POSSIBLE DELETION OF MEDROXYPROGESTERONE FROM THE 14TH WHO MODEL LIST OF ESSENTIAL MEDICINES

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Application: To perform a quick review of medroxyprogesterone acetate tablet in order to decide on its deletion from the 14th Edition of the WHO Model List of Essential Medicines. The question is whether there is an urgent case for deletion or whether a fuller systematic review is required.

Background
In 2004, WHO Pharmaceuticals Newsletter reported a Pfizer Canada advice originated by results of new clinical studies that suggest the association between use of medroxyprogesterone acetate suspension for injection and substantial loss in bone mineral density. The publication stressed: “The loss in bone density is greater with increasing duration of treatment. The loss in bone density may not be completely reversible. In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than two years. In women with significant lifestyle and/or medical risk factors for osteoporosis, other methods of contraception should be considered”.

Long-term use of the injectable contraceptive depot medroxyprogesterone acetate (DMPA) is associated with a reduction in bone mineral density (BMD), particularly in the lumbar spine. The cause of DMPA-associated bone loss is not known, but the relative estrogen deficiency induced by DMPA use could be responsible. Actually, in the 13th WHO Model List of Essential Medicines (section 18.7 Progestogens) a medroxyprogesterone acetate tablet was included. It seems that oral use of MPA (commonly associated to estrogens) could have a different consequence in bone metabolism.

Aims of the search: To review the contemporary clinical uses of medroxyprogesterone acetate with evidenced efficacy. To assess the available literature in order to evaluate negative pharmacological effects of oral and injectable formulations on bone mineral density, as well as evaluate clinical outcomes such as fractures. Thus, to weigh the potential medical benefits versus its potential risks.

Methods: A Medline search (“medroxyprogesterone bone effects”) for systematic reviews and randomised controlled trials (RCTs), from 2000 to 2005, yielded no meta-analyses and 36 RCTs. Most of them analysed surrogate endpoints (bone mineral density) or presented secondary analyses (for instance from WHI, HERS and PEPI studies), some associated with MPA injection, other ones with estrogen and progestogen combination for RHT.
Medroxyprogesterone acetate (MPA) is a C21 steroid with selective activity very similar to that of progesterone itself. Oral MPA was widely used with estrogens for postmenopausal hormone replacement until this combination therapy had evidenced more risks than benefits (WHI study). Even though progestogens alone are still used for treating menopausal symptoms (hot flushes). Four RCTs found that progestogens alone reduced vasomotor symptoms compared with placebo and one RCT found no significant difference in vasomotor symptoms between progestogens and placebo. One RCT found no significant difference in vasomotor symptoms between progesterone alone and oestrogen alone. There are no RCTs examining effects of progestogens alone on urogenital symptoms2. The depot form of medroxyprogesterone injection is used as a long-acting progestogen only contraceptive (administered intramuscularly, a 150mg dose provides effective contraception for three months. Other clinical indications are secondary amenorrhoea, uterine bleeding disorders, luteal-phase support to treat infertility, and premature labour. Additionally, MPA have been used as a palliative treatment for metastatic endometrial carcinoma and renal carcinoma.

More recent studies evidencing some benefits
A RCT3 compared a high-dose oral MPA (1 g for 9 months) with tamoxifen as adjuvant hormone therapy for early-stage breast cancer. The relapse-free survival rate at 7 years in the tamoxifen arm was 93%, versus 81% in the MPA arm (P = 0.02).

Another study4 examined the effect of an oral MPA therapy in 12 HIV-infected patients under appropriate nutrition for anabolism, concluding that MPA might improve the efficacy of an oral protein-rich nutritional support in HIV-infected patients.

A Japanese randomized controlled study5 evaluated the efficacy of add-back therapy by every-other-day administration of 0.625 mg conjugated equine estrogen (CEE) and 2.5 mg medroxyprogesterone acetate (MPA) on GnRH agonists (GnRH-a) treatment in Japanese women with symptomatic endometriosis. At the end of treatment, the frequency of genital bleeding revealed no significant differences between the two groups. The add-back group could prevent the loss of bone density.

