BACKGROUND
MM is a 51-year-old right-handed woman with a more than 20-year history of chronic headaches. She was initially examined in 2001. She described 2 different types of headache. The first type of headache was a dull, bilateral nonpulsating headache that she initially experienced on a daily basis; this particular headache was not associated with nausea, vomiting, or photophobia that we diagnosed as chronic tension-type headache. A second type of headache was described as unilateral in nature (left greater than right) and was associated with nausea, vomiting, and marked photophobia that we diagnosed as migraine. The patient has chronic daily headache and initially averaged approximately 6 severe migraine headaches/month in addition to her daily, low-level, tension-type headaches (TTH). She took an unspecified, but reportedly large, amount of over-the-counter analgesic medication on a daily basis for her pain.

MEDICAL HISTORY
Medical history also was significant for peptic ulcer disease, environmental allergies, and fibromyalgia.

PHYSICAL EXAMINATION/IMAGING STUDIES
Neurologic examination was nonfocal with the exception of several trigger points elicited over the trapezius muscles bilaterally. Previous magnetic resonance imaging of the brain and magnetic resonance angiography of intracranial vessels were normal.

MEDICATIONS/THERAPEUTIC INTERVENTIONS
MM was originally started on nortriptyline 25 mg at bedtime with the eventual target dosage of 100 mg daily; she also was given samples of sumatriptan 50-mg tablets to try for abortive therapy.

After approximately 3 months with a target dosage of 100 mg of nortriptyline, the patient continued to report headaches; she did not feel that she was receiving any significant benefit from her current medication regimen and was reporting adverse effects, including a 10-lb weight gain and dry mouth. MM also developed an increased frequency in her migraine headaches, now occurring twice weekly. She was switched to verapamil for the next several weeks, and her headaches improved somewhat. MM was asked to keep a detailed headache calendar, and at that point, she also was scheduled for botulinum toxin type A injections, at her request.

Her initial round of botulinum toxin type A injections included only the frontalis and temporalis muscles (total dosage of 100 U). During her 4-month follow-up visit, after receiving botulinum toxin type A injections and changing to a calcium channel blocker, the patient was quite pleased to report that her current headache frequency and severity averaged only 1 mild headache/week, and that she had had only 2 breakthrough migraine headaches during the 4-month period. Over the next 2 years, MM continued to receive botulinum toxin type A injections every 4 months.

Her current migraine headache frequency is now 1 every 60 days, and she experiences TTH approximately 5 days/month. MM is currently receiving a total of 200 U of botulinum toxin type A into the frontalis, temporalis, masseter, occipitalis, and splenius capitis muscles. She receives injections into the masseter muscles for bruxism. On rare occasions, she also will receive a total of 250 U into the trapezius muscles (Figure). With the botulinum toxin type A injections, the patient has been able to reduce her use of rescue medications considerably to triptan.

CASE STUDY

CHRONIC DAILY HEADACHE PROPHYLAXIS: BOTULINUM TOXIN TYPE A APPLICATIONS

David Morledge, MD

Dr Morledge: In my center, there is a large consensus of patients that want a non-Western medicine approach to their clinical condition, and they view botulinum toxin type A as cutting edge or off the beaten path. This particular patient wanted to avoid oral medications and was interested in an alternative.

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CASE STUDY

and occasional ibuprofen (twice monthly) and a maximum of 4 sumatriptan every 30 days as her low-grade chronic daily TTHs have essentially resolved.

MM has not been to the emergency department (ED) for a severe migraine headache in more than 3 years. The patient is on a managed healthcare plan, and reimbursement continues for botulinum toxin type A therapy despite its off-label use.

DISCUSSION

Dr Morledge: I believe this treatment modality is justified, given that the patient has reduced her use of triptans significantly and has not had to go to the ED for acute care in 3 years. I would appreciate feedback from the panel.

Dr Dodick: I’m going to be the Devil’s Advocate here. You scheduled botulinum toxin type A at a time when a patient had considerable or remarkable improvement with verapamil. My question is, how do you know she’s doing better because of the botulinum toxin type A? Does she continue to wear off before the next injection, or are these just scheduled injection visits that she comes back and receives?

Dr Morledge: She starts calling approximately 3 weeks before her scheduled visit and is telling me that her headaches are coming back. Thus, I clearly feel her benefit is related actually more to the botulinum toxin type A versus the verapamil.

Dr Mondell: When the patient reports that her headaches are “coming back,” about which type of headache or headaches are we speaking? Additionally, does she have interictal pain in her neck muscles and trapezius muscles, or when she gets a headache, does the pain involve that area?

Dr Morledge: Do you mean, does she have cervicogenic pain?

Dr Mondell: Well, not cervicogenic, but ictally. Certain patients will say that their necks become stiff or tender or painful during an attack, but on physical examination with palpation of those muscles, the examination is normal.

