**DEFINITION ISSUES**

*Dr Lipton.* The preceding presentations raised a number of issues for me, starting with the definition of menstrually related migraine (MRM) without aura. I’ve struggled with this definition. Essentially, a woman would have migraine without aura in 2 out of 3 cycles between day -2 and day +3, plus headaches at other times of the month. Based on chance alone, a woman with relatively frequent migraine, say 5 to 6 days a month, would likely meet this definition even if there was absolutely no association between her menses and her migraine headaches. Because the menses lasts 5 days and the cycle is 28 days long, that’s 18% of the month. Based on chance alone, we would expect roughly 1 out of 5 migraine attacks to occur with menses.

For pure menstrual migraine (MM), the attacks are clearly associated with menses. In my view, the definition of MRM without aura ought to specify that the association with menses exceeds that which we would expect based on chance alone given that woman’s attack frequency.

*Dr Brandes.* If you keep the diaries, it is usually easy to see which attacks are menstrually related and which are not, because they really do fall out. To me, the issue is whether or not menstrually related attacks respond differently to acute therapy. MacGregor has shown that they are more difficult to treat. I certainly understand your point, but I have some difficulty saying that attacks that occur around the time of the menstrual period are the same as nonmenstrual attacks unless they behave exactly like nonmenstrual attacks.

*Dr Lipton.* I do not doubt for a second that attacks occur more frequently in association with menses in some women with migraine. From a biologic perspective, it may be that MRM is not a different type of migraine. Rather, menses may be a robust hormone factor. The narrow issue I was trying to raise is that we shouldn’t say a woman has MRM unless the migraine occurs in association with menses with greater than chance frequency. The issues that you raise are whether the headache phenotypes in association with menses are different and whether they are due to a robust trigger that is present all the time or to fundamental differences in biology.

*Dr Freitag.* If the headaches really are menstrually related, they should be occurring with more than chance frequency on the same day of the cycle. If that is happening, it’s likely that the same biologic and biochemical factors are initiating the headache and that it could be predicted with much greater reliability to occur on the same day of the cycle each month; for example, always day -1 or always day +1.

*Dr Cady.* What’s interesting to me as a clinician is that MRM is not due entirely to hormone changes. I see the association between migraine and menstruation as 1 of several risk factors. It’s just that this one is predictable. If you look at other times that migraine may occur, where there are multiple trigger events,
these too are more difficult or to treat. It may be because you are building on this one predictable risk factor and then adding all these other synergistic risk or trigger factors.

**Classification Issues**

**Dr Silberstein:** I have a problem with the classification of MRM and daily persistent headache. I think we should call MRM any migraine headache that occurs in that period of time. Then, we can talk about things like tightness of association and subtypes, as we have with frequent or infrequent tension-type headache. We don’t know if this is a population of patients with a very tight association or a population with a loose association. Then, we can see if the difference is in the biology. As it now stands, we are making the assumption that it is a 1:1 relationship in women with this association. And it may not be the trigger; it may be the physiology.

**Dr Brandes:** One of the difficulties with the classification, and one of the things that we face in this country, is the issue that migraine with aura by definition cannot be MM.

**Dr Silberstein:** The absurdity of MRM in the first draft of *The International Classification of Headache Disorders* was that men with migraine would be classified as having non-menstrually related migraine. How would you like to tell your male patients that they have non-menstrually related migraine? Part of the problem was that so much of the argument surrounding the first draft focused on eliminating non-menstrually related migraine in men. MRM should have a definition and studies should be done based on that definition.

**Dr Brandes:** Migraine auras also were eliminated.

**Dr Silberstein:** I think we forgot about migraine with aura because we were so concerned about non-menstrually related migraine in men. MRM should have a definition and studies should be done based on that definition.

**Dr Brandes:** I was confused by the definition in the Appendix with regard to migraine with aura and migraine without aura. In the study that Dr Brandes described (Stewart et al. *Neurology*. 2000;55:1517-1523), patients with several different headache types were included, which reflects what we frequently see in clinical practice. In that study, migraine without aura tended to occur with menstruation. But that doesn't mean that the patients didn't also have migraine with aura at other times.

However, when you look at the definition in the Appendix, my feeling is that you don't even have MM with aura. Some of those women aren't going to have aura, and some are, but they don't have it every time.

**Dr Silberstein:** That's the same study that included daily persistent headache, which made it sudden-onset, tension-type headache. Our argument would be, find somebody who has a headache, and then describe the phenomenon. The problem with the classification is that it should really describe that, and then you can continue with tightness of association and biology so that you can ask, "Does it associate with aura or without aura?" That's the purpose of the Appendix, to make it loose so people could study it, as opposed to making it so defined that you can't.

**Dr Brandes:** Quite frequently, we see patients who have migraine without aura who start birth control pills, either for contraception or to treat their headache. Then they develop an aura, and we tell them it is randomly associated with menstruation and has a different phenomenology.

