BOTOX® onabotulinumtoxinA injection

CHRONIC MIGRAINE

BOTOX® for Chronic Migraine?

is it time to get started?

BOTOX® prevents headaches in adults with Chronic Migraine: 15 or more headache days a month, each lasting 4 hours or more. BOTOX® is not approved for 14 or fewer headache days a month.

BOTOX® prevents, on average, 8 to 9 headache days and migraine/probable migraine days a month (vs 6 to 7 for placebo).

It's time to think differently about how you treat your Chronic Migraine.

It's time to talk to your doctor about BOTOX® and ask if samples are available.†

in a survey,

92%

of current BOTOX® users wish they'd talked to their doctor and started treatment sooner!*

and

97%

of current BOTOX® users plan to keep using it!*

By participating in the BOTOX® Savings Program, you acknowledge and agree to the full Terms & Conditions set out at BOTOXSavingsProgram.com/TermsandConditions. Patients enrolled in Medicare, Medicaid, TRICARE, or any other government-reimbursed healthcare program are not eligible. Other restrictions and maximum limits apply.

text SAVE to 27747‡

you may pay

$0

BOTOXChronicMigraine.com

*2020 BOTOX® Chronic Migraine Patient Market Research BOTOX® Current Users (n=71).
†Only a doctor can determine if BOTOX® is right for you. Sample availability may vary by provider or location.

‡See Privacy & Terms: http://bit.ly/2RvxiWr. Message & data rates may apply. Message frequency may vary. Text HELP for help or STOP to end.

Indication

BOTOX® is a prescription medicine that is injected to prevent headaches in adults with chronic migraine who have 15 or more days each month with headache lasting 4 or more hours each day in people 18 years or older.

It is not known whether BOTOX® is safe and effective to prevent headaches in patients with migraine who have 14 or fewer headache days each month (episodic migraine).

IMPORTANT SAFETY INFORMATION

BOTOX® may cause serious side effects that can be life threatening. Get medical help right away if you have any of these problems any time (hours to weeks) after injection of BOTOX®:

- **Problems swallowing, speaking, or breathing,** due to weakening of associated muscles, can be severe and result in loss of life. You are at the highest risk if these problems are pre-existing before injection. Swallowing problems may last for several months
- **Spread of toxin effects.** The effect of botulinum toxin may affect areas away from the injection site and cause serious symptoms including: loss of strength and all-over muscle weakness, double vision, blurred vision and drooping eyelids, hoarseness or change or loss of voice, trouble saying words clearly, loss of bladder control, trouble breathing, and trouble swallowing

Please see additional Important Safety Information about BOTOX® on the adjacent page.

Allergan
an AbbVie company

Summary of Information about BOTOX® (onabotulinumtoxinA)

What is the most important information I should know about BOTOX®?

BOTOX® may cause serious side effects that can be life threatening. Call your doctor or get medical help right away if you have any of these problems any time (hours to weeks) after injection of BOTOX®:

- **Problems swallowing, speaking, or breathing,** due to weakening of associated muscles, can be severe and result in loss of life. You are at the highest risk if these problems are pre-existing before injection. Swallowing problems may last for several months
- **Spread of toxin effects.** The effect of botulinum toxin may affect areas away from the injection site and cause serious symptoms including: loss of strength and all-over muscle weakness, double vision, blurred vision and drooping eyelids, hoarseness or change or loss of voice, trouble saying words clearly, loss of bladder control, trouble breathing, and trouble swallowing

There has not been a confirmed serious case of spread of toxin effect away from the injection site when BOTOX® has been used at the recommended dose to treat Chronic Migraine.

BOTOX® may cause loss of strength or general muscle weakness, vision problems, or dizziness within hours to weeks of taking BOTOX®. **If this happens, do not drive a car, operate machinery, or do other dangerous activities.**

BOTOX® dosing units are not the same as, or comparable to, any other botulinum toxin product.

What is BOTOX®?

BOTOX® is prescription medicine a medical professional injects into muscles to prevent headaches in adults with chronic migraine who have 15 or more days each month with headache lasting 4 or more hours each day in people 18 years and older.

It is not known whether BOTOX® is safe or effective to prevent headaches in people with migraine who have 14 or fewer headache days each month (episodic migraine).

Who should not receive BOTOX®?

