Editorial

›› Andrew M. Kaunitz, MD, and David A. Grimes, MD

AN APPEAL TO THE FDA

Remove the black-box warning for depot medroxyprogesterone acetate!

Guidance about DMPA in the black box isn't evidence-based, and the warning deprives women of long-term use of this safe and effective contraceptive

The Food and Drug Administration (FDA) should remove the black-box warning regarding skeletal health that the agency inserted into labeling for the injectable contraceptive depot medroxyprogesterone acetate (DMPA; Depo-Provera) in 2004. The black box **1)** indicates that use of DMPA for longer than 2 years may reduce peak bone mass and place a woman at increased risk of osteoporotic fracture and **2)** suggests that ObGyns order bone-density assessment in women who use DMPA long-term.

This warning is not based on scientific evidence. By depriving women of long-term use of a safe, effective contraceptive, the black-box warning damages women's health and the public health.

Dr. Kaunitz is Professor and Associate Chairman, Department of Obstetrics and Gynecology, University of Florida College of Medicine–Jacksonville. He serves on the OBG Management Board of Editors.

Dr. Grimes is Clinical Professor, Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, NC, and a Distinguished Scientist at FHI 360.

Dr. Kaunitz receives grant or research support from Bayer, Agile, Noven, Teva, and Medical Diagnostic Laboratories, is a consultant to Bayer, Merck, and Teva, and owns stock in Becton Dickinson.

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The scientific argument for removing the black box

Although DMPA does cause reduced ovarian estradiol production, with a decline in bone mineral density (BMD), complete recovery of BMD occurs approximately 1 or 2 years after discontinuation in adolescent girls[1,2] and 3 years after discontinuation in adult women.[3,4] BMD trends observed with the use of DMPA parallel those associated with another normal but hypoestrogenic state: breastfeeding. Although BMD declines noted in nursing mothers are similar to those associated with DMPA, breastfeeding one or more infants has not been reported to increase the risk of subsequent osteoporotic fractures.[5] The FDA does not warn women against breastfeeding for fear of a theoretical negative impact on skeletal health.

BMD can help predict a risk of osteoporotic fracture in menopausal women, but it is not a valid surrogate endpoint for fracture in women of reproductive age.[6] **Basing clinical recommendations on invalid surrogate endpoints can cause harm.**[7-9] Clinical recommendations, including those from the FDA, should be based on sound studies that address important clinical outcomes.

No convincing evidence links the use of DMPA for contraception to fracture. Studies of menopausal women have not suggested that prior use of DMPA increased their risk of osteoporosis.[10-12] Two recently published case-control studies, one using a Danish National Patient Registry[13] and one based on the United Kingdom Family Practice Research database,[14] have demonstrated that DMPA is associated with an elevated risk of fracture in reproductive-age women. However, a cohort analysis using the same British Family Practice database clarifies that the elevated fracture risk observed in women using DMPA occurred before initiation of injectable contraception and was not the result of DMPA use.[15]

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Instant Poll

Has the FDA's warning about DMPA had a chilling effect?

Does the black-box warning prevent you from prescribing DMPA? Or does it alter your approach to using it? How? Tell us, via e-mail at obg@qhc.com. Include your name and city and state. We'll publish responses in an upcoming issue.

A clearly harmful effect on women's health

The black-box warning for DMPA has caused clinicians and women to reduce use of this effective method of contraception. The 2008 National Survey of Family Growth shows that the overall percentage of US women, 15 to 44 years of age, who now use DMPA has declined—from 3.3% in 2002 to 2.0% in 2006 to 2008.[16]

In fact, a survey of ObGyns in Florida found that **1)** almost one half of respondents place a time limit on duration of DMPA and **2)** two thirds of those respondents base that restriction on the black-box warning.[17] Restricting the use of DMPA can lead to more unintended pregnancies and induced abortions.

In the Florida survey, two thirds of respondents order BMD assessment in women who use DMPA, with 58% of those physicians who do so attributing their decision to, again, the black-box warning. Indeed, more than 5% of respondents reported that they selectively prescribe bisphosphonates to women of reproductive age who use DMPA—an expensive practice that is not evidence-based and is potentially dangerous.

FDA guidance is far out of step

The black-box warning for DMPA is not in accord with the guidance provided major medical and public health organizations. The World Health Organization,[6] the American College of Obstetricians and Gynecologists,[18] the Society for Adolescent Medicine,[19] and the Society of Obstetrics and Gynecology of Canada,[20] have all stated that skeletal health concerns shouldn't restrict the use of DMPA, including the duration of use.

In the US Medical Eligibility Criteria for contraceptive use, the Centers for Disease Control and Prevention declared that use of DMPA is Category 1 (no restriction on use) in women 18 to 45 years of age and Category 2 (advantages of the method generally outweigh theoretical or proven risks) in younger women.[21] The FDA's black-box warning is therefore inconsistent with the recommendation of its sister agency.

An opportunity to improve the health of women

The FDA appropriately takes action when a pharmaceutical company mislabels a product or promotes it in a way that isn't based on sound evidence. Shouldn't the FDA apply the same scientific standards to itself? Guidance included in DMPA's black box is not evidence-based—and that reduces use of DMPA in US women and increases the potential for harm. Removing the black box would encourage use of this convenient, effective, and safe contraceptive[22] and, in turn, improve the health of women and their families.

Again: We urge the FDA to promptly remove the black-box warning from labeling for DMPA.

Do you agree? We want to hear your opinion: Write to us in care of The Editors, at obg@qhc.com!

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NEWS FROM THE MEDICAL LITERATURE

Long-acting reversible contraceptives are safe, effective for most women, study shows

But most use other methods because of lack of knowledge and cost concerns

Long-acting reversible contraceptives (LARC) are safe and effective for almost all women of reproductive age, according to an ACOG practice bulletin published in the July issue of *Obstetrics & Gynecology*.

Eve Espey, MD, MPH, and Rameet H. Singh, MD, MPH, from ACOG in Washington, DC, and colleagues compiled the latest recommendations on LARC use. The recommendations identify candidates for LARCs and help obstetricians and gynecologists manage LARC-related clinical issues.

The investigators reported that the LARC methods currently available have few contraindications, and that most women are eligible to use them. Intrauterine devices (IUDs) are suitable for women with a previous ectopic pregnancy and for women immediately after abortion or miscarriage. Routine antibiotic prophylaxis is not recommended before IUD insertion.

Copper IUD inserted up to 5 days after unprotected intercourse is the most effective method of postcoital contraception. The copper IUD can be used and remains effective for up to 10 continuous years. The levonorgestrel IUD may be effective for up to 7 years.

IUD complications are rare and include expulsion, method failure, and perforation. Implants can be safely inserted at any time after childbirth in non-breastfeeding women, or after 4 weeks for breastfeeding mothers. All LARC methods are safe for nulliparous women and adolescents.

The use of IUDs increased from 1.3% to 5.5% from 2002 to 2006-2008. Despite the benefits of LARCs, the majority of women choose other birth control methods, probably due to lack of knowledge about LARCs and cost concerns.

"LARC methods are the best tool we have to fight against unintended pregnancies, which currently account for 49% of US pregnancies each year," Espey said in a statement.

Read more: http://journals.lww.com/greenjournal/Citation/2011/07000/Practice_Bulletin_No__121__Long_Acting_Reversible.31.aspx