New low-dose, extended-cycle pills with levonorgestrel and ethinyl estradiol: an evolutionary step in birth control

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Aim: To review milestones in development of oral contraceptive pills since their introduction in the US 50 years ago in order to better understand how a new formulation with low-dose estrogen in an extended-cycle pattern fits into the evolution of birth control pills.

Methods: This is a review of trends in the development of various birth controls pills and includes data from phase III clinical trials for this new formulation.

Results: The first birth control pill was a very high-dose monophasic formulation with the prodrug estrogen mestranol and a first-generation progestin. Over the decades, the doses of hormones have been markedly reduced, and a new estrogen and several different progestins were developed and used in different dosing patterns. The final element to undergo change was the 7-day pill-free interval. Many of these same changes have been made in the development of extended-cycle pill formulation.

Conclusion: The newest extended-cycle oral contraceptive formulation with 84 active pills, each containing 20 µg ethinyl estradiol and 100 µg levonorgestrel, represents an important evolution in birth control that incorporates lower doses of estrogen (to reduce side effects and possibly reduce risk of thrombosis), fewer scheduled bleeding episodes (to meet women’s desires for fewer and shorter menses) and the use of low-dose estrogen in place of placebo pills (to reduce the number of days of unscheduled spotting and bleeding). Hopefully, this unique formation will motivate women to be more successful contraceptors.

Keywords: extended-cycle oral contraceptives, low-dose extended-cycle pills, Lo Seasonique

Introduction

The recent introduction of a low-dose, extended-cycle oral contraceptive pill with levonorgestrel (LNG) and ethinyl estradiol (EE) represents an important evolutionary step in contraception, reflecting the importance of reducing the hormone levels of the active pills while eliminating hormone-free intervals entirely.

To appreciate each of these advances, it is necessary to review briefly the history of oral contraceptives (OCs). Such a review is especially relevant as we are celebrating the 50th year of the introduction of birth control pill in the United States. Despite 50 years of pill and the availability of many effective contraceptives, nearly half of US pregnancies are still unintended. In typical use, the first-year failure rate of OCs is 8.4%.1 It has been estimated that one million pill users get pregnant each year, usually as a result of inconsistent pill use.2,3 In order to help women achieve the full contraceptive potential offered by pills with correct and consistent use, several innovative strategies have been employed over the years. Lower doses of estrogen have been used to reduce side effects such as breast tenderness and nausea, but those lower-dose formulations
increased the risk of unscheduled spotting and bleeding, and early discontinuation. At the same time, lower-dose pills may not suppress ovarian activity as well as higher-dose OCs. The pill-free interval has been shortened in some formulations and eliminated in others to reduce ovarian folliculogenesis during the pill-free interval and, thereby, decrease spotting and bleeding and the risk of escape ovulation. Noncontraceptive benefits have been popularized to incentivize women to use pills more consistently.

The first formulation approved for contraception (Enovid-10®) was a monophasic pill with 21 active pills and 7 placebo pills. Each active pill contained 150 μg mestranol and 9.85 mg norethynodrel. By today’s standards, this is an enormous amount of progestin; if a woman were to swallow all at once every one of the 21 active pills in a pack of a modern pills (eg, Ovcon 35®; Warner Chilcott, Rockaway, NJ, USA), she would get less progestin than women consumed every day with one tablet of Enovid.

While these high doses of sex steroids caused considerable side effects, women took these early birth control pills with enthusiasm because the pills provided women for the first time in history an opportunity to reliably control their fertility and the timing of their bleeding. The importance of this second feature has not received adequate recognition. Rather than having to rearrange their lives at the time of their menses, women on the pill could plan their lives around predictable (and usually lighter and less painful) scheduled bleeding episodes. Both of these features contributed significantly to the ability of women to compete more successfully in the job market.

The use of placebo pills to induce monthly scheduled bleeding (which the user would recognize as the menses) was essential to the original acceptance of the pill. Some have suggested that the placebo pills were included for political reasons – to obtain papal approval of the pill – but at the time of the pill introduction there were important patient-based reasons for the placebo pills. Many of the side effects that women endured with the early, high-dose pills mimicked pregnancy. Nausea and vomiting were frequent problems. Breast tenderness and abdominal bloating were also common. Melasma was rampant. In the face of all these symptoms, it was important that women using the pill be reassured that they were not pregnant. The only pregnancy test available in 1960 was not suitable because it required 6 weeks of amenorrhea before it could detect pregnancy and took 2 to 3 days to perform. However, periodic bleeding induced by placebo pills provided users with timely reassurance that they were not pregnant and could confidently start use of another cycle of pills. The bleeding also calmed women’s concerns about possible adverse impacts the pill might have on their reproductive system and long-term fertility.

