Letters to the Editor

Thomas Jefferson's Headaches: Episodic Daily Migraines

I thoroughly enjoyed reading Cohen and Rolak's fascinating analysis of Jefferson's headaches.[1] I believe that his headaches are consistent with migraine as well. It is only appropriate that one of the founders of our country and the namesake of the medical school where the president of the American Headache Society (Dr. Stephen Silberstein) is director of the headache clinic had migraine. One unusual aspect of the headaches was the occasional occurrence and long duration from days to weeks.

Medina and Diamond described "cyclical migraine" in 27 migraineurs whose headaches occurred in recurrent cycles separated by headache free intervals with an average of 5 cycles per year lasting an average of 6 weeks.[2] Many of the patients had a constant low-grade headache with superimposed severe headaches lasting an average of 25.5 hours occurring several times per week. Complete or partial control of the headaches was obtained in 19 out of 22 patients treated with lithium carbonate. (The response to lithium, however, is unusual for migraine.)

I have seen other patients with somewhat similar patterns. The terms episodic daily migraine (to be used in contrast to chronic daily headache or chronic migraine) or episodic very long duration migraine may be more descriptive than cyclical migraine. Or perhaps Jefferson's migraine variant would do just nicely. Two case descriptions follow.

CASE 1

This 16-year-old male reported episodic severe bifrontal throbbing headaches with nausea, light, and noise sensitivity without aura or vomiting lasting up to 24 hours since the age of 13 occurring about 4 to 5 times yearly. Hot dogs were a trigger. Two years ago, he had the same severe headaches occurring on a daily basis for 1 month and then reverting to an occasional basis. Several months ago, he again had the same severe headaches occurring almost daily for about 2 months with none following. Triptans would decrease the intensity of the headaches. His sister also has migraines. Neurological examination was normal. An MRI scan of the brain was normal.

CASE 2

A 33-year-old woman described periods of recurring headaches since the age of 20 years about every 3 to 4 months that were rather constant for 2 to 5 weeks and she would then be headache-free in between. The headaches were described as bitemporal and behind the eyes throbbing with an intensity ranging from mild-moderate associated with light and noise sensitivity and, at times, nausea, rare vomiting, but no aura. Topiramate and venlafaxine were not effective as preventives. Propoxyphene and acetaminophen combination medication and acetaminophen and codeine would decrease the pain. Almotriptan and frovatriptan did not help. There was no family history of migraine. Neurological examination was normal. An MRI scan of the brain was normal.

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Misguided Precedent is not a Reason to Use Permuted Blocks

To the Editor:

My letter in the February issue drew a response that contains statements that I consider to be in error and thus deserving some comment.[1,2] The first involves the authors confusing the frequency with which a method is used with the appropriateness of its use. It *may* be true that permuted blocks remain the most commonly used randomization method, but this, even with endorsements by those who should know, in itself does not justify the continued use of a method whose time has come and gone. I previously have detailed

reasons why permuted blocks should not be used.[1,3,4] Precedent notwithstanding, I feel, these reasons remain uncontested.

The second error resides in the authors' supposing that it is only permuted blocks with fixed block sizes that should not be used. In fact, because one need not be certain of upcoming allocations to be able to successfully predict them, varied block sizes are often worse not only than the maximal procedure but also than the permuted blocks procedure with fixed block sizes.[3,4] That is, knowing only how many allocations have been made so far to each treatment group allows one to guess the treatment that so far has been allocated less often. When investigators use this convergent strategy in an unmasked trial, the maximal procedure outperforms (eg, better controls the true Type I error rate) permuted blocks with fixed block sizes, which in turn outperform varied block sizes.[4] In some cases, this difference can be quite pronounced. For example, with blocks of size 8, selection bias can inflate the true Type I error rate from the nominal 5% to 35% (maximal procedure), 49% (fixed block size 8), or 61% (varied block sizes no greater than 8).

The authors also stated that permuted blocks are the only procedure that can be used with stratification, but they offer no support for their contention. In fact, stratification entails creating a separate allocation sequence for each stratum, so any form of restricted randomization, including the maximal procedure, can be applied within each stratum in the same way that permuted blocks can be. The authors object that its use is "cumbersome, and likely to require an advanced knowledge of biostatistics and mathematics to employ."[2] As such, Nicholson et al seem to be endorsing a research technique simply because it will allow the methodologically challenged to conduct medical research.

Imperfect medical research may lead to false conclusions that can produce and influence the content of guidelines, in turn leading to bad prescribing practices that harm real patients. The authors "take exception to [my] implication that investigators who are in some fashion able to unblind the allocation will. . .reap rewards," and counter that no method can prevent a researcher from biasing a trial; most researchers have no intention of biasing a trial; and permuted blocks will suffice when the researcher is not trying to bias the trial.[2] This third point is true but why stop there? If there is no intention to bias a trial, and if we can infer therefore that no actual bias may occur, then why not dispense with not only these "cumbersome" randomization techniques, but also with randomization itself; and even with control groups?

Their first point is incorrect; unrestricted randomization in fact can completely eliminate selection bias, although at the expense of introducing chronological bias.[3,4] There may be a better way to eliminate selection bias, and we will return to this issue. The authors claim that it is not necessary to use the Berger-Exner test[5] because it is not endorsed by CONSORT.[5] While compliance with CONSORT is required to conduct a methodologically sound trial, such compliance alone may not be sufficient. If we can agree that CONSORT's failure to include the Berger-Exner test is a deficiency of CONSORT and not of the Berger-Exner test, then we can consider the merits of the test itself. The Berger-Exner test remains the only reliable way to detect selection bias.[4,5] Returning to the authors' point regarding the inability to prevent researchers from acting unethically, one could argue that it is precisely this defeatist attitude that allows unethical researchers to fly under the radar. If the Berger-Exner test was applied routinely in randomized trials, perhaps then the threat of exposure of unethical conduct possibly could serve to eliminate selection bias resulting from the prediction of future allocations.

Because the challenges to a hypothesis—and hence the set of challenges that may offer the most robust evidence in favor of the hypothesis—are necessarily varied, there may still be a role for blocked randomization as part of a "sensitivity design."[6] Multiple studies of a given treatment for a given disease should not use identical protocols; similarly, within a given study, varying the randomization procedures across strata will vary the susceptibility to the different types of biases. Thus, if many strata are used, then perhaps there is a rationale for permuted blocks. But let us not confuse this with using permuted blocks in every stratum in an unmasked design, which serves to maximize the susceptibility to selection bias. In such a case, if the Berger-Exner test is not performed, then any apparent treatment effect can be explained completely by selection bias and it will be impossible to conclude that the treatment under study is effective. For this reason, there can be no valid defense for not using the Berger-Exner test in a randomized trial with any type of restricted randomization, especially in unmasked trials and/or when permuted blocks are used, even with varied block sizes.[5]

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