Quality of life and costs associated with micronized progesterone and medroxyprogesterone acetate in hormone replacement therapy for nonhysterectomized, postmenopausal women

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of a micronised natural progesterone (MP) or synthetic derivative (medroxyprogesterone acetate, MPA), combined with hormone replacement therapy (HRT), to improve the general health and quality of life (QoL) of menopausal women without increasing the associated risks. MP (Prometrium; Solvay Pharmaceuticals Inc.) was given at a dose of 200 mg on days 12 to 25 of a 30-day cycle. MPA (Provera; Pharmacia Corporation) was given at a dose of 5 mg on days 12 to 25 of the 30-day cycle. HRT (Premarin; Wyeth-Ayerst Pharmaceuticals) was given as 0.625 mg conjugated equine estrogens on days 1 to 25 of the 30-day cycle.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised postmenopausal, nonhysterectomised women, aged between 45 and 65 years, who had been amenorrheic for at least for 6 months. In addition, they had to have displayed symptoms of oestrogen deficiency, a body weight within 30% of the ideal for their height, follicular stimulating hormone levels greater than 40 IU/L, and estradiol levels lower than 110 ng/L. Women who had undergone bilateral oophorectomy or had used hormones, glucocorticoids, or drugs that influenced cognition or vigilance within 3 months of study enrolment were excluded.

Setting
The setting was unclear, although it appears to have been the health service (since primary, secondary and tertiary care seem to have been considered in the study). The study was carried out in Canada.

Dates to which data relate
Data on the effectiveness and resources used were collected for a 9-month period, beginning November 1995. The unit costs and prices were obtained from studies published between 1992 and 1997. The price year was 1997.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
Resource use was mainly obtained prospectively from the same sample population as that used in the effectiveness study. In addition, some costs appear to have been estimated following prescribing guidelines.
Study sample
Calculations were performed in the planning phase of the study. These showed that a sample size of 178 was required to detect a 25% difference between treatment groups in the scores of the Women's Health Questionnaire (WHQ), with 80% power and a Type I error equal to 0.05. The study sample was recruited from 12 sites during the study period, according to the inclusion criteria (see Study Population). The final study sample comprised 182 patients, of which 89 were in the MP group and 93 in the MPA group. The authors did not report any evidence that the study sample was representative of the study population.

Study design
This was a randomised, open label, multi-centred controlled trial (patients from 12 sites were included in the study). The period of follow-up for the patients was 9 months. A total of 14 MP patients and 13 MPA patients did not complete the trial (6 and 9 of them, respectively, because of adverse events). Although the study was an open label study, the authors did not report that a blinding method was applied when assessing the outcomes.

Analysis of effectiveness
The analysis of the clinical study appears to have been conducted on the basis of treatment completers only. The primary health outcome assessed was QoL, using two generic instruments (the SF-36 and the Nottingham Health Profile, NHP) and a specific-condition instrument (the WHQ). The secondary outcome measures were:

- menopausal symptoms, as assessed by patients and physicians by means of the Kupperman Index;
- the bleeding patterns (i.e. the number and percentage of women experiencing amenorrhoea, the average days of bleeding, and the blood flow, assessed at baseline and after 9 months of follow-up based on reports in patients' diaries); and
- the compliance rates, assessed at the 3-, 6- and 9-month visits and based on pill count.

The study groups were shown to be comparable in terms of mean age, mean height and mean body weight, racial distribution, years since the offset of menopause, work status, type of insurance, and prevalence of alcohol use. MPA patients showed a higher prevalence of smoking and lower income than MP patients.

Effectiveness results
There were no significant differences in the SF-36 scores between assessments at baseline and after 9 months of follow-up for either study group. Nor were there any differences between the study groups at 9 months.

There were significant improvements in all the domains of the NHP between baseline and final assessment, (p<=0.008), but not between the study groups at 9 months.

The results for the WHQ showed that there were significant improvements in terms of QoL at 9 months, compared with the baseline assessment, (p<=0.004). In addition, after 9 months, MP patients had a significantly better perception of QoL in terms of the cognitive difficulties domain, (p=0.015) and the menstrual problems domain, (p=0.018) than MPA patients.

There were significant improvements in the menopausal symptoms (as measured by the Kupperman Index) for both patient groups during the study period, (p<0.001), although the differences between MP and MPA patients at 9 months were not significant.

A higher percentage of MP women than MPA women reported no bleeding at 9 months, 28 MP patients (39%) versus 9 MPA patients (12%), (p=0.001). MP patients presented a significantly lower number of days of bleeding (4.3 +/- 4.6 versus 6.2 +/- 4.4; p=0.01) and a significantly lower blood flow (0.9 +/- 0.8 versus 1.4 +/- 0.7; p<0.001) than MPA patients.

Ninety-three per cent of the MP patients and 94% of the MPA patients were compliant with the study medication.
Clinical conclusions
Both MP and MPA treatments improved the perception of QoL for postmenopausal women during the study period, as shown by the NHP and the WHQ scores. Women receiving MP showed significantly better results in terms of the menstrual problems and cognitive domains of the WHQ, experienced less days of bleeding, and had lower blood flow than MPA patients.