A more appropriate approach would be to define MRM in the Appendix criteria as any headache that occurs in that time window, and then you have the tightness of the associations. This would then enable us to look at studies and say, “This is random, this is a random oscillation type, this is a very tight association.” The tightest association would be pure menstrually related migraine. Then we can look at patients with random associations and see if the biology is different, and we can look at the criteria that are currently used and have 3 subsets under MRM. Then we can study it.

**Dr Lipton:** Let’s take a step back. One possibility is that menses is simply a trigger of migraine. If this is so, then having an entity called MRM doesn't make any more sense than having an entity called red wine-triggered migraine or chocolate-triggered migraine.

**Dr Tietjen:** I was confused by the definition in the Appendix with regard to migraine with aura and migraine without aura. In the study that Dr Brandes described (Stewart et al. *Neurology*. 2000;55:1517-1523), patients with several different headache types were included, which reflects what we frequently see in clinical practice. In that study, migraine without aura tended to occur with menstruation. But that doesn't mean that the patients didn't also have migraine with aura at other times.

**Dr Lipton:** The difficulty I have with what you are saying is that all women who have menses and migraine will, on occasion, get migraine with menses by chance.

**Dr Silberstein:** What I’m suggesting is the creation of subsets in the Appendix criteria. Subsets could be called coincidental or random, and then you could look at the attack in 2 populations. With the current definition of MRM, it is impossible to determine whether it is due to differences in biology or whether
they probably shouldn’t be on birth control pills based on current recommendations. So these patients, who have developed hypercoagulability, stop taking the pills. It’s not quite clear why they developed aura, but it’s thought to be a risk factor for stroke, as is hypercoagulability. It’s interesting, with regard to pathophysiology, that we don’t see that much migraine with aura in women on birth control pills around the time of withdrawal bleeding or during the natural hormone cycle. It should be an area of further study.

**Dr Brandes:** We should state plainly that we agree that MM can be migraine with aura. That’s a definition when regulatory agencies look at it.

**Dr Silberstein:** We are concerned that it excludes migraine with aura and needs to be studied further.

**Dr Cady:** I’ve been thinking about membrane excitability due to elevation of estrogens, which was observed during the early days of high-estrogen birth control pills and associated with migraine with aura. In my clinical practice, there are many women who have MRM and also have migraine with aura. My gut feeling is that the association might actually be stronger in the general population than one might anticipate and might be very interesting to look at epidemiologically. It would make sense physiologically that, if this priming is occurring, many non-menstrually related attacks would be associated with aura and some menstrually related attacks might not be.

**Triggering Mechanisms**

**Dr Lipton:** I like to think of migraine attacks as events that are triggered. I think aura and headache probably are linked; that aura actually activates trigeminal afferents to produce pain. In that context, aura may be such a robust trigger that it triggers migraine pain in the presence or the absence of estrogen withdrawal.

**Dr Cady:** I agree with that.

**Dr Silberstein:** I was struck by the comment about the triggering mechanism. If you don’t think that menstruation is a trigger, why don’t all women who menstruate have migraine headaches? What is different about the menstruating woman who doesn’t have a migraine vs one who does?

**Dr Brandes:** The strongest argument that menstruation is the trigger is that mismatch technically occurs in every woman with every single period she has. It is only the migraineur who is vulnerable. That speaks to many of these points we’ve been discussing. It’s not that these women are different, and it’s not that menstrual migraine or even pure MM is a different entity. It’s either you have migraine or you do not, and then the ability for menstruation to trigger it depends on whether you have it.

**Dr Zacur:** I have been accused of being mystical when I talk to patients about why things are worse during the menses. I talk about “reserves” within the body that exist to combat things that happen. When your reserves are lowered, the menstrual event tips you over the edge.

**Dr Lipton:** Are other pain disorders exacerbated during menses? Or is there a general lowering of the pain threshold during the menses?

**Dr Silberstein:** The pain threshold is lowered during menstruation. Paradoxically, epilepsy is worse premenstrually than menstrually.

**Dr Lipton:** What other pain disorders and pain thresholds are affected during menses?

**Dr Silberstein:** Low back pain and fibromyalgia.

**Dr Cady:** I see many patients who are referred from a variety of different specialties because their particular ailment is worse at the time of menses.

**Dr Brandes:** There is a small study from a group at UCLA that looked at women who have undergone hysterectomy, women who are postmenopausal but not hysterectomized, and men. The investigators gave estrogen to the women, and the pain thresholds actually diminished when hormone replacement began. It’s an interesting phenomenon. I like to believe that women have a much higher pain threshold than men. You’ll often hear that with respect to lumbar punctures. But in reality, the hormonal replacement study by the UCLA group would suggest that it is lower.