The choice of the number of placebo pills (7) was more scientifically based. Even though the so-called “first generation” progestins (norethindrone) had relatively short half-lives (4 to 8 hours), circulating levels of progestin were so high that it often took 4 to 5 days for those levels to drop sufficiently to permit endometrial sloughing. To allow for variations in metabolic clearance rates so that virtually women would start bleeding, 7 days of placebo were used.

**New hormones and lower doses for birth control pills**

Early in the 1960s, the medical hazards posed by high-dose estrogen (hypertension and venous and arterial thromboembolism) became apparent. Although these serious events were relatively rare, they developed more frequently in vulnerable women. In response to these problems, restrictions were placed on women who were candidates for oral contraceptive use and the doses of estrogen were reduced. Women with histories of deep venous thrombosis, myocardial infarction, stroke or hypertension were no longer offered pills. The dose of mestranol was reduced first to 100 μg, then to 80 μg, and later to 50 μg. The doses of progestin were decreased to balance the estrogen doses.

With each reduction in the estrogen (mestranol), a measurable decrease was observed in venous thrombosis (and pulmonary embolism). Mestranol is a prodrug and requires hepatic cleavage to convert it into its active form – ethinyl estradiol. The conversion rate varies between individuals, but 50 μg mestranol is generally equivalent to 35 to 40 μg EE. EE replaced mestranol in most of the 50 μg formulations and in all the sub-50 pills.

However, as the sex steroids in the active pills were reduced, women started to complain more frequently about unscheduled spotting and bleeding. In order to minimize that problem, longer-acting progestins were developed. Norgestrel and LNG (the biologically active dl-norgestrel form) significantly decreased the problem of what was called at that time “breakthrough bleeding”. Paired with 30 μg EE, these new formulations were very popular because they also reduced many of the estrogen-related side effects, most notably melasma. While LNG provided significant cycle control in both its monophasic and multiphasic formulations, some users were sensitive to its relatively high androgenicity and complained about acne and hirsutism. Clinicians also voiced concerns about possible adverse metabolic impacts.
of the relatively androgenic compounds on lipids, especially HDL-C and LDL-C.16

In response to those concerns, long-acting progestins with less androgenic impact (gestodene, norgestimate and desogestrel) were developed. More recently, an antiandrogenic progestin derived from 17β-spirolactone has been marketed. These newer progestins have added on-label noncontraceptive benefits that have been appreciated by users. The first approved formulation for treatment of mild to moderate acne was a multiphasic norgestimate pill (Ortho Tri-Cyclen®; Ortho-McNeil-Janssen Pharmaceuticals, Raritan, NJ, USA). A low-dose drospirenone-containing formulation (Yaz®; Bayer HealthCare, Tarrytown, NY, USA) is Food and Drug Administration (FDA) approved for two noncontraceptive applications: the treatment of mild to moderate acne and the treatment of premenstrual dysphoric disorder (PMDD) in women using OCs for birth control. These new applications increased both provider and user enthusiasm for their use.

The newer, less androgenic progestins allowed fuller expression of the estrogen on hepatic production of SHBG (pivotal to success in treatment of acne). As a result, there were concerns that hepatic production of thrombotic and antithrombotic factors would also be altered by these less androgenic formulations and result in increased risk for thromboembolism. Large epidemiologic studies in the 1990s suggested that the LNG compounds may be associated with lower incidence of venous thromboembolic (VTE) events (deep venous thrombosis and pulmonary embolism) than the less androgenic progestin formulations.17–20 Unfortunately, issues of selection bias and recency of use may have compromised the strength of those early findings. However, many manufacturers of third-generation progestins in the US amended their product labeling to allow for the possibility higher risks of VTE with pills with these progestins.

