

Commentary

Surrogate markers, emboldened and boxed warnings,
and an expanding culture of misinformation:
Evidence-based clinical science should guide FDA
decision making about product labeling

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As health care providers, we are committed to the best possible patient care. The ability to provide that level of care to our patients is based in no small part on the availability of accurate clinical information about drug and device usage that reflects actual clinical issues of importance to the clinical decision-making process. The dissemination of inaccurate, misleading or nonclinically relevant information, regardless of the intentions or reasons, can lead to innuendo, presumption and conjecture concerning clinical outcomes and do harm to the very patients such information is meant to protect.

The development of safe and effective contraceptive options for women is the direct result of advances in laboratory-based research, which has provided an important foundation for the development of an evidence-based approach to contraceptive management. This marriage of

laboratory and clinical investigation has not only served to better delineate pathophysiological processes but also has expanded our understanding of the mechanisms of therapeutic actions. However, when laboratory-based studies alone are used to explain clinical outcomes, prediction of clinical outcomes can be corrupted by a lack of clinical information and replaced by a process replete with unsupported assumptions, premature declarations and unfounded concern about the safety and effectiveness of therapeutic interventions. Such a disingenuous application of high-quality laboratory investigation is unfortunately now more commonly used to predict clinical risks of contraceptive use. In several instances, warnings and specific language have been included in the package inserts of contraceptives based on nonclinical studies.

Nonclinically based outcome variables, or surrogate markers, are studied to ostensibly better understand the pathophysiological basis of clinical outcomes associated with the use of particular drugs or therapeutic interventions. However, when such surrogate markers are studied to

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predict clinical outcomes in the absence of data assessing clinical outcomes, they may lead to unsubstantiated clinical predictions. An example of a surrogate marker and its inappropriate application for predicting clinical outcomes is the measurement of the size and number of ovarian follicles among users of oral contraceptive pills. Those pills associated with more numerous and larger ovarian follicles are “assumed” to be less potent and thus place a woman at a potential increased risk for pregnancy while using that pill. However, the presence or absence of follicles has never been actually correlated with contraceptive pill efficacy. Only a direct determination of pregnancy rates among users of specific contraceptive methods can provide meaningful information about the actual effectiveness of a given contraceptive.

Grimes and Schultz [1] penned a commentary in the May 2005 edition of *Obstetrics and Gynecology* concerning the use of surrogate markers for predicting clinical outcomes. Regardless of the reasons for using surrogate markers (faster results, fewer subjects needed, etc.), Grimes and Schulz called for researchers to avoid assessing them in clinical trials unless they have been shown to be valid predictors of clinical outcomes. The authors presented several examples in their commentary where studies of nonclinical outcomes that could in theory be linked to specific clinical events actually predicted an outcome that markedly differed from results of later trials with clinical outcomes. Grimes and Schulz state that although the study of such surrogate markers has a “seductive appeal” in the potential ability of such nonclinical markers to predict clinical outcomes, they found that such studies frequently waste resources, provide ambiguous information, do not measure what one wants to study and frequently lead to patient harm [1].

In the past, the language of the package insert and all emboldened and boxed warnings communicated well-defined clinical risks, such as the increased risk of adverse cardiovascular events in women who smoke and use estrogen-containing oral contraceptives after the age of 35. Unfortunately, the language and warnings of package inserts have increasingly incorporated surrogate marker studies to arrive at pronouncements of clinical risk. For example, a black box warning in the package insert of Depo-Provera CI warns that the use of the product will diminish the calcium stored in bones and that this could cause an increased risk of fracture. Have studies consistently shown reduced bone mineral density among women using Depo-Provera CI? Yes, studies of a wide spectrum of women using Depo-Provera CI have consistently demonstrated reduced bone mineral density measurements among Depo-Provera CI users. But has there been any study that has demonstrated an increased risk of fracture among any women (pre- or postmenopausal) using Depo-Provera CI? The answer is no. The measurement of bone mineral density in reproductive-age women is a surrogate marker with no known clinical relevance. Moreover, the suggestion that women should consider using an alternative method after 2 years of Depo-

Provera CI use is not based on scientific or clinical evidence and may cause clinicians to inappropriately switch their patients to less effective contraceptives. Such changes will place women at increased risk for unintended pregnancy and induced abortion [2].

Finally, the language of the Depo-Provera package insert also suggests that clinicians “test the bones” of women who wish to continue this method for more than 2 years. As bone densitometry has been shown to be ineffective and inappropriate for assessing fracture risk in the vast majority of premenopausal women, what test is being suggested?

Another package insert that fails to provide accurate or relevant clinical information is that of Yasmin®, a combination contraceptive pill containing 30 µg ethinyl estradiol and 3 mg drospirenone. Drospirenone is a novel progestin with anti-aldosterone activity that is related in structure and function to spironolactone. Although there is a theoretical risk of hyperkalemia in women who use Yasmin, ongoing experience with millions of months of exposure to Yasmin in women worldwide has failed to demonstrate an increased risk of hyperkalemia, even among women with a higher baseline risk for it. Indeed, a recent study of a menopausal formulation containing a 3-mg daily dose of drospirenone found no adverse impact on potassium levels compared to placebo, even in those women using ACE inhibitors or angiotensin II receptor antagonists [3].