The following are excerpts of discussion that took place by panel members following presentations by Drs Cady and Silberstein.

**Migraine Screening in Primary Care**

**Dr Cady:** Menstrually related migraine (MRM) is a great educational opportunity, not only for obstetricians and gynecologists (OB/GYNs) but also for primary care providers. Because it is predictable for women and their healthcare providers, there is opportunity to plan and initiate treatment in advance of the
migraine attack. The fact that many women visit an OB/GYN for regular examinations and as primary care providers represents a great opportunity to do a broader health assessment. We have to integrate migraine as part of that health assessment and help medical providers and patients understand the value of identifying, diagnosing, and treating migraine.

Dr Brandes and I made a joint presentation with Dr Lee Shulman on MRM at the American College of Obstetricians and Gynecologists in early May of this year and it was well received. As headache specialists, we need to do more of this for OB/GYNs and primary care physicians. We need to increase awareness of MRM, provide some very simple tools to allow diagnosis and initiate treatment, and define when to refer patients to a headache specialist. If we can provide that, we can help a lot of women.

Dr Brandes: One reason we should encourage screening for migraine among OB/GYNs is that many women do not begin to have severe MRM until their perimenopausal years. They have not been recognized as migraineurs because their headaches in the past responded to over-the-counter products and were attributed to late luteal dysphoric disorder or premenstrual syndrome (PMS). Then they hit perimenopause, and their headaches become very intense. Because many of these women, at least in my clinical experience, do not have a diagnosis of migraine, they do not receive appropriate treatment promptly. Often, that delay in treatment results in medication overuse headache, so they develop headache patterns that are much more difficult to treat.

Screening is also important because many women have their first attack of migraine with aura when they start birth control pills. It also was reported decades ago that oral contraceptives might increase the risk for chronic daily migraine or chronic migraine in women. We really need to partner with the OB/GYN community. As Dr Zacur pointed out, women who have migraine are vulnerable to worsening headaches at any time during the menstrual cycle because of hormone changes.

Another thing that is important to me, as a woman who has migraine and a physician who treats women with migraine, is not to overemphasize the behavioral influence of the menses. It’s important to talk about avoiding or reducing headache triggers such as red wine, change of altitude, and working like a maniac. And it’s important to emphasize general health measures such as better sleep, more healthful eating, and regular exercise. But we should also impress on women with MRM and the physicians and nurse practitioners caring for them that this is a neurobiologic event.

I’ve been doing some work with a celebrity spokesperson who has pure menstrual migraine. She was told for years that it was all in her head, that she should just get over it, that she was simply too stressed, and so on. That is the wrong approach. We should continue to reinforce that this is a genetic biologic disorder influenced by hormones.

Dr Cady: I strongly believe that migraine is a biologic disorder, but being a biologic disorder should not diminish the important influence that environmental factors and behavior play in the management of migraine. I know many women who, in anticipation of an MRM attack, go into a frenzy of activity prior to the onset of headache because they are going to be down for a couple of days. Reassurance that the headache is real and treatable is important, but sometimes we have to uncouple certain behaviors that may add to the burden and severity of the migraine attack.

Dr Brandes: I help my patients unstack the triggers over which they have some control. If alcohol is a trigger, I tell them that this is not the best time to have alcohol. If lack of sleep is the trigger, I tell them it’s not the best time to be sleep deprived.

Dr Zacur: I can’t speak for all OB/GYNs, but I can speak for myself with regard to our involvement in migraine screening. In the past, when I have had patients who presented with something that I thought was a migraine headache, it was off to the neurologist to confirm my suspicions. What would be appropriate for an OB/GYN with a patient who appears to be presenting with these headaches? How far should we go? Should we make the diagnosis and treat? Or do we send them to you?

Dr Cady: I think OB/GYNs, like other primary care providers, can make the diagnosis without necessarily getting a neurologic consultation. The diagnosis is largely based on history. If there is a stable pattern of disabling headache in an otherwise healthy person, the most likely diagnosis is migraine. Headache attacks associated with menses, positive family history, and normal function between episodes of headache further support the diagnosis of migraine. These can be viewed as comfort signs.

There are some worrisome features of headache, as well. These include the onset of a new or different headache, especially after the age of 40; a headache...
that is associated with fever, hypertension, or systemic disease; or headache patterns that are progressive over time. Neurologic consultation is indicated at this time or whenever the clinical picture is unclear or produces uncertainty for the medical provider or the patient. However, in most instances, the diagnosis of migraine is readily apparent from the history and description of the headache and headache pattern.

