BEBRF Database Survey

(Please Print)

First name: _____

Middle name: _____

Last name: _____

Title: (Mrs, Dr, Mr, Miss, Ms) _____

Preferred name/nickname: _____

1) What year were you born? _____
2) Gender: _____
3) Mailing Address:

   Address: _____

   City: _____

   State/Province: _____

   Zip Code: _____

   Country: _____
4) Permission to contact you by US mail? (Including newsletters)

   O Yes

   O No
5) Phone Numbers:

   Home: _____

   Cell: _____

   Other: _____
6) Email Address: _____
7) Permission to contact you by email?

   O Yes

   O No
8) Do you currently attend BEBRF Support Group Meetings?

   O Yes

   O No
9) Year you last attended? (Please estimate if you're not sure) _____

10) Diagnosis: (Check all that apply)

- O Blepharospasm
- O Hemifacial spasm
- O Meige
- O Other _____

11) Age when symptoms began: _____

12) Age when you were diagnosed: _____

13) Who diagnosed you?

- O Self
- O Family physician
- O Ophthalmologist
- O Other _____
- O Neurologist
- O Neuro-ophthalmologist
- O Internet

14) Areas of spasm in addition to eyelids: (Check all that apply)

- O Meige/Lower face
- O Jaw Clenching
- O Diaphragm/Breathing muscles
- O Shoulders
- O Neck/Cervical muscles
- O Vocal cords/Speech

15) Are you currently receiving botulinum toxin injections?

- O Yes
- O No

16) When did you start receiving botulinum toxin?

- O _____ (Enter year)
- O I'm not sure

17) Which botulinum toxin are you currently receiving? (Generic names included)

- O Botox (onabotulinum toxin A)
- O Xeomin (incobotulinum toxin A)
- O Dysport (abobotulinum toxin A)
- O Myobloc (rimabotulinum toxin A)

18) Who is your current treating physician/injector? _____

19) Injecting doctor's specialty:

- O Neuro-ophthalmology
- O Neurology
- O Other _____
- O Ophthalmology
- O Oculoplastic Surgery

20) Doctor's address and phone number:

Address: _____

City: _____

State/Province: _____

Zip Code: _____

Phone Number: _____

21) Have you had surgery for your blepharospasm/dystonia?

- O Yes
- O No

22) What type of surgery did you have? (Check all that apply)

- O Myectomy complete
- O Myectomy partial
- O Blepharoplasty (lid lift)
- O Ptosis repair (levator tendon repair)
- O Frontalis sling
- O Punctal plugs/punctal occlusion
- O Brow lift/brow pin
- O Deep brain stimulation
- O Ectropion repair
- O Microvascular decompression
- O I'm not sure
- O Other _____

23) Name, address and phone number of doctor who did your surgery:

Name: _____

Address: _____

City: _____

State/Province: _____

Zip Code: _____

Phone Number: _____

24) Do you have a family history of blepharospasm, dystonia, or movement disorders?

- O Yes
- O No
- O I don't know

25) If yes, which relatives? (Check all that apply)

- O Mother
- O Father
- O Maternal grandmother
- O Maternal grandfather
- O Paternal grandmother
- O Paternal grandfather
- O Brother
- O Sister
- O Cousin
- O Maternal aunt
- O Maternal uncle
- O Paternal aunt
- O Paternal uncle

26) What is/was your relative's diagnosis? (Check all that apply)

- O Blepharospasm
- O Hemifacial spasm
- O Meige
- O Spasmodic torticollis
- O Other (please specify) _____
- O Spasmodic dysphonia
- O Parkinson's
- O Writer's cramp
- O Essential tremor

27) Name of spouse/partner: (if applicable) _____

28) How would you prefer to receive the BEBRF newsletter?

- O US mail
- O Email
- O No thank you, I don't want the newsletter

29) How did you learn about BEBRF?

- O Internet search
- O Doctor
- O Other _____
- O Friend
- O Relative

30) Are you on Social Security Disability due to your blepharospasm/movement disorder?

- O Yes
- O No

31) Would you be willing to share your experience regarding your disability application process?

- O Yes
- O No

Thank you!

Medical Glossary: A Reference for BEBRF Patients

Apraxia of eyelid opening − a neurologic condition characterized by difficulty keeping the eyes open because the muscles that open the eyes don't work, not because of spasms of the muscles that close the eyes

Artane® (generic term, trihexyphenidyl) − An anti-movement drug taken by mouth that is used to treat some patients with Blepharospasm or Meige syndrome; said to help about 30% of patients

Artificial tears − lubricant eye drops used to treat the dryness and irritation associated with deficient tear production (dry eyes)

Basal ganglia − areas deep inside the brain that are believed to play a major role in the coordination of voluntary muscle movement

Benign − does not kill; is not fatal or malignant

Benign Essential Blepharospasm (BEB) – see "Blepharospasm"

Blepharo − Greek word meaning eyelid

Blepharitis – an infection of the eyelid

Blepharospasm − involuntary forcible closure of the eye by the eyelid muscles

Primary blepharospasm – usually occurs without the symptoms of any other neurological or metabolic disease; considered to be caused by changes in the brain that have not yet been identified; most common type of blepharospasm

Secondary blepharospasm − attributed to an outside factor such as physical trauma, exposure. to certain medications, or additional neurological or metabolic diseases; sometimes associated with brain lesions or drugs