Another study6 compared oral MPA with tamoxifen as an adjuvant hormonal therapy for two years in the early stages of endometrial cancer. After a median follow-up period of 56 months (range 3–199 months), no differences in the disease-free and overall survival rates were observed with both medicines. Side effects were more frequent and severe in the MPA-group than in the tamoxifen group.

In the 16,608 postmenopausal women participating in WHI trial, who were randomly assigned to a combination of conjugated equine estrogens (0.625 mg per day) plus MPA (2.5 mg per day orally) or placebo, the potential benefits in colorectal cancer were determined by blinded central adjudication. There were 43 invasive colorectal cancers in the hormone group and 72 in the placebo group (hazard ratio: 0.56; 95%CI= 0.38 - 0.81; P=0.003). Then, relatively short-term use
of estrogen plus progestin was associated with a decreased risk of colorectal cancer.

**Potential risks (or benefits?) on calcium metabolism**

**MPA INJECTION**

A randomised clinical trial compared the effect of depot medroxyprogesterone acetate (DMPA) and two types of oral contraceptives (OC) on bone mineral density (BMD) among women 18-33 years of age with those not using hormonal contraception (controls). Users of DMPA experienced a mean **BMD loss** of 2.74% over 12 months compared with controls who sustained a 0.37% loss ($P = 0.01$). Users of OCs generally demonstrated a gain. Observed changes in BMD among DMPA users differed from women who used either type of pill ($P < 0.002$). So, DMPA has an adverse effect on BMD, in comparison with OCs or nonhormonal methods, when used for 12 months.

The same group of investigators performed a new study with similar design, but longer. A comparison among **MPA injection** use, oral contraception (pills) and nonhormonal contraception (controls) measured their effect on bone mineral density after 24 months. Women using DMPA for 24 months experienced, on average, a 5.7% **loss in bone mineral density**, with a 3.2% loss occurring between months 12 and 24. Bonferroni-adjusted pairwise comparisons demonstrated that bone mineral density changes from baseline to 24 months among DMPA users differed significantly from changes experienced by either of the pill groups or the control group. So, loss of bone mineral density associated with DMPA use appears to be linear during the first 2 years of use.

A randomized, double-blind controlled trial undertaken in 38 premenopausal women with a minimum 2 year DMPA use allocated the participants to receive conjugated estrogens (0.625 mg/d orally) and a matching placebo. All continued with regular **DMPA injections** throughout the study (2 years). In the estrogen-treated group, mean lumbar spine BMD increased 1%, whereas in the placebo group it fell 2.6%, over 2 years. These data support the view that the likely cause of DMPA-associated bone loss is estrogen deficiency and demonstrate that it can be arrested by estrogen replacement therapy.

**MPA TABLETS**

A prospective, randomized, double-blind, placebo-controlled, crossover trial compared the effectiveness of administering **MPA (20 mg/d orally)** in either the first (protocol A) or last (protocol B) 12-week period as well as a 6-month course of leuprolide acetate (1 mg/d, SC) on calcium (Ca) metabolism. Estimated Ca balance decreased significantly during GnRH-a treatment alone. The addition of MPA **attenuated the decrease in estimated Ca balance**.

Another study evaluated the effects of low-dose continuous combined **conjugated estrogens and MPA** on several parameters, including bone density in postmenopausal women. Low-dose continuous combined hormone replacement therapy can provide an effective **protection** against the activation of bone turnover and osteoporosis.