Measure of benefits used in the economic analysis
No summary measure of benefit was used in the economic analysis. The study was therefore categorised as a cost-consequences analysis.

Direct costs
The direct costs considered in the economic evaluation were those of the health service and out-of-pocket expenses incurred by the patients (including travel costs and feminine hygiene products). The health service costs included costs related to outpatient care, such as physician fees, annual monitoring and associated laboratory tests (e.g. mammographies, Pap smear tests, blood tests), drug and concomitant medications (including dispensing fees), and hospitalisation costs.

The resources used were obtained from the effectiveness analysis. The unit costs came from the provincial Ontario Drug Benefit Formularies, the PPS listing of pharmaceutical prices, the Ontario Health Insurance Plan Schedule of Benefits, the 1992 OHIP Schedule of benefits, the Hamilton Health Services Corporation Corporate Costing Model, the Rep-Pharm Inc. Catalogue, prices from local pharmacies, and some published studies. Therefore, the costs were estimated on the basis of actual data. Some resource quantities were reported separately from the costs. Some prices appear to have been used instead of costs. Discounting was not performed, although it was not required since the period considered for the costing was 9 months. The costs reported were standardised 9-month costs per patient. The price year was 1997.

Statistical analysis of costs
The costs were treated stochastically. The average and standard deviations for the different categories of costs considered in the economic evaluation were reported.

Indirect Costs
The indirect costs considered in the economic evaluation were those associated with the time lost from work. The sources of the indirect costs were a questionnaire filled in by patients, and the average Canadian industrial aggregate weekly rate obtained from Statistics Canada. Therefore, the indirect costs were also based on actual data. Discounting was not performed, but it was not necessary since the period considered for the economic evaluation was shorter than 2 years. The resource quantities were reported separately from the costs. The price year was 1997.

Currency
Canadian dollars (Can$).

Sensitivity analysis
One-way sensitivity analyses were performed. The authors considered the costs associated with all of the patients, even those lost to follow-up, for the cost estimation, and the inclusion of time lost from usual activities other than paid work.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

**Cost results**
The total 9-month cost per patient was Can$367 (+/- 120) for the MP group versus Can$360 (+/- 369) for the MPA group.

The results from the sensitivity analyses showed some variations in the cost estimation when all of the patients (even those lost to follow-up) were considered (Can$372 +/- 117 for MP patients versus Can$363 +/- 375 for MPA patients), or when time lost from usual activities (other than paid work) was included (Can$390 +/- 167 for MP patients versus Can$447 +/- 769 for MPA patients).

**Synthesis of costs and benefits**
The estimated benefits and costs were not combined, and a cost-consequences approach was undertaken.

**Authors' conclusions**
Women receiving hormone replacement therapy (HRT) with oestrogen and micronised natural progesterone (MP) may experience improved quality of life compared with those receiving oestrogen and medroxyprogesterone acetate (MPA), because of lower rates of bleeding and improved cognitive measures. The costs of MP compare favourably with those of MPA treatment.

CRD COMMENTARY - Selection of comparators
The authors chose MPA combined with HRT as the comparator because it was the practice traditionally used in their setting to reduce the risk associated with HRT in postmenopausal women. You must decide whether this is a widely used preventive measure in your own setting.

**Validity of estimate of measure of effectiveness**
Since the study was open label, and neither patients nor physicians appear to have been blinded, the effectiveness results might have been subject to assessment and performance bias. Moreover, the authors reported that two of the questionnaires used to assess QoL were generic and they might not have been sensitive enough to detect clinically significant variations in QoL between the study groups. Although the authors did not report evidence that the study sample was representative of the study population, this might have been the case since the patients were recruited from 12 different sites. The basis for the effectiveness analysis appears to have been treatment completers only, which might have led to biased results. Appropriate statistical analyses appear to have been performed for the results of the effectiveness outcomes. It should be highlighted that the authors did not use outcomes that reflected the aim of the preventive treatments considered at analysis, which was the reduction of risks associated with HRT. This was due, probably, to the short follow-up period considered at analysis.

**Validity of estimate of measure of benefit**
No summary measure of benefit was used in the economic analysis. The study was therefore categorised as a cost-consequences analysis.

**Validity of estimate of costs**
The authors adopted a societal perspective, which was the desired perspective to be adopted. All the relevant costs related to this perspective appear to have been included in the economic evaluation. There was a detailed description of the cost estimation, with some resource use reported separately from the costs. This would enhance reflation exercises to other settings. The authors reported that there was large within-group variability in both patient groups, which should be considered when interpreting the results. The costs were treated stochastically and some sensitivity analyses, which considered cost variations, were performed. The price year was reported and this will aid any possible inflation.
exercises. Discounting was not needed since the period considered was shorter than 2 years.

**Other issues**
The authors made some comparisons of their findings with those from other studies in terms of the QoL achieved by postmenopausal women, and stated that there was consistency across the trials. The issue of the generalisability of the results was not specifically addressed. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis.

**Implications of the study**
The authors recommended further research using more specific instruments, such as the Menopause-specific Quality-of-life questionnaire, to further identify differences between MP and MPA as add-on therapies to HRT for postmenopausal women.

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**Other publications of related interest**


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