More recently, several very large epidemiologic studies with a variety of designs have re-examined this issue. Two large-scale studies required by the FDA for post-marketing surveillance of drospirenone-containing pills. One study provided prospective information on women in Europe (the EURAS study).21 In the US a claims-based study compared VTE risk using an array of different progestins and different doses of estrogen. Those studies found that, when adjusted for estrogen dose and known risk factors for thrombosis (such as age, obesity), there were no significant differences among the rates of VTE, although one study found that the LNG formulations did have lower risk of VTE.22 All formulations had much lower VTE risk than pregnancy. Two recent claims based and registry based studies from Europe have added additional, but less accurate information. The authors of those studies concluded that LNG pills posed slightly less DVT risk than drospirenone or third-generation progestins, but more importantly, they also demonstrated that pills with 20 µg EE had lower risk of thrombosis than did 30 to 40 µg formulations.23,24

Changes in the placebo pills

As early as the 1970s, clinicians found that birth control pills could help arrest the growth of endometriotic implants by inducing a “pseudo pregnancy” state. When clinicians eliminated the placebo pills for months at a time, pills also provided relief from the severe dysmenorrhea which women with endometriosis suffered.25,26 The most common pills used for this indication contained norgestrel/LNG, because the long-half of this progestin limited unscheduled bleeding and spotting and its potency induced marked therapeutic changes in the endometriotic implants. Later, uninterrupted pill use was recommended to help women who suffered from menstrual migraines.27,28 Episodically, women extended their pill cycles to prevent bleeding at inopportune times (honeymoons, travel dates, religious holidays). The first product to formally change the standard 7 placebo pills, was a low-dose desogestrel-containing formulation, (Mircette®; Duramed Pharmaceuticals, Pomona, NY, USA) which replaced the last 5 placebo pills with 5 tablets each with 10 µg EE. This substitution was made to try to reduce “estrogen withdrawal” symptoms during the scheduled bleeding episodes and as well as to decrease unscheduled spotting/bleeding in the subsequent cycle.

A more sustained change in the placebo pills was prompted by landmark research conducted by Sulak et al.29 These investigators persuaded women who wanted to discontinue their OCs because of unpleasant side effects to continue using the pills and to chronicle the timing those problems in the cycle. If the problems had been randomly distributed, the prevalence of problems would have been 3 times greater during the 3 weeks of active pill use compared to the 1 week of placebo use. If the side effects were due to the hormones of the birth control pills, the frequency of problems during active pill taking days would be even higher. However, distribution of complaints over the cycle was found to be exactly opposite. Women suffered problems such as headache, pelvic pain and cramping, breast tenderness, bloating and swelling and used pain relievers most often during the placebo-pill days (see Table 1). In a follow-up study, Sulak et al found that 74% women with pill-free interval problems (such as migraine, dysmenorrhea, heavy bleeding, and acne) were stabilized on extended-cycle regimens.30
Willis et al demonstrated the importance of shortening (or eliminating) the pill free interval to control ovarian activity with low-dose pill formulations. Gonadotropins (LH and FSH) and ovarian follicular activity (measured by estradiol and inhibin B levels) were found to increase greatly after only 3 to 4 days of placebo use. However, this rise was blunted if active pills were started early.31 In another study, women who had a 7-day pill-free interval experienced less follicular suppression than did women who were supplemented by estrogen alone or estrogen plus progestin.32 Ovarian activity in overweight women was even less suppressed than seen in normal-weight women. Kippling et al demonstrated the impact of shortening the pill-free interval by measuring follicle size, estrogen and progesterone levels. With the 7-day pill-free interval, no ovulation was observed, but the mean dominant follicle size in the next cycle reached 10 mm. With a 3-day delay in a start of the next pill pack, that dimension reached almost 15 mm, quite capable of ovulation.33 It should be noted that with shorter-acting progestins, shortening the pill-free interval from 7 to 4 days did not change ovarian activity measured by follicle size, Hoogland scores, and ovarian steroid hormone production, or change bleeding patterns.34