One study was undertaken in 2,763 postmenopausal women enrolled for the study HERS to determine if estrogen plus progestin reduces the incidence of
fractures. Women were randomly assigned to either 0.625 mg of conjugated equine estrogens plus **2.5 mg of medroxyprogesterone acetate in 1 tablet daily** (n = 1,380) or placebo (n = 1,383). During 10,554 person years of follow-up, 286 women experienced a fracture: 138 in the treatment group (26.3 per 1,000 person years) and 148 in the placebo group (28.0 per 1,000 person years) [HR= 0.94; 95%CI: 0.8-1.2; \( P = 0.61 \)]. There was no evidence of a reduction in the incidence of fractures in older women not selected for osteoporosis.

In the Women's Health Initiative trial of **estrogen-plus-progestin therapy**, women assigned to active treatment had **fewer fractures**. To test the hypothesis that the relative risk reduction of estrogen plus progestin on fractures differs according to risk factors for fractures, a randomized controlled trial\(^1\) was performed in 16,608 postmenopausal women (WHI participants). Women were randomly assigned to receive conjugated equine estrogen, 0.625 mg/d, plus **medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet** (n = 8,506) or placebo (n = 8,102). Seven hundred thirty-three women (8.6%) in the estrogen-plus-progestin group and 896 women (11.1%) in the placebo group experienced a fracture (HR= 0.76; 95%CI: 0.69-0.83). This study demonstrates that estrogen plus progestin **increases BMD and reduces the risk of fracture** in healthy postmenopausal women.

A double-blind, randomized, placebo-controlled study\(^15\) was conducted over 3 years, to determine whether the positive effects of hormone/estrogen replacement therapy (H/ERT) on postcranial bone density are accompanied by similar positive effects on oral bone mass. A total of 135 postmenopausal women (aged 41-70 years) with no evidence of moderate or severe periodontal disease were randomized to receive daily oral conjugated estrogen (0.625 mg) alone or in combination with **medroxyprogesterone acetate** (0.625 and 2.5 mg, respectively) or placebo. Hormone/estrogen replacement therapy significantly increased **alveolar bone mass** compared with placebo (+1.84% vs. +0.95%; \( P =0.04 \)) and increased **bone mineral density of the proximal femur, neck, and trochanter**, but not the lumbar spine.

A two-year randomized, double-blind, placebo-controlled substudy of the Women's Health, Osteoporosis, Progestin, Estrogen trial\(^1\) investigated the effect of lower doses of equine estrogens with **medroxyprogesterone acetate** on spine and hip BMD, total body bone mineral content (BMC), and biochemical markers of bone turnover in postmenopausal women. At 24 months, women assigned to all of the active treatment groups had significant gains from baseline (\( P<0.001 \)) in spine and hip BMD and total body BMC. These changes were significantly different from those in the placebo group, in which losses of bone mass in spine and total body were evident over the course of the study (\( P<0.001 \)).

The data from the Postmenopausal Estrogen/Progestin Interventions Trial (PEPI) were re-analysed\(^1\) to address the frequency of bone loss among women using postmenopausal hormone replacement therapy. During the first 12 months, **hormone users lost BMD** (-3% per year) at the lumbar spine (1.5%) and the total hip (2.3%); during months 12 to 36, only 0.6% and 0.4% of treated women lost spinal and total hip BMD to this degree, respectively. With 95.0% certainty, corresponding to an approximate loss of -2.5% at the spine and hip, 31.3% and 11.7% of placebo-adherent women lost spinal BMD in the first 12 and last 24 months, respectively. Parallel figures for the hip were 32.3% and 7.9%,
respectively. So, bone loss while taking postmenopausal hormones is rare, and bone loss among untreated women is far from universal.

**Conclusion**
The effects on bone mineral density and incidence of fractures are different under use of DMPA and oral MPA. Oral MPA is commonly used in association with estrogens. These estrogens seem to protect against bone loss. More randomized studies with a stronger experimental design (hard clinical outcomes instead of surrogate outcomes; primary analyses instead of sub-analyses) are needed to clarify the effect of MPA therapy on fracture risk among women with and without osteoporosis.

**Recommendation**
Based on contemporary evidences, MPA tablets could still be included in the 14th EDL. Further studies should be carried out to modify this decision or not.

**References**


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