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CLINICAL REVIEW

Drospirenone: Retrospective of a New Drug and Optimistic Promises

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Drospirenone is a synthetic progestogen compound with unique anti-mineralocorticoid and anti-androgenic activity. Introduced in 1994 in a study funded by Schering, its pharmacology most resembled that of natural progesterone (P4) when compared to other progestins of that era.¹ It was later sold as a popular combination oral contraceptives under the brand names, Yasmin and Yaz.

In 1982, a novel drug, chemically related to spironolactone, was analyzed therapeutically. A newly identified metabolite was later named drospirenone and was noted to have 5 times the anti-aldosterone activity of spironolactone.² Reductions in blood pressure and serum testosterone levels due to drospirenone were twice as large compared to spironolactone. This property, along with its progestin effects, introduced a potentially new therapeutic arm to drospirenone beyond contraception. Early on, researchers in 1995 suggested that drospirenone might be used to negate the undesirable effects of combined oral contraceptives and hormone replacement therapies.³ It could potentially be used to treat “acne and seborrhea,” “result in reduced weight gain,” and ameliorate “other side-effects possibly related to estrogen-induced water retention, such as breast tension, nausea and headache.”

The progestogen components in combination oral contraceptives (COC) have great variability and have been altered synthetically in an attempt to decrease side effects and increase compliance. Since the development and marketing of COC in 1957, the type of progestogen used within COC has varied. Progestogens (both natural progesterone and synthetic progestins) normally produce a wide array of effects including androgenic, anti-androgenic, and anti-mineralocorticoid activity. Androgenic side effects in women long have been assumed to include acne and hirsutism. Common hyperandrogenic states like polycystic ovarian syndrome are typically associated with these conditions. The estrogen component, most commonly ethinyl estradiol, in COC has stayed virtually the same over the last few decades except for a dramatic decrease in dosage. In the first COC marketed, the dose of ethinyl estradiol was 50 mcg; since then, dosages have gradually been reduced to doses less than 15 mcg.

Overall, progestins have undergone four significant developments and are often categorized primarily on the year of their release: first generation oral progestins (e.g., norethindrone), then second generation progestins (e.g., levonorgestrel and norgestrel), and third generation progestins (e.g., desogestrel and norgestimate). Third generation progestins were developed with significantly less androgenic activity than either first or second generation progestins.⁴ The

later addition of novel progestins with both anti-mineralocorticoid and anti-androgenic activity created a new, unclassified group that includes drospirenone. (Though some call this unclassified group “fourth generation progestins,” it is not universally accepted.)

Yasmin and Yaz, comprised of ethinyl estradiol and drospirenone, were released in Europe in 2000. In the USA, Yasmin received FDA approval in May 2001; Yaz received approval in March 2006. While both had FDA approval for the prevention of pregnancy, Yaz had added secondary indications for the treatment of premenstrual dysphoric disorder (PMDD) and moderate acne vulgaris in women.⁵ Yaz was unique and marked a new milestone in contraception; it was the first COC that was FDA approved for purposes beyond that of contraception. Prior to this, most COC were prescribed for such indication but without the necessary FDA approval that assured insurance coverage.

Two controversies later arose. The first concerned the risk of thrombotic events associated with Yasmin noted in early pre-marketing studies and, second, in regards to direct-to-consumer advertising for Yaz. The general relationship between all COC and increased venous thrombotic events (VTE) had been recognized soon after the introduction of COC into general use.⁶ As far back as 1968, it was also noted that age less than 35, duration of use greater than 3 months, and decreased estrogen dose were all associated with decreased risk of VTE. The safety of progestogen-only preparations was already noted and found to present VTE risk comparable to those of COC non-users. As the dose of estrogen decreased from 50 mcg to 30 mcg, the risk of VTE decreased accordingly but, as doses decreased further, there was no consistent and additional decrease in risk. As comparisons between new progestins and their predecessors (first and second generation) revealed an unexpected increase in thrombotic risk, despite factoring in other risk factors, attention turned to the interaction of progestins within COC and the subsequent risk of thrombotic events that was created. Newer progestins, such as desogestrel and drospirenone, were confirmed to have an increased risk of venous thrombosis, even when the dose of estrogen, patient age, and the duration of use was controlled.⁷ This factor did not stop drospirenone from achieving outstanding success as an ingredient in the popular and well-known COC, Yasmin and Yaz.