What concerns many primary care physicians and, I suspect, OB/GYNs as well, is the idea that medical providers have to be able to perform a complete, detailed neurologic examination to diagnose migraine. Given that using a funduscope or interpreting finger-to-nose and similar neurologic tests is not within the scope of most OB/GYN practices, the need is for simple and practical ways to determine the normalcy of neurologic function. If patients are walking, talking, and thinking and acting normally as they describe a stable pattern of headache activity, they are likely neurologically intact. In addition, changes in neurologic function can be detected if a provider is willing to follow up with a patient in a timely manner. Given that much of the neurologic examination is designed to determine and localize neurologic disease, I think it would be useful to define what aspects of the examination are needed to confirm normal function. In addition, the provider can assess treatment outcome; if it is not what was anticipated, a neurologic or medical consultation is warranted. If you have any questions, your neurology colleagues and, in many instances, your colleagues in primary care and family medicine, are there to assist you.

Dr Cady: Guidelines would be helpful.

Dr Zacur: Some of the impact-based diagnostic tools are very good for screening. They are not perfect, but that’s true for any disorder we treat.

However, even if you are the best neurologist in the world, you can get fooled sometimes if you don’t look at larger populations and follow up the way primary care does to help patients stay out of trouble. If patients aren’t doing well, you have to get them back in. It’s not a consultation for migraine, where this is the Supreme Court and here’s your 1 chance. It’s an opportunity to engage in more longitudinal care.

Dr Brandes: The real issue is diagnosis and if you’re comfortable with the diagnosis. The diagnostic criteria for migraine with and without aura are important because they reflect pattern stability, time frames (ie, the aura doesn’t last more than an hour), and factors that worsen the headache. They also serve as red flags in headache management.

Dr Mondell: They also raise comfort levels.

Dr Cady: From this point of view, you are talking for the most part about a headache that isn’t going to be associated with aura, a headache that has been occurring for months or years without much change.

Dr Freitag: There also is the issue of when to do diagnostic testing. We know that in patients who have multiple neurologic examinations, the chances of a positive magnetic resonance imaging or computed tomography scan are extremely low.

Dr Brandes: You’re right. The guidelines from the American Academy of Neurology state that patients with a stable pattern for 2 years, a normal neurologic examination, and no history of seizures don’t have to be imaged. Looking at that in terms of comfort level and red flags allows us to save imaging for situations where we really need them and to move forward with treatment.

Dr Freitag: It raises the comfort level for the OB/GYN and saves worrying about ordering the scan.

Hormonal Approaches to Therapy

Dr Freitag: Many women who have menstrually associated migraine don’t respond well to therapies, and this raises the question of using oral contraceptives as prophylaxis where you go from 12 menstrual migraines a year down to 4. How long can we go?

Dr Zacur: You don’t have to stop. The pill-free interval was an arbitrary design. The dilemma is that the continuous combination pill has not been studied for safety, although you could deduce that from the total doses given over 28 days vs 21 days. It’s less with lower-dose pills, but it shouldn’t present a problem physiologically. I have given it indefinitely to many patients, but you should obtain informed consent.

Dr Tietjen: That was my understanding. If you are going to use continuous therapy, you can just use any monophasic pill, and you don’t need a pill break at 3 months.

Dr Silberstein: The investigators who did the original studies found that breakthrough bleeding occurred at 3 to 4 months, so they recommended a pill break after 3 months. It was not because of safety issues.

Dr Zacur: On one of your slides, Dr Silberstein, you noted that estrogen alone can inhibit ovulation. In my lectures, I make it very clear that the key ingredient to
inhibiting ovulation and conception is the progestin.

**Dr Silberstein:** It is high-dose estrogen or both in lower doses.

**Dr Zacur:** Estrogen is in current formulations of combination pills to prevent breakthrough bleeding. There is an entity that nobody quite understands called progesterone-induced breakthrough bleeding. The combination pills are progesterone weighted, and when you take them continuously for a long period of time, that is what occurs.

**Dr Brandes:** I’ve found that a lot of women respond well to extended-release formulations. Some of these women, however, will have breakthrough bleeding at week 7 or even at week 5. What I’ve done is discontinue the birth control pills and then put these women on short-term prophylaxis for that week. Is that a reasonable thing to do?

**Dr Zacur:** Yes. Many patients on birth control pills for migraine and premenstrual tension syndrome feel like they are going to have a period, and they’ll have the same sort of event that you were trying to prevent by inhibiting ovulation and providing a continuous hormonal milieu. If the patient knows that something is going to happen at a certain point in time, then what you are doing is fine.

**Dr Brandes:** OB/GYNs often use the birth control pill to usher perimenopausal women through the perimenopause and into menopause. Are there any safety data in women after age 55 or from age 50 to 55?

**Dr Zacur:** The Food and Drug Administration has no age restriction on oral contraceptive use, period. The major restriction related to age is not prescribing pills to women older than 35 who smoke. I prescribe the pill for women up to age 55. The new low-dose pills have as little as 20 mcg of ethinyl estradiol, and some newer ones that are coming out may have only 10 or 15 mcg. Standard hormone replacement therapy (HRT) has 5 mcg of ethinyl estradiol. In Europe, they have used ethinyl estradiol 10 to 20 mcg for hormone replacement, which is comparable with the estrogen in a low-dose pill. Clinically, the pill appears to be safe in older premenopausal women, but we don’t have the data to prove it for menopausal women.