Do not receive BOTOX® if you are: allergic to any of the ingredients in BOTOX® such as botulinum toxin type A and human serum albumin; had an allergic reaction to another botulinum toxin product such as Myobloc® (rimabotulinumtoxinB), Dysport® (abobotulinumtoxinA), or Xeomin® (incobotulinumtoxinA); or have a skin infection at the planned injection site.

What should I tell my doctor before treatment?

Tell your doctor about all your muscle or nerve conditions, such as amyotrophic lateral sclerosis (Lou Gehrig's disease), myasthenia gravis, or Lambert-Eaton syndrome, as you may be at increased risk of serious side effects.

Tell your doctor if you have or have had breathing problems such as asthma or emphysema; swallowing problems; bleeding issues; plan to or have had surgery; have forehead muscle weakness such as trouble raising your eyebrows; drooping eyelids; or any changes to your face.

Tell your doctor if you are pregnant, plan to become pregnant, are breastfeeding or plan to breast feed. It is not known if BOTOX® (onabotulinumtoxinA) can harm your unborn baby or if BOTOX® passes into breast milk.

What Are Common Side Effects?

The most common side effects include neck pain; headache; migraine; slight or partial facial paralysis; drooping eyebrows; eyelid drooping; bronchitis; musculoskeletal stiffness; muscular weakness; pain in 1 or more muscles, ligaments, tendons, or bones; muscle spasms; injection site pain; and high blood pressure. Other side effects have been reported including allergic reactions e.g. itching, rash, red itchy welts, wheezing, asthma symptoms, or dizziness or feeling faint.

These are not all of the possible side effects. Call your doctor for medical advice if you experience any side effects after treatment with BOTOX®.

What Should I Tell My Doctor About Medicines and Vitamins I Take?

Using BOTOX® with certain other medicines may cause serious side effects. **Do not start any new medicines until you have told your doctor that you have received BOTOX® in the past.** Tell your doctor if you have received an injection with another botulinum toxin product in the last 4 months, such as Myobloc®, Dysport®, or Xeomin®. Be sure your doctor knows which product you received.

Tell your doctor about all prescription and over-the-counter medicines, vitamins and herbal supplements you take; recent antibiotic injections; anticholinergics; muscle relaxants; allergy or cold medicine; sleep medicine; aspirin-like products; and blood thinners. **Ask your doctor if you are not sure whether your medicine is listed above.**

To Learn More

If you would like more information, talk to your doctor and/or go to BotoxChronicMigraine.com for full Product Information.

You may report side effects to the FDA at www.fda.gov/medwatch or call 1-800-FDA-1088.

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So What Else is New?

A parade of new migraine therapies!

For this issue's migraine treatment of the month we featured an "old" therapy, onabotulinumtoxinA (BotoxA). While even after more than a decade of clinical use in that clinical setting BotoxA remains an attractive alternative for prevention/suppression of chronic migraine, new therapies that are no less attractive have emerged. Chronic migraine aside, there are also a number of new choices for the prevention of episodic migraine and for acute migraine treatment. While it's nice to have so many new options, the number of new therapies and the rapidity with which they have arrived has had a dizzying effect. The following is intended to serve as a simple overview of the "newbies". Readers can drill down deeper to learn more by utilizing the links provided, but what is presented here should provide them with the basics of how these new therapies are grouped and what is/are the specific clinical indications for each.

[Please note: while this article will focus on new medications for migraine, there have been many advances in the use of devices and other non-pharmacologic options for headache management as well; these non-pharmacologic therapies will be the subject of an upcoming article]

For Migraine Prevention

The anti-CGRP monoclonal antibodies

We addressed this new class of migraine medications in some detail in past issue of the magazine and subsequently in a blog posted on the magazines website. To recap, there are three anti-CGRP monoclonal antibodies (Mabs) available for prevention of episodic migraine or suppression of chronic migraine which are self-injected subcutaneously (under the skin) once monthly (with the option for every three month therapy: erenumab (***Aimovig***), galcanezumab (***Emgality***) and fremenezumab (***Ajovy***); with Ajovy there is the option of administering the medication monthly or every three months. Joining these self-administered anti-CGRP Mabs epitenzumab (***Vyepti***), administered intravenously every three months. Even to a therapeutic cynic, it is difficult to find much of anything bad to say about these four Mabs aside from the fact that dealing with insurers to navigate the prior authorization maze is driving providers crazy. Their short and long-term safety appears excellent, and they typically are well-tolerated. A large proportion of patients who choose one of these treatments experience a significant reduction in migraine burden that may start to become evident as soon as the first week following initiation of treatment. Insurer-related roadblocks aside, all of these represent excellent options for migraine prevention therapy.