Despite these earlier studies, when introduced to the United Kingdom in 2002, it was noted by the manufacturer (Bayer/Schering) that the comparative effect on VTE between Yasmin and other COC was unknown.⁸ By 2004, a UK study related to Yasmin and prescription-event monitoring (PEM)

reported the increased occurrence of venous thrombosis and pulmonary embolism compared to other COC.⁹ Additional post-marketing studies of Yasmin had variable results. Manufacturer sponsored studies (US-based i3 Ingenix¹⁰ [2007] and the European based EURAS¹¹ [2007]) showed comparable thrombotic risk to the second generation COC containing levonorgestrel. However, an increased risk of both arterial and venous embolism was noted in an independent FDA-funded study¹² that compared Yasmin to similar low-dose estrogen COC. In 2010, the FDA required a black box warning to be placed on Yasmin stating the suspected increase in risk.

Yaz has a lower ethinyl estradiol dose of 20 mcg and was not included in the studies mentioned previously. Yaz was the first COC approved for multiple uses other than contraception. Yaz generated increasing US sales from \$262 million the year prior to \$616 million in 2008, thanks in part to aggressive marketing to consumers. Two 60-second ads that aired in 2008 were specifically targeted by the FDA. The FDA's Division of Drug Marketing reviewed the presentations critically and subsequently presented a warning letter to Bayer Healthcare Pharmaceuticals in October 2008.¹³ The ads were singled out for being visually distracting, substantially downplaying potential complications and overstating the role of Yaz in treating acne and mood disorders. In particular, the use of energetic music, vivid animation, and images of women attacking their symptoms were felt to be misleading to consumers. Symptoms visually demonstrated included the following: "IRRITABILITY," "MOODINESS," "FEELING ANXIOUS," "BLOATING," "FATIGUE," "MUSCLE ACHES," "HEADACHES," "INCREASED APPETITE," and "ACNE." These were all broad generalizations that could be misconstrued by consumers to include treatment for PMS, weight gain, and acne of all types; neither ad clearly relayed its specific FDA indications (PMDD and moderate acne). Furthermore, the agency criticized the underwhelming audio presentation of the serious risk disclosures during both commercials, misleading consumers as to the safety of Yaz. Bayer later withdrew these ads. Under an agreement with the FDA and several state attorney generals, Bayer was required to submit new ad disclaimers that clearly stated the correct indications for using Yaz; in addition, the new ads would effectively state the known side effects. A 2009 *New York Times* article referenced the controversy regarding Yaz in its title, "A Birth Control Pill that Promised Too Much."¹⁴ The article addresses concerns that the FDA with a "staff of 52 people cannot keep up with the tens of thousands of marketing and advertising items produced annually by drug manufacturers."

The choice of COC among individual women is complex; it has been shown to reflect non-contraceptive benefits (treatment of acne, menstrual irregularities, dysmenorrhea, premenstrual syndrome, etc.);¹⁵ pregnancy prevention; patient's age, race, risk factors, insurance-status; and physician characteristics.^{16,17} In the case of drospirenone, Yaz, and Yasmin, decision making was split between patient, physician, and marketing forces. The role of direct-to-consumer advertisement as well as physician counseling in patient choice has not been clearly delineated in any study so far. Given the limited manpower of the FDA, physicians in the United States must approach the discussion of contraception, and perhaps all pharmaceuticals, with a skeptic's

eye, being sure to address the needs of the patient against the prevailing populist tide.

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