**Dr Brandes:** Some of the gynecologists I work with use an estrogen patch in menstruating women who have breakthrough bleeding and need to have placebo or a withdrawal week. Could you comment on that?

**Dr Zacur:** I think that’s a very good strategy. I think there is 1 birth control pill that does this orally: there are 21 active pills and then low-dose estrogen only for the next 4 to 5 days.

**Dr Brandes:** I wish I could say that it was as successful for MM (menstrual migraine) as I hoped it would be, but it wasn’t. That may be due in part to the oral absorption of the formulation.

**IMPACT OF THE WOMEN’S HEALTH INITIATIVE**

**Dr Tietjen:** I find that many women have extraordinary concerns about hormone therapy since the results of the Women’s Health Initiative (WHI) were published. I continue to see women who have stopped therapy because of fear or because their gynecologists have advised them to do so. I have seen many women who were completely stable, completely controlled, maybe down to 1 migraine attack every 2 to 3 months and able to respond to acute triptan therapy very successfully, who discontinued HRT because of fear. These are women who do not have a first-degree relative with breast cancer. Could you comment on the WHI?

**Dr Zacur:** I first became involved with HRT under the mentorship of Dr Trudy Bush, one of the first epidemiologists to report in the late 1980s that HRT could reduce the risk of heart disease. I was involved in the Postmenopausal Estrogen-Progestin Intervention (PEPI) study and the Heart and Estrogen/Progestin Replacement Study (HERS).

There are 2 points about the WHI and HERS. First, there’s the misconception about the results of WHI, which was conducted to see if you could reduce the risk of heart disease in menopausal women. It was not designed to assess the safety of HRT or its efficacy in treating menopausal symptoms. If you want to include migraines as a menopausal or perimenopausal symptom, it certainly is appropriate to consider HRT for these individuals.

The second point—and this is very upsetting—is misinterpretation of the HERS results. The women in the study had documented heart disease and received HRT. During the first year of the study, they had a higher rate of cardiovascular events. After that, HRT did not present a risk and adverse events declined.

**Dr Silberstein:** There was a follow-up study, HERS-2, showing that the benefit didn’t persist after the first year.

**Dr Zacur:** Right, but it wasn’t a risk. The WHI initially reported a relative risk of 1.29, 29% increased
risk in heart disease, but no increased risk when the investigators reevaluated their data 1 year later and reported their findings in the *New England Journal of Medicine* (Manson et al. 2003;349:523-534). You would expect no increase because these were women who didn't have documented heart disease.

**Dr Silberstein:** What was even more important was the route of administration and the type of estrogen used in the trial. Many people believe the results reflect an artifact of conjugated equine estrogens and the oral route of administration. People who don't believe the data are actually going to fund their own studies with the patch showing that this is an artifact of the formulation and the route of administration. How do you feel about that?

**Dr Zacur:** The point about the transdermals is that it avoids the first-pass effect on the liver and thereby results in less effect on lipids. Companies producing the patches would also like to say that use of the patch reduces the coagulability risk, but there are no data that I am aware of to support that hypothesis.

**Dr Brandes:** Do you think the data on lipid metabolism are accurate? Do the data substantiate that the transdermal route is better in women who have hypercholesterolemia?

**Dr Zacur:** I think it is the reverse. As a matter of fact, in the PEPI study, the investigators didn’t use the transdermal formulation because the suppliers of the patches feared that the estrogen level on the patch would not be high enough to get a first-pass effect on the liver and a resultant increase in HDL (high-density lipoprotein) and decrease in LDL (low-density lipoprotein). It remains to be seen whether, in fact, the transdermal route will be safer than oral administration.

The other point that needs to be made about the WHI study is that there was an almost statistically significant decrease in breast cancer risk in the estrogen-only arm. This wasn’t widely publicized. Of interest is the fact that this result may not be due to estrogen per se or its route of administration. The real question, I think, was the progestin used and whether giving it continuously could have been a factor. Medroxyprogesterone acetate 2.5 mg, given orally on a daily basis, was used in the estrogen and progestin arm of the study.

**Dr Silberstein:** Another major criticism of the WHI has been that women who are menopausal for a long period of time before starting estrogen replacement therapy or HRT are physiologically different from women who start therapy at menopause. The physiology of delayed treatment is very different from that of immediate treatment, and again this may be an artifact of the way the patients were dosed.