In addition to reducing pill-related complaints, extended-cycle pills provide significant health benefits. Reducing the numbers of scheduled bleeding episodes results in less blood loss. This can be very important to women with sickle cell anemia, fibroids, bleeding distresses or conditions that require use of medications that interfere with vitamin K synthesis. The pain and suffering that women experience with their monthly bleeding is generally reduced with conventional pill use, but extended-cycle use enhances that benefit. With menses women suffer back pain, abdominal pain, bloating, constipation, headache, breast tenderness, irritability, depressed mood, fatigue, nausea and even vomiting. These complaints are decreased with an extended-cycle oral contraceptive regimen.35 Complaints about headache, mood changes and pelvic pain were clearly diminished with extended-cycle use of a drospirenone-containing pill compared to its cyclic use.36 Estimates are that nearly one-third of the 2.5 million US women with menstrual disorders report spending an average of 9.6 days in bed each year because of these problems.37 Monthly episodes of these complaints result in lower productivity, more lost days of work and less opportunity for career advancement. Dysmenorrhea has been reported to be the number one cause of lost days of school and work in women up to age 25.38 In a Harris poll, 35% of women in every age group agreed with the statement that they had periodic cramps, and other symptoms that caused interference with social events, friends and family, physical/athletic opportunity and professional commitments.39

### Oral contraceptive formulation with extended cycle: first FDA-approved product

The first FDA-approved oral contraceptive pill to reduce the numbers of scheduled bleeding episodes was a monophasic formulation with 84 days of pills with 30 µg ethinyl estradiol and 150 µg LNG, followed by 7 days of placebo pills called Seasonale® (Duramed Pharmaceuticals, Pomona, NY, USA). Although there was relatively slow uptake of this product, women who used it found that it helped them overcome another real world barrier that pill users often face – the need to return to pharmacies for monthly refills. By packing 3 cycles in 1 packet, women had to invest less time physically obtaining their pills. The advantage of this can be seen in a study of timely contraceptive prescription refills which followed 1.7 million women who initiated use of wide variety of hormonal contraceptive methods. Of all the products studied, there were only two that 30% of women refilled on a timely basis for 1 year. Seasonale® was one of these products.12

Total numbers of days of spotting and bleeding are fewer with the 84/7 formulation (48.2/year) compared to the conventional 28-day packets of the same formulation (50.8/year).40 Most remarkably, the number of days of scheduled bleeding and spotting was not only less with the 84/7 formulation (10.6/90 days) than with the conventional 21/7 formulation (34.4/90 days), but the number of days of scheduled bleeding after 84 active pills was less than the number of days of bleeding during any one scheduled bleeding episode using 28 day cycles. The endometrial stripe measured of extended-cycle pill on day 84 was also thinner than the endometrial stripe at day 21 with conventional cycling. This is an

| Complaints | Percent of women complaining |
|------------|-------------------------------|
| Pelvic pain | 21% 70% |
| Headache | 53% 70% |
| Breast tenderness | 19% 58% |
| Bloating/swelling | 16% 38% |
| Use of pain medication | 43% 69% |

From data of Sulak et al.29

*P* values for all complaints < 0.001 versus placebo.
important finding, because women who have experienced a cycle or two of anovulation know that when their bleeding ultimately starts, the flow is heavier and longer than usual. Many women worry that extended-cycle OC use will consolidate their bleeding into heavier periods. Reassuring them that scheduled bleeding is lighter and shorter may remove another unspoken fear.

Table 2 shows that total number of days with spotting and/or bleeding was less with use of extended-cycle OCs, but the median number of days of unscheduled bleeding and spotting days (37.6) was greater than that seen in monthly cycling OC users (14.8). However, the median number of days of unscheduled spotting and bleeding dropped from 12 days in the first 3 months to 6 days in the next 2 cycles. By the last packet, the unscheduled spotting and bleeding days with extended cycle (about 1 day per 28-day cycle) was the same as seen with 28-day-cycle pills. Unscheduled bleeding and spotting is a feature clinicians fear because of past experience with complaints of “breakthrough bleeding” with low-dose pills. Counseling before initiation of the extended-cycle pill use can diminish those concerns. Women who enrolled in the clinical trials were counselled about the probability of temporary increase in the numbers of unscheduled days of spotting and bleeding; only 7.7% of subjects discontinued pill use for “unacceptable bleeding.”