Despite the accumulation of increasing data concerning serum potassium levels and clinical outcomes in Yasmin users showing no increased risk of hyperkalemia with routine use [4], the emboldened warning concerning hyperkalemia and Yasmin use continues to occupy a prominent position in the package insert. In addition, the conditions that would increase the likelihood of hyperkalemia among Yasmin users are mostly conditions that would preclude the use of this or any other oral contraceptive.

Unfortunately, this trend in drug warnings continues with the recently added language and new warnings incorporated into the package insert of the transdermal patch Ortho-Evra®. The new emboldened warning for Ortho-Evra is not based on studies of clinical outcomes, but rather nonclinical pharmacokinetic studies that have found that women who use the transdermal contraceptive patch have a greater overall exposure (approximately 60%) to ethinyl estradiol than those women who use a conventional oral contraceptive with 35 µg ethinyl estradiol. A recent study by van den Heuvel et al. [5] compared the exposure to ethinyl estradiol among users of the transdermal patch, the vaginal ring (Nuva Ring) and an oral contraceptive containing 30 µg ethinyl estradiol and 150 µg levonorgestrel (Microgynon), and found that although women using the oral contraceptive had higher peak serum levels of estradiol than the other two agents, users of the transdermal patch had an overall higher exposure to estrogen (AUC or “area under the curve”) than users of the other two formulations. The authors state that a lower exposure to ethinyl estradiol is desirable because of reduced “estrogen-related side effects. . .”

However, the term “estrogen exposure” that is used in the above study is actually a surrogate marker that the authors are using to predict the risk of estrogen-related adverse events with these products. No epidemiological data exist that demonstrate that the use of Ortho-Evra® results in higher rates of estrogen-associated adverse outcomes such as thromboembolic events. It is essential to have epidemiological information derived from rigorously performed clinical trials to make such clinical predictions. In the case of the three agents studied, the different doses and delivery systems likely are important for determination in the actual contraceptive effectiveness and safety. To this end, what if the peak concentration of ethinyl estradiol associated with the use of a contraceptive (C_{max}) turns out to be the most important predictor of adverse outcomes instead of the area under the curve? Only epidemiological data will provide an accurate comparison of clinical risks between transdermal and other contraceptives. In fact, the new language in the Ortho-Evra® package insert specifically states that it is not known whether the pharmacokinetic differences are associated with an increase in the risk of serious adverse events in women using the contraceptive patch compared with women using oral contraceptives containing 35 µg ethinyl estradiol. If the package insert is meant to provide clinical warning concerning the use of a particular drug, this statement, which appears in various forms throughout the package insert, truly defies logic.

Women who use Ortho-Evra®, or any other estrogen-containing contraceptives, have an increased risk of developing a thrombotic event. However, a greater increase in the risk of such events compared to users of combination oral contraception has thus far not been determined to be present in the more than 5 million women who have used Ortho-Evra®. Unfortunately, the assumption that will be made by many who read the new package insert language, the van den Heuvel et al. study and the resulting press releases is that the transdermal patch is associated with an even higher rate of adverse events because the “area under the (estrogen) curve” was greater than that observed with vaginal ring or oral contraceptive use. Indeed, a recent article in the *Wall Street Journal* [6] reports that numerous physicians and clinics are actually encouraging women to consider other contraceptive options or to discontinue the use of the patch altogether. Why would clinicians do this without any clinical evidence of an increased risk of adverse events? And why would an organization or agency communicate such information knowing full well the likely response of many women’s health care providers?

There are no answers to these rhetorical questions, but there is one fundamental fact that must be in the forefront of contraceptive study and practice: without epidemiological data to support a clinical correlation, outcomes from surrogate marker studies can result in poor clinical practice. The irony is that the women who should be the beneficiaries of these package inserts changes actually become the unknowing victims of poor clinical practice.

Recommendations made in the absence of data on clinical outcomes may lead to choices that increase the likelihood of unintended pregnancy.

In addition to the potential harm of using surrogate markers to develop warning statements concerning the risks associated with the patch or any other contraceptive option, another potential adverse outcome of continuing this practice is the eventual loss of confidence in our regulatory agencies and professional organizations to provide accurate information for professionals and consumers alike. The continuing inappropriate use of nonclinical studies to formulate warnings about the safety of contraceptives and other drugs may result in an interpretation to disregard these warnings by professionals and the public that will obscure real clinical risk associated with a particular drug or device. The true risks may be obscured by the continuing barrage of innuendo and pseudo-science on the package inserts of many drugs and devices.

Clinicians must demand that the package insert be an up-to-date and updatable document of relevant and useful clinical information concerning specific drugs or devices. Clinicians should reject labeling and usage guidance that have been haphazardly compiled from irrelevant studies and recycled from earlier package inserts of similar products that are not independently analyzed for scientific accuracy. It is well past the time for the incorporation of responsible clinical and scientific processes from the very organizations charged with upholding such practices as they pertain to the health and well-being of our society. In this regard, we must encourage and support the funding and performance of clinical studies that assess not only the short-term outcomes needed for drug approval but also long-term clinical outcomes in women who use contraceptives for short or long periods of time. Only then will clinicians have the requisite information to help women make truly informed decisions concerning contraceptive choices and other therapeutic interventions. These decisions will have a profound and lasting impact on their lives and their families.

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