**Dr Zacur:** I agree. In WHI, the investigators who designed the study were, I believe, so confident that estrogen would reduce the risk of heart disease that they deliberately enrolled older women. This was done, I think, not only to save money (the study cost over $750 million), but perhaps in the hope that older women would be more likely to have subclinical heart disease so that a beneficial effect would be seen more quickly. By design, two thirds of the women in WHI had to be older than 59 at study entry. The average age was 63. The average age of the women in the HERS study, where the participants had documented heart disease, was 66. Furthermore, women who were having hot flushes or other menopausal symptoms were, as stated in the study design paper, actively discouraged from participating because it was a prospective, double-blind clinical study. Thus, this population of women was very different in terms of age and symptoms from the population of women who had taken hormone replacement previously.

**Dr Tietjen:** What about the WHI findings on the increased stroke risk?

**Dr Zacur:** I have gone over the data in some detail. For estrogen-only users, the investigators annualized the risk to 10 000 women. In the placebo group, there were 32 strokes in 10 000 women in 1 year. In the estrogen-only group, there were 44 strokes in 10 000 women. Whereas the relative risk seems high (39%), the absolute risk is low, approximately 0.1%.

**HORMONE REPLACEMENT THERAPY DOSING ISSUES**

**Dr Brandes:** Do you believe that micronized progesterone with estrogen is preferable to medroxyprogesterone with estrogen in women, particularly women with migraine, who need and want hormone therapy?

**Dr Zacur:** When we looked at lipid profiles in the PEPI study, progesterone was the best progestin to use with estrogen in terms of maintaining the best lipid profile. However, if you look at Dr Tom Clarkson’s work on the effects of HRT on the coronary arteries of ovariectomized monkeys, the type of progesterone really didn’t make any difference in terms of protective effect on the coronary arteries.

**Dr Silberstein:** In the headache literature, studies comparing the patch with the tablet clearly showed
that headache was worse with tablets.

**Dr Zacur:** I would absolutely agree. I think that has to do with fluctuations because when you take an oral contraceptive pill, you have a peak level of estradiol in 1 to 2 hours, then a decline, a secondary rise, and another decline. It looks like this horrendous sawtooth pattern, and it differs every single time you take that pill. You do not see this with transdermal steroid administration.

**Dr Brandes:** What about the women who still have a uterus and are going to be on estrogen and progesterone? Let’s take a perimenopausal woman who is having significant perimenopausal symptoms, including exacerbation of migraine, and she has no primary history of breast cancer and she is essentially healthy otherwise. What would be your first, second, and third choices for her, hormonally? What would you recommend as an ideal approach if you were managing her acutely, maybe even with MM prophylaxis?

**Dr Zacur:** It depends. As I said, HRT is not going to inhibit ovulation and she still needs contraception. If you give her hormone therapy when she is in the menopausal part of perimenopause, you have benefit. But if she ovulates, you are now giving her the same steroids that her ovary is suddenly making; she will now have higher steroid levels than her body is ready for, and she will do worse. If you give a low-dose contraceptive pill, you can inhibit ovulation, and some women will do better. It’s a matter of discussing the options and then trial and error as to what works best.

**Dr Brandes:** Then the diary, or the calendar, becomes all-important, particularly in the management of migraines.

**Dr Zacur:** I tell patients that they need to spend a month or 2 with a diary, listing everything that ails them so they have a background to share with you. Then I will go with 1 medication, 2, 3, see how they do, and have them keep the same record so they know what is working and what is not.

**Dr Brandes:** How long do you tell a perimenopausal woman to take a mini-pill and evaluate the diaries?

**Dr Zacur:** If you are treating hot flashes, you have to use whatever you are using for at least 2 weeks because that’s how long it takes to get an effect. I encourage patients to stay with it for as long as possible, hopefully 2 to 3 months, but at least for 1 month.

**A Collaborative Approach**

**Dr Cady:** Menstrually related migraine warrants a collaborative approach to diagnosis and management. We need to build bridges among the specialties to promote collaboration and break down barriers within our own specialties that prevent it. The neurologic examination is a big barrier for non-neurologists. OB/GYNs, family physicians, and other primary care practitioners should not shy away from doing a standard screening neurologic exam in women with migraine, just as neurologists should be comfortable discussing the influence of hormone changes on migraine. I suspect all physicians do this to some extent, but as members of professional disciplines we should work to develop these necessary skill sets.

**Dr Zacur:** I refer patients with migraine to a neurologist I know when something doesn’t make sense to me. But it doesn’t mean that I need to do that to confidently diagnose and manage patients with migraine. This is the kind of barrier breakdown we need to do to bring multiple specialties together. We have so much to learn from one another.

**Dr Mondell:** Absolutely, because barriers explain why we are stalled at a certain level. Why have we not moved beyond that? Breaking down barriers and adopting a collaborative approach is an opportunity to move forward. It would be worthwhile to share American Academy of Neurology practice guidelines for migraine management with colleagues who are not neurologists.