Dr Morledge: She has definite trigger points I would consider to be almost akin to allodynia on her trapezius muscles and up into the splenius capitis muscles.

Dr Mondell: Let us return to the initial request for feedback on designing a plan for therapy. I want to bring up the issue of timing and selection of an agent. For example, how does the panel position the selection and initiation of botulinum toxin type A among other treatment options? And, I would add, on what basis?

Dr Morledge: We are on the stepped care approach. In other words, we try inexpensive, oral medications first, proceed to try more expensive off-label and on-label medicines, such as anticonvulsants, and eventually botulinum toxin type A, massage therapy, acupuncture—that is, traditional approach to untraditional approaches.

Dr Mondell: Am I correct in speaking for the other panelists that such decisions really depend on the individual patient? Thus, how do we reconcile evidence-based medicine, practice paradigms, and current prescription patterns that for some patients, botulinum toxin may be first-line therapy, and for others it may never be used? Obviously, there is that very small minority of patients who are totally against botulinum toxin. Far more patients, as in this case, have an expressed preference. And, this is not without good reason because currently available oral preventative therapies are not consistently high yield in terms of success and certainly not without potentially troublesome and limiting side effects. All of us have patients who not infrequently report previous experience with weight

Figure. Common Injection Sites: Botulinum Toxin Type A

<table>
<thead>
<tr>
<th>Procerus, corrugator, frontalis, temporalis, masseter (optional), occipitalis</th>
<th>Trapezius, semispinalis, splenius capitis</th>
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Procerus, corrugator, frontalis, temporalis, masseter (optional), occipitalis
Trapezius, semispinalis, splenius capitis

5–10
5–10
5–10
10–20
10–25
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gain, sedation, impaired thinking, lightheaded dizziness, or other “intolerable” side effects and, thus, jump at the opportunity to have botulinum toxin injected. Additionally, compliance problems resulting from needing to take medication every day are no longer an issue, as is the potential for undesired medication-medication reactions. Better yet, the duration of effect of a single effective treatment is often in the range of 3 to 4 months. Thus, it really depends on the patient and informed decision making. No doubt, arbitrarily designating any single treatment as first-, second-, third-, or fourth-line therapy does not make any sense at all for the patients about whom we are speaking. Do any members of the panel have any additional thoughts?

Dr Morledge: Does anyone use serotype B much?

Dr Forde: I haven’t had much success with it. I tried it when it first came out, and I was disappointed, therefore I don’t use it anymore.

Dr Morledge: I use about 70% type A and about 30% type B.

Dr Forde: I want to make a point about patients who grind their teeth at night. I believe that if you give them a bite plate, that’s an impetus to grind even more. Hence I think botulinum toxin type A in those patients is more valuable. With regard to patients who have true trigger points—and you have to make a distinction between trigger points and tender points—botulinum toxin type A also is very effective.

Dr Dodick: Because MM only gets 3 months’ benefit, and she is calling you back repeatedly 3 weeks before her next injection, have you thought about giving her injections every 3 months instead of every 4 months?

Dr Morledge: I’m a little concerned about antibody production.

Dr Forde: Antibodies used to be the case before they reformulated the product. That is no longer an issue, at least in my practice.

Dr Morledge: Maybe if I injected her every 3 months I could lower the dose.

Dr Johnson: We clearly don’t know what the optimal injection interval is. I tend to look at botulinum toxin type A as a great preventative, because you are giving something that is not going to interact with anything else. All things being equal, we know our preventatives have about a 40% to 50% efficacy rate. I tell my patients that we’ll do their first 2 sets of injections and emphasize that the treatment is a series of injections, because it’s my belief that there may be some effect over time. Then, if it’s like any effective preventative, they get better and better, and then at 9 to 12 months, you may put some patients into remission. And you can back off their preventative, whether it’s a pill or botulinum toxin type A. Thus, what I’ve tended to do is get them on a 3-month schedule for 2 or 3 cycles. If they are doing well, with reduced headaches and using very little acute headache medication, then I let them have a longer time between treatments—just as I would start withdrawing any other preventative that they were on if they were doing well.

Dr Rothrock: I only know of 2 studies in the literature that have looked systemically at carryover effect. Ours with valproic acid was a negative study. When we looked at valproic acid, and effective suppression of chronic migraine for a mean of 8 to 10 weeks, we found that prophylaxis for this time frame wasn’t long enough. We did not demonstrate good carryover effect when we stopped the drug. However, another study by Dr Robert Kaniecki et al using a variety of prophylactic agents demonstrated that the patients remained relatively free of migraine and without the need for further prophylactic therapy for a period extending at least 18 months.

Dr Johnson: The difference between the study time period for these 2 investigations was 8 months versus a year?