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**Oral contraceptive formulations with extended cycles: changes in the placebo pills**

In an attempt to reduce the numbers of days of unscheduled bleeding and spotting without increasing the number of scheduled bleeding episodes, the next product introduced replaced the 7 placebo pills with 7 pills each containing 10 µg EE (Seasonique®; Duramed Pharmaceuticals Pomona NY, USA). In a study of pituitary–ovarian activity in 3 different formulations: 21/7, 84/7 (7 placebo pills) and 84/7 (7 pills with EE), investigators found that those receiving the 10 µg EE pills had significantly lower levels of both FSH and E2 (P < 0.05). In addition, fewer developing follicles were seen during the active pills of the next cycle. As expected, both the 84/7 placebo and 84/7 EE formulation users reported less menstrual flow than did women on 21/7-day regimen. In a cross-study analysis comparing the outcomes of the phase 3 trials for each 84/7-day product, it was seen that scheduled bleeding with the 84/7-EE regimen was less during in each of the scheduled bleeds compared to the 84/7-placebo regimen. Also, unscheduled bleeding decreased more quickly with the 84/7-EE regimen, with significant differences seen during the third cycle. On an intent-to-treat basis, the Pearl Index was 1.27 for the newer formulation. This included 2 pregnancies in women which occurred within 14 days of discontinuing the pills. The FDA now requires that these pregnancies be counted as contraceptive failures, rather than using them to demonstrate rapid return to fertility.

**Oral contraceptive formulations with extended-cycle: lower-dose formulations**

Kwiecien et al compared the effects of low-dose (20 µg EE) LNG (100 µg) pills given cyclically (21/7) to extended-use 163/7. Total bleeding days were fewer in the extended-cycle group (25.9 vs 34.9 days) and there were fewer bleeding days requiring protection in the extended-cycle group (18.4 vs 33.8 days P < 0.01). They also reported significantly fewer days of bloating and menstrual pain with extended-cycle use. When the same pill was used in a randomized, controlled study comparing 12 cycles of uninterrupted use to a conventional 21/7 regimen, fewer total days of bleeding occurred in the continuous-use arm. In a different study, which directly compared days of amenorrhea with
extended-cycle use, the LNG arm with 20 µg EE pills resulted in a higher median number of days of amenorrhea during the first 90 days (71 days) than was seen in the 30 µg EE/LNG arm (67 days). There were also fewer days of spotting in the lower-dose arm.46

The FDA approved a low-dose continuous regimen of 20 µg EE/90 µg LNG pills that were used for up to 13 cycles of use (Lybrel®; Wyeth Pharmaceutical, Philadelphia, PA, USA). The Pearl Index pregnancy rate was 1.60 on-treatment. The onset of amenorrhea (no bleeding or spotting) was somewhat slow with this formulation, but by cycle 13, 58.7% of subjects had complete amenorrhea and another 23.0% had only spotting but no bleeding. Only 921 of the 2134 women who took at least 1 dose of drug completed the 12-month study; 56% of study participants discontinued early.47

More recently, a randomized open-label European study of daily use of pills with 20 µg EE/90 µg LNG vs cyclic use of pills with (21/7) 20 µg EE/100 µg LNG, reported that there were no pregnancies in the continuous OC arm, but the Pearl Index in the cyclic OC arm was 1.19. Amenorrhea was achieved by 40% of women in the extended-cycle arm by pill pack 7 and by 53% by the last cycle. Another 26% had only spotting by that last cycle.48 The discontinuation rate for the continuous formulation was 33.1% compared to 21.7% in the cyclic arm. Many other features of this formulation have been reported. Continuous pill use completely suppressed ovulation, with little evidence of follicular development during a 90-day study. Return of ovulation after cessation was rapid.49 In a study of explicit return to fertility, the pregnancy rate was 52% by 3 months after cessation, and 86% at 13 months.50 Median return to menses was 32 days; 98.9% of women had return of menses or pregnancy by 90 days.51 To prevent possible confusion between anovulatory causes of amenorrhea (which could place a woman at risk for endometrial hyperplasia) and menstrual suppression with continuous combination OCs, endometrial safety with this continuous formulation was demonstrated by endometrial aspiration at the end of 13 cycles; no hyperplasia or malignancy was detected.52 Finally, adverse menstrual-cycle related symptoms were significantly improved within 3 months of initiation or continuous OCs.53 The Endicott Work Productivity Scale also showed improved with continuous OC use compared to baseline.54 Only 18.6% of women in this study discontinued pill use.