**Dr Silberstein:** One interesting issue that is emerging and lends itself to a multispecialty approach is the comorbidity of pelvic pain and migraines. In a large study of women who have had pelvic surgery for pain, we convinced them to complete a migraine questionnaire, and we found that about 67% had migraine (Karp et al. *Neurology*. 2004;62(suppl 5):A337). Preliminary data from other studies support the association between chronic pelvic pain and migraines.

**Dr Zacur:** It gets back to what actually is causing the migraine. There are triggering events or general changes.

**Dr Lipton:** It is worth making a distinction between factors that initiate headache and factors that make it more severe. Estrogen withdrawal is a very robust trigger of migraine in many women. Inflammatory changes or other hormone effects or allodynia may make the headaches more painful once they are initiated. Those may by the same thing, but they probably are not.
**Dr Silberstein:** One thing that needs to be done is to look at preventive trials to see the differential effect between menstrual and nonmenstrual headache. My bias is that most headache drugs alleviate all headaches except for those associated with menstruation.

**Dr Freitag:** We should look at metabolism issues as well because changes in estrogen levels and liver metabolism could lower drug levels and blunt the prophylactic effect. In a trial using low doses of propranolol, there was an effect on estrogen receptors of approximately 25% to 30%, which could have implications in migraine (Re et al. *J Vet Pharmacol Ther.* 1993;16:328-334). Additionally, estradiol levels can produce up to a 50% change in propranolol pharmacokinetics, which could easily account for the observed alteration in prophylactic effect occurring perimenstrually (Walle et al. *Br J Clin Pharmacol.* 1996;41:305-309).

**Dr Silberstein:** If we could show that to be real, then the next step would be to find a drug and do kinetic studies.

The following are excerpts of discussion that took place by panel members following presentations by Drs Tietjen and Lipton.

**STAGING MIGRAINE PROGRESSION**

**Dr Cady:** A method of staging patients according to where they are in the progression of migraine disease is needed to help medical providers describe the spectrum of headache patients seen in medical practice. People who have 1 migraine that lasts 24 hours every 2 months may be nonproductive for the day of their attack, but these attacks end and normal activity is quickly resumed. In fact, human nature being what it is, these individuals will, in most instances, make up for that lost productivity, and their migraine probably isn’t going to affect an employer to any significant degree. On the other hand, if a person has many migraine attacks and is very disabled, the impact of migraine is quite measurable. These individuals probably have gone through the downward psychosocial-economic spiral and their next step is to go on disability or get demoted or switched to a position at work with less impact. Thus, although there is tremendous personal disability, there may not be extreme disability for the employer.

Somewhere in the middle is a population of migraineurs whose control or lack of control of migraine through succeeding years could have a huge impact on an employer. To define these migraineurs, we need to be able to stage them appropriately, prevent the progression to disability, and prevent careers from spiraling downward. There is a point at which their headaches are truly affecting their productivity at work and other aspects of life, as well. I am very interested in how we can stage patients who evolve along this spectrum. We all do this intuitively. We see patients and we say here is where they are today, and if we don’t treat them well, we have an idea where they are going to be tomorrow. I wonder if there is any way to do that kind of modeling in these patients to help medical providers better understand and manage the population of migraine patients at risk for transforming from episodic to chronic migraine.

**Dr Lipton:** I totally agree with that thought, but I didn’t go there largely because we are talking about menstrual migraine (MM). I don’t know if MM is one of the factors that predicts a poor headache outcome. I have examined predictors of headache progression with Ann Scher. We showed that headache progression is predicted by attack frequency, medication overuse, obesity, head trauma, sleep disturbance, stressful life events, and being a woman (Scher et al. *Pain.* 2003;106:81-89).

We know a lot about how to identify a group of headache sufferers at risk for progression. We don’t know if intervention can alter the natural history and keep them from progressing, although I hope that we can. Preventing progression may be a crucial step towards improving the lives of headache sufferers, and may well be cost effective.

**Dr Cady:** We’re very good at recognizing individual events, but I think in almost every other sphere that we understand, it’s the synergy and combination of events. We need to develop a staging classification that looks at the patient and not just the type of headache, or the type of risk factor, and pinpoint where they are in the progression spectrum so that we can identify where they might be a year from now.

**Dr Lipton:** To some extent, I’ve referred to the Migraine Disability Assessment Score (MIDAS) grade I through IV as disability stages. We have a study in the field in which we are going to see if the MIDAS score predicts progression above and beyond headache frequency. Joel Saper has developed an extensive staging model. His intent was not to predict outcome, but
to help match the place where patients got their treatment with the severity of their illness. The staging system includes comorbidities, which certainly are important drivers of refractoriness and may affect prognosis as well. I think a staging system is a great idea, but it has to be simple, similar to what is done with disability in patients with heart failure.