Dr Rothrock: No. We used valproic acid for 8 to 10 weeks, because our population was concerned about adverse effects, such as weight gain and hair loss. After having seen the results of these 2 studies, I now cut the difference, and I use 4 to 6 months of prophylactic therapy. But I’ll say that having extensive experience with chronic methadone therapy, we can get virtually no one off methadone who has responded successfully to it. Unlike the antiepileptic drugs (AED) that seem to work for migraine, as soon as you stop the drug—even 2 years out—headaches come back again. I sincerely hope that we can get carryover effect with botulinum toxin type A, thus you can suppress the headache for 1 to 2 years.

Dr Mondell: Lest we not forget that the natural history of this disorder can be to remit. We certainly have patients who have left our care because they get better. Thus, we need to keep that in mind. Therefore, is it the carryover effect or is it the natural history of their disease?

Dr Rothrock: I’d like to ask the panel if they have noticed a similar pattern of pain relief with occipital nerve blocks, or suboccipital nerve blocks, to the botulinum toxin type A injection pattern?


**Dr Forde:** Absolutely. It’s very close.

**Dr Mondell:** Any ideas why that would be?

**Dr Rothrock:** Patients who respond dramatically to suboccipital nerve blocks seem to remain responders, often obtaining up to 3 or 4 months of headache relief. This pattern seems very similar to what I’ve observed in patients whom I’ve treated successfully with botulinum toxin type A.

**Dr Morledge:** I agree. If anything, with occipital nerve blocks, it tends to be more of an all or nothing response than with botulinum toxin type A.

**Dr Rothrock:** When we first treat a patient with headache with botulinum toxin type A, we are looking for any strong hint of a positive treatment response, and we use headache diaries to help buttress the patient’s subjective impression.

**Dr Morledge:** It is all or none with nerve blocks; with botulinum toxin type A there is a gradual onset of improvement, a gradation of response if you will.

**Dr Forde:** Those patients who may get 1 or 2 weeks of relief from an occipital nerve block are the patients in whom I would go ahead and use botulinum toxin type A. They will usually get effective and longer-lasting relief from botulinum toxin type A—3 months instead of 1 to 2 weeks.

**Dr Mondell:** Then, how do we best define the ideal candidate for a specific line of treatment?

**Dr Johnson:** Some people don’t want to take botulinum toxin type A, because of a fear factor. I emphasize the relative safety of botulinum toxin type A treatments. I explain, “This is the safest thing I can give you. You’ll take these pills with all their side effects, yet botulinum toxin type A has virtually no systemic effects.” I also emphasize that we have used botulinum toxin type A for medical therapeutics for 25 years.

**Dr Dodick:** If you give them a menu of options and the most common side-effect profiles, patients will select a drug based on the side-effect profile they most want to avoid. For example, although I think it’s an excellent drug for some patients, I have stopped topiramate in at least 33% of the patients I put on it because of cognitive side effects.

**Dr Forde:** What if you adjust the dose or schedule?

**Dr Dodick:** They take a 15-mg dose to start, and they are already having difficulties. You titrate it up, and you can’t get it to a dose that’s clinically effective.

Yet, others take 400 mg and don’t bat an eye. But it’s the most difficult drug I use. It may be one of the most effective, but it’s the most difficult.

**Dr Johnson:** I’ve used every single one of the AEDs, including gabapentin, and they all can have some cognitive side effects. They are all in the same class. I don’t find as high an incidence as Dr Dodick, perhaps more like 10% to 15% coming off because of cognitive effects. The second thing that I hear about is the sexual dysfunction that occasionally happens with AEDs. Thus, if I can pick something that’s not going to cause any of that, I would select botulinum toxin type A, because I am very comfortable with it. We’ve been using it for so long.

**Dr Dodick:** And not just that, but it’s the habitual having to take a medication every day.

**Dr Rothrock:** The topiramate trial results involving patients with chronic migraine are pending. What if the US Food and Drug Administration (FDA) approves topiramate for use in chronic migraine?

**Dr Johnson:** I’m still going to go with botulinum toxin type A. You are still going to have the same side effects with topiramate as in the population of patients with episodic migraine.

**Dr Rothrock:** You’re going to use a drug that’s not indicated for the condition under treatment rather than a drug that is indicated for that condition?

**Dr Johnson:** Absolutely. I’ve been doing that forever.

**Dr Rothrock:** In preference to a drug that is indicated and possesses class I evidence supporting its use?

**Dr Johnson:** Absolutely.

**Dr Rothrock:** If this is the case, then why do we do clinical trials? It is different when you are in a situation where you don’t know that one therapy is better than another, where you don’t have an approved therapy for the condition. It’s hard to turn one’s back on an evidence-based approach.

**Dr Johnson:** We’ve got 2 different things you are talking about: evidence based versus US FDA approved. What’s driving us now is US FDA approval. I think we have evidence for botulinum toxin type A and topiramate, but not US FDA approval for botulinum toxin type A.

**Dr Dodick:** Evidence-based medicine is incorporating evidence by exercising one’s clinical judgment. It’s not taking the results of the clinical trial and using that as dogma.

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**CASE STUDY**