The "gepants"

Atogepant (***Qulipta***) recently received FDA approval as a prevention medication for patients with episodic migraine (remember: episodic migraine implies less than 15 days of headache per month, while chronic migraine implies 15 or more days). Like the Mabs mentioned above, Qulipta blocks the action of calcitonin gene related peptide (CGRP) in the biologic circuit that conducts migrainous head pain signal, but it is a much smaller molecule, is not classified as an antibody and may be administered orally. Taken on a daily basis in one of three available doses, it is notable for its safety, effectiveness and the rapidity with

which many patients begin to experience a reduction in headache burden.

Rimigepant (***Nurtec***) initially was developed as a treatment for acute migraine headache and is FDA-indicated for that purpose. Subsequently it was found to be effective as a prevention therapy for episodic migraine when taken orally on a scheduled every other day basis. More on this intriguing "gepant" in the "**Hybrid**" section of this article.

For Acute Migraine Treatment

The "gepants" again

The introduction of ubrogepant (***Ubrelvy***) and rimegepant (***Nurtec***) offers migraine patients a very welcome alternative to the triptan class for acute migraine treatment. As with the anti-CGRP Mabs and Qulipta, these anti-CGRP "small molecules" that are administered orally appear to be safe, generally well-tolerated and often highly effective. At 11 hours, Nurtec has a half-life longer than Ubrelvy's and considerably longer than any of the "fast-onset" triptans, but whether that longer presence in the body clearly translates to a lower incidence of early recurrent headache must await an active comparator trial evalkuating Nurtec vs UBrelvy or another therapy known to be effective for acute migraine treatment.

Ubrelvy is available in two doses, 50 and 100 mg, and the Nurtec dose is 75 mg only. While the patient instructions for Ubrelvy will be familiar to any veteran of oral triptan therapy ("take 1 for acute migraine headache; may repeat after 2 hours as needed; max 'x' doses per 24 hours"), the instructions for Nurtec may seem oddly abbreviated ("take 1 as needed for acute migraine headache"), with no provision for a second dose or stipulation as the total maximum amount to be taken in any 24 hour period. For both drugs this is a direct reflection of how the clinical research studies that earned them their FDA approval were conducted. In the case of Nurtec, there was no provision for repeat dosing in the study protocol. This "one and done" aspect does not indicate that it would be *unsafe* to take a second dose in, say, 8 hours if one's headache recurred. Nor is *safety* of repeat dosing implied. At this time there simply are no reliable safety data to guide us in recommending for or against administering a second dose of Nurtec within 24 hours of the initial dose.

In comparing Ubrelvy with Nurtec it's all too easy to wander off into the weeds. More important to keep in mind than differences in half-lives and dosing instructions is that both medications represent excellent alternatives for patients who fail to respond to oral triptans or cannot tolerate the triptan class. Some patients will love Nurtec. Others will love Ubrelvy. Others will love both. Some will find neither effective. Such is the nature of migraine therapy, and thus the need for options.

The "ditans"

Lasmiditan (***Reyvow***) represents the first of the long sought-after "ditans", medications for acute migraine treatment that – like the triptan - would activate a receptor in the migraine circuitry which inhibits conduction of head pain signal but do so without also producing potential constriction of blood vessels. While Reyvow is burdened by a less favorable side effect profile than the gepants (with sedation and "dizziness" as the leading side effects) and by the need for it to be prescribed as a "controlled" medication, for some patients it nevertheless represents a very nice alternative to either the tripans or the gepants for acute migraine treatment. It is an orally administered drug available in two doses: 50 and 100 mg.

> **To have so many new therapies arrive so rapidly has had a dizzying effect.**

Dihydroergotamine (DHE)

And then there is an old dog doing new tricks.