**FACTORS AFFECTING PROGRESSION**

**Dr Brandes:** It’s a first step, and OB/GYNs (obstetricians/gynecologists) can be at the forefront because women may well be at risk for worsening migraines every time there is a hormone change. Early recognition and diagnosis of migraine allow the OB/GYN to monitor patients so that if there is an increase in frequency or disability, acute, short-term prophylaxis, or preventive treatment can be instituted. That could happen while the model is being prepared.

We also should be aware of women who have endometriosis, severe menorrhagia, or dysmenorrhea. They may be at even higher risk, so they should be screened and continually watched.

**Dr Zacur:** Are there data showing that MM worsens over time? Will it increase in severity and number of attacks?

**Dr Lipton:** There is a strong anecdotal impression that there is a subgroup of migraine sufferers who begin with episodic migraine and develop headaches that occur with increasing frequency over time. There is a clinic-based longitudinal study done in Germany that shows headache progression to chronic daily headache in patients with episodic migraine. In that study, which also included men, 14% of migraine sufferers seen in specialty care progressed to chronic daily headache 1 year later. Among the men and women who progressed, all had more frequent headaches and headache in patients with episodic migraine. In that study, which also included men, 14% of migraine sufferers seen in specialty care progressed to chronic daily headache 1 year later. Among the men and women who progressed, all had more frequent headaches and headache intensity or frequency.

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**Dr Tietjen:** One of the things we are presenting in poster form is the interrelationship between symptom indices and headache frequency. It’s quite complicated. Patients with higher scores on the PHQ-15 (somatic symptom scale) and the HIT-6 (headache impact) had higher depression regardless of the headache frequency, but patients with chronic headache had much higher depression scores, higher somatization scores, and higher HIT-6 indices than those with episodic headache. Naomi Breslau has shown a nice bidirectionality between headache and depression (Neurology, 2003;60:1308-1312), but she didn’t find that more severe depression correlated with headache intensity or frequency.

**Dr Lipton:** I want to understand the link between endometriosis and chronic daily headache a little better. One possible explanation for the linkage is that there is something about the hormonal milieu that makes endometriosis more likely and that it drives chronic daily headache. Another possibility is that it’s just having another pain disorder. We looked at arthritis and found that it was a risk factor for headache progression. A third possibility is that it’s the medication to treat all the pain that exacerbates the headache.

**Dr Tietjen:** We controlled for nonsteroidals and other analgesics that patients were using to treat their headaches and other types of pain, but we still found that there was an association. When we separated out endometriosis versus nonendometriosis, ill-defined conditions such as fibromyalgia and chronic fatigue fell out as well. These are pain disorders, but endometriosis is different in that it has a pathological diagnosis.

**Dr Lipton:** I’ve considered the nervous system of the migraineur as being more sensitive and vigilant than the nervous system of the nonmigraineur, and that this increased sensitivity is primarily determined by the genetics that underlie migraine. If that is true, then, would we think that the only manifestation of this genetically sensitive nervous system is observed during headache? Clinically, providers intuitively understand that the migraine population shares several common clinical features; we define many of these as comorbidities. When you care for patients, you start to see that these other ways are all around us. I have even
started changing some of the terminology in my own thinking: I call it co-sensitization. The more you get, the more you get. And we watch for it all the time.

Dr Lipton: And for other signs of dysfunction. It's mood, it's affective things.

**LINKS TO INFERTILITY AND IMMUNE FUNCTION**

Dr Brandes: Infertility clinics are beginning to report that there is an increased incidence of migraine in women seeking their assistance. A report presented at the American Academy of Neurology last year also showed that these women have elevated levels of C-reactive protein and a higher incidence of the presence of antiphospholipid antibodies. If you look at the reasons for infertility, endometriosis hits the list. It's interesting, as the story unfolds, to see those relationships, and to see that they didn't report chronic migraine, but more frequent migraine.

Dr Zacur: This was just infertility? Not women undergoing hormonal stimulation, or anything like that?

Dr Brandes: It was just in women who presented to an infertility clinic. They had a greater risk for migraine in general.

Dr Tietjen: About 20% to 40% of infertility has been associated with endometriosis. Whether it's the cause, I don't know.

Dr Silberstein: The problem with endometriosis is that 67% of women with endometriosis and pelvic pain have migraine (Karp et al. Neurology. 2004; 62(suppl 5):A337). If you just do the statistics, you can see where 40% of your infertile population will have endometriosis and migraine if you get a large enough sample.

Dr Brandes: What are the top 3 diagnoses that account for infertility in women?

Dr Zacur: Endometriosis, tubal disease, and adhesive disease are the top 3.

Dr Mondell: What other issues require further clarification? What other issues could be further explored? Are there any final thoughts?

Dr Frietag: Immunologic factors play a role. You have to explore the relationship to the nervous system and immunologic deviation, and the effects of drugs used for treatment on immune function. We may be seeing some other effects and other systems being brought into play that we have yet to explore.