The latest FDA-approved in extended-cycle contraceptive pill is an 84/7 formulation with 84 tablets of 20 µg EE/100 µg LNG and 7 tablets with 10 µg EE each – Lo Seasonique® (Duramed Pharmaceuticals, Pomona, New York, USA). This formulation builds on the popularity of low-dose estrogen. This formulation has a slightly higher dose of progestin (100 µg vs 90 µg) than the prior FDA-approved 13-cycle product (Lybrel®). The 100 µg dose is equivalent to the dose used in the open label European study of continuous OCs. Four scheduled bleeding episodes are induced each year to meet the desires of many women to reduce, but not eliminate their “menstruation” and to more rapidly reduce the numbers of days of unscheduled bleeding and spotting.

In the phase 3 clinical trial, 2,185 women provided 20,937 28-day cycles of exposure.56 Women aged 18 to 40 were studied for safety outcomes. Pregnancy rates were calculated for the group as a whole and for women age 18 to 35. The Pearl Index for pregnancies in the 18 to 35 age group in their intent to treat population adjusted for use of other methods was 2.74, including pregnancies that occurred within 14 days of drug cessation. Three of the pregnancies were never verified and 4 occurred in the second week following pill cessation. Interestingly, the weight of the subjects in this study was very representative of typical American women; they ranged from 87 to 381 pounds (40 to 175 kg), with a mean weight of 158.7 pounds (72.8 kg). Over a quarter of women were obese and 12.4% had BMI > 40. Earlier retrospective studies had voiced the concern that lower-dose OCs may be associated with higher pregnancy rates among women weighing more than 70 kg.57,58 In this clinical study, there was no trend to increased pregnancy rates in heavier women. Distributing the women into deciles based on weight at entry into the study, the lowest pregnancy rate (0.47%) was seen in the sixth decile and the highest (2.75%) was found in the fifth decile.

Scheduled bleeding and/or spotting usually lasted 2 to 3 days every 91-day cycle. Unscheduled spotting and bleeding diminished progressively with longer use. The median number of days with unscheduled bleeding in the first 91-day period was 15 and unscheduled spotting added a median of 10 days during the first 91-day cycle (2.5 days/28 day cycle). By the fourth cycle, the median number of unscheduled bleeding days was 0, and the median number days of unscheduled spotting was 3 per 91-day cycle. Looking at the data another way, it can be seen that 44% of women had at least 20 days (more than 6 days per 28-day cycle) of unscheduled bleeding and spotting the first cycle, but by the fourth cycle only 19% of women had that extensive a problem. Interestingly, of those 19%, only 3% had prolonged bleeding; the other 16% experienced only prolonged spotting. Complete amenorrhea was reported by 6.2% of subjects first cycle and by 17.4% in the last cycle. In this study, 57.2% of women completed the entire trial; 9.6% discontinued early,
at least in part due to bleeding and/or spotting. These numbers compare quite favorably to the pattern seen with higher-dose (30 µg EE) 84/7 (placebo) formulation. The safety profile was reported to be similar to that found with other OCs. Importantly, even in this heavier, older study population, there were no reports of venous thromboembolic events.

**Conclusion**

As we celebrate the 50th anniversary of the first birth control pill, it is interesting to reflect on the many changes that birth control pills have undergone in response to patient preferences and safety considerations. One of the last features of the birth control pill to change was the number and content of placebo pills. Once it was recognized that scheduled bleeding with birth control pills has no medical benefit and can cause suffering and discontent with pills, products with extended cycles were introduced. Those products have over time repeated much of the history of the earlier monthly cyclic formulations. This latest extended formula represents many of the evolutionary changes that have been made to “the pill” to increase pill safety (decreased estrogen doses) and to encourage correct and consistent pill use by minimizing side effects (unscheduled bleeding and spotting) and by providing important noncontraceptive benefits (decreased numbers of scheduled bleeding episodes). It has been tested in women who more accurately reflect the US population in weight. By advancing in all of these important directions, this new formulation represents an important new option to help women more successfully contracept.

**Disclosures**

Research (Grants): Bayer HealthCare, Pfizer (Wyeth), Teva; Speaker’s Bureau (Honoraria): Bayer, Merck (Schering-Plough), KV Pharmaceuticals, Pfizer (Wyeth), Teva; Advisory Boards (Honoraria): Bayer, Merck (Schering-Plough), Ortho-McNeil, Proctor and Gamble, Teva, Xanodyne.

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