Dihydroergotamine (DHE) is an interesting drug that has been used to treat migraine for at least four decades. For many years it has been administered intravenously to patients with acute, severe migraine resistant to self- administered treatment, and it remains a therapeutic mainstay in ERs and headache infusion centers. In an intriguing trial that few now remember, subcutaneously administered DHE was almost as rapidly effective in relieving moderate to severe acute migraine headache than was subcutaneously administered sumatriptan; DHE has a far longer half-life in the body than subcutaneously administered sumatriptan, and not surprisingly the study demonstrated a much lower rate of early headache recurrence with DHE. Had not the effort to establish a patentable DHE paired with an auto-injector fallen just short of FDA approval, migraine patients today would have an attractive alternative to injectable sumatriptan for "rescue" from their most severe headaches.

A previous attempt to bring intranasally administered DHE to general clinical practice was successful, and the results of that effort, Migranal, still is used by some migraineurs. For a variety of reasons, however (the drug's unfortunate tendency to produce unpleasant nasal congestion and its relatively high cost amongst them), Migranal is infrequently prescribed.

And now there is ***Trudhesa***, like Migranal an intranasal spray formulation of DHE but administered via a device that seeks to direct the medication to the area of the nasal passage where it will be absorbed rapidly. Hopefully this provide

for patients disinclined to self-inject and requiring a faster alternative than orally administrated medication for their more severe headaches a new, well-tolerated and effective alternative.

The "Hybrid"

Nurtec is a bit of an oddball. In the one-year safety study that followed the phase 3 clinical research trial which earned Nurtec its FDA indication for acute migraine treatment, the drug was safe, well-tolerated and persistently effective over the follow-up period, but more interesting to clinical investigators was the observation that those patients with relatively high frequency episodic migraine who took open-label Nurtec for acute headache treatment during the one-year safety study experienced not only headache relief on those days when the medication was administered but also a tendency to experience a progressive decline in headache frequency over the ensuing months. In other words, the "acute" therapy appeared to have a "downstream" migraine prevention effect.

This led to a conventional Nurtec versus placebo prevention trial for episodic migraine patients which confirmed that Nurtec is effective for migraine prevention when taken on a an every other day scheduled basis. Interesting treatment. For those disinclined to start a prevention therapy but desiring both acute relief from acute headache and an overall decline in headache frequency, liberal use of "as needed" Nurtec *might* represent a particularly attractive option.

Other potential indications for this hybrid include taking Nurtec on a scheduled basis for 5-7 days for "miniprophylaxis" of menstrually-associated migraine, reverting to "as needed" use for the remainder of the female migraineurs cycle, or doing the same to suppress and prevent the "wearing-off effect" experienced by so many patients receiving serial onabotulinumA (Botox) injection therapy as they are nearing the end of the 12 week cycle between treatments. In both cases the use of Nurtec seems to make sense but as yet lacks scientifically sound evidence.

Roadblocks

So are there any trolls lurking under the bridge with the potential to spoil this sudden abundance of options for the pharmacologic treatment of migraine?

It depends upon your perspective. Recently published data suggest Botox and Aimovig may be synergistic in treating chronic migraine. If you are a physician who wishes to prescribe, say, Aimovig for suppression of chronic migraine to a patient who has experienced a partial positive response to serial Botox injection therapy, good luck. Few are the insurers who will authorize treatment with both therapies. Suppose you simply want to prescribe Aimovig for a patient with chronic migraine who is entirely naïve to prevention therapy? You, the provider, will find that the patient's insurer typically will require your patient to try and fail three "conventional" (i.e., cheap/generic) oral therapies that lack any FDA indication for chronic migraine and in most cases lack even a thin evidence base for use in that clinical setting before he/she may receive Aimovig. To try (and quite likely fail) three such therapies may take months, and the longer the patient continues to experience chronic migraine, the more difficult it may become to extricate her/him from that particular swamp. These are but two of the myriad of insurer vs provider problems that arise when the provider deigns order one of the new medications described above.

Your choice as a provider: "dance with the Devil", and endure without any financial compensation or particular gratitude from any source the effort of plowing through the prior authorization and appeal process, all the while attempting to respond positively to your patient's annoyance with you or your staff's inability to get tha patient what you preferred to prescribe in the first place. Or…disengage; take yourself out of the equation and leave the patient to do the dancing without your intervention. It is not a happy situation, and it's getting worse. More on this in a future issue.