combination preparations, especially those used in Germany should be considered. With this in mind, the information discussed in the medical section of this HTA-report concerning a balanced benefit / risk ratio, needs to be carefully considered to decide whether it is wise to model the area of primary preventive HT application, to avoid osteoporosis and cardiovascular disease using data specific to Germany.
Further research is needed into the treatment of hot flushes and night sweats, especially for long-term use (> 1 year) and for perimenopausal women, as little is known about it at this stage. Prescription of HT to treat hot flushes and night sweats should also be limited to cases where the women concerned are suffering a significantly reduced quality of life. Comprehensive, helpful information for the patient about the benefits and risks she can expect in her actual situation should underpin a decision about therapy. This is not only ethically advisable but also important for subsequent therapy compliance / adherence. This significantly influences the

medical efficacy and the economic efficiency of the treatment.

Conclusions

In the present HTA-report, the concern about using hormone therapy, first to treat hot flushes and night sweats and secondly to prevent osteoporosis and cardiovascular disease in postmenopausal women, was reviewed from the standpoint of medical efficacy and cost effectiveness. It can be concluded, based on the publications identified and evaluated, that HT is medically effective for the treatment of hot flushes and night sweats. Despite a large variation in the medications and combinations of hormones used, all the HT products examined were effective in reducing the number of hot flushes per day. Up until now there has been very little research into the benefits and risks of HT for menopausal problems over the longer term (several years). General, large scale use of HT cannot be recommended due to the possible risks of serious, long-term complications such as thromboembolic events. For shared decision making, (meaning a mutually-agreed decision about therapy) the patient should be given comprehensive information about the expected benefits and risks in her particular situation. Temporarily stopping HT is also recommended currently to evaluate the need for long-term therapy, but there are as yet no results available from good quality studies concerning the optimal procedure when stopping HT. Studies of this kind are currently being carried out in the United States. The currently available health economic evaluations provide no clear statement as to the cost effectiveness of HT for treating hot flushes and night sweats. This is due to the variability in medications examined as well as the lack of studies carried out based on the German health system. However the economic efficiency of this form of HT could be accepted considering the relatively low cost of the medication and the simultaneously significant medical benefit in reducing vasomotor symptoms like hot flushes and night sweats. Further health economic research is necessary to confirm the accuracy of this hypothesis. The results of the articles analysed show that HT is not suitable for the primary prevention of osteoporosis and cardio-vascular disease for postmenopausal women. The pharmacological and non-pharmacological alternatives available need to be looked at more closely for the prevention of these diseases.

References

1. Lyerly AD, Myers ER, Faden RR: The Ethics of Aggregation and Hormone Replacement Therapy. In: Health Care Analysis 9 (2001): S. 187-211.

Contact at DAHTA@DIMDI:
Head: Dr. Alric Rüther
E-Mail: dahta@dimdi.de