Botulinum neurotoxin (BoNT) – a biologic nerve toxin derived from bacteria which when injected directly into the muscles, temporarily weakens the muscle fibers so they remain relaxed and no longer contract, thus preventing uncontrollable muscle spasms. Note: This is the BEB "treatment of choice." It is known to wear off in about 3 months so injections need to be repeated. Individual patients will spasm differently and therefore require different dosages at different intervals. Examples are: Botox® by Allergan and Xeomin® by Merz

Brow pin – a micro−screw device surgically implanted to help hold open the eyelids

Chemodenervation – used to describe BoNT injected into overactive muscles to paralyze or weaken them

Deep Brain Stimulation (DBS) − continuous, high−frequency electrical stimulation in the brain by means of an implanted electrode controlled by a battery just below the clavicle; these signals block those from the brain that cause spasms and tremors; most successful on larger muscles

Dopamine − neurotransmitter chemical found in the brain and believed to play a role in many dystonias

Dry eye syndrome – an ocular surface condition in which there is a decrease in the quality or quantity of tears, resulting in drying out of the ocular surface causing discomfort, visual disturbance, secondary tearing, or a foreign body sensation

Dystonia − a neurological movement disorder in which involuntary, sustained and repetitive muscular contractions result in abnormal movements. Some frequent types: blepharospasm (eyes), cranial (mouth & jaw), cervical dystonia or torticollis (neck), spasmodic dysphonia (larynx), writer's cramp (hand), and generalized (throughout the body)

EMLA cream – An anesthetic cream that can be used to reduce the discomfort of BoNT injections; applied to the injection sites 45 minutes before the injections are to be performed

Epiphora – Another word for "tearing"

Essential − the isolated critical feature

Etiology – the cause, set of causes, or manner of causation of a disease or condition

Focal dystonia – a subtype of dystonia in which a single body part is affected with contractions; with BEB it is in the eyelid muscles

FL−41 glasses − a special type of rose colored lenses that filter certain wavelengths of light and which might reduce symptoms of photophobia

See other side

Functional blindness – although the term "functional" has many meanings, in this context it means blindness that limits or prevents daily functions or activities (example: driving)

Genotype – the complete set of genes or genetic material present in a cell or organism

Idiopathic − of unknown cause

Hemifacial spasm – a neuromuscular disorder characterized by spasming seen on only one side of the face; this is not a dystonia but rather thought to be caused by compression of the facial nerve; treatment sometimes similar to BEB; surgery might relieve symptoms for some patients

Klonopin® (generic, clonazepam) − An anti−movement drug taken by mouth that is used to treat some patients with blepharospasm or Meige syndrome.

Levator muscle − main muscle in the upper eyelid responsible for raising the eyelid

Meige syndrome – a form of facial dystonia named after Henri Meige, in which blepharospasm is associated with involuntary movements of the mid and lower facial muscles; symptoms include forceful contractions and thrusts in the mouth, jaw or tongue causing difficulty in opening and closing the mouth and can affect chewing and speech. It is now often called cranial dystonia.

Movement disorder − neurological condition that affects the ability to control muscle movement; common disorders are Dystonia, Essential Tremor, and Parkinson's disease

Myectomy (**limited or radical)** – surgical procedure to remove some or most of the muscles that close the eyelids; sometimes performed on patients for whom BoNT is not effective; often BoNT injections are still needed

Orbicularis oculi muscle – the main muscle that closes the eyelid; it is shaped like an ellipse encircling the whole eye

Oromandibular (OMD) − pertaining to the mouth, jaw or tongue.

Pathophysiology – the functional changes that produce a particular syndrome or disease

Patho – Greek word meaning relating to disease

Physiology branch of biology that deals with the normal functions of living organisms

Phenotype − the set of observable characteristics of an individual resulting from the interaction of its genotype with the environment

Photophobia – extreme sensitivity to light; **not** the fear of light

Plasticity – the quality of being shaped or molded; the adaptability of an organism to changes

Ptosis – (pronounced \to−ses\, drooping or falling of eyelid(s) that limits the ability to fully open the eye which can result in decreased vision

Ptosis crutches − elevate the eyelid and allow the eye to be opened; mounted on the top inside of eyeglasses to help hold the upper lid open

Procerus muscle − a small pyramidal slip of muscle deep to the superior orbital nerve, artery and vein; its Latin meaning − tall or extended

Punctal Plugs – also known as tear duct plugs or lacrimal plugs, these are small medical devices inserted into the tear duct (puncta) to treat dry eye. They block the duct and prevent drainage of liquid from the eye; used to treat dry eye. Artificial tears are usually still required

Residual functional capacity − the most you can do despite physical or mental limitations that affect what you can do in a work setting

Spasm – involuntary contraction of muscles that can be sudden

Synapse – a junction between two nerve cells or between a nerve and muscle, consisting of a minute gap across which chemical signals (neurotransmitters) pass

Thalamus – a deep midline brain region that relays sensory and other information to higher levels of the brain (cerebrum) helping to control voluntary movements and higher mental functions

Drugs That May Cause Dystonia (tardive dyskinesia):

This drug list is intended to provide information only. We do not advocate any particular treatment option. Therefore, it is strongly suggested that patients do not change their method of treatment without first consulting with their physician.

GENERIC	TRADE NAME	CLASSIFICATION
acetophenazine	Tindall®	neuroleptic
alprazolam	Xanax®	anti-anxiety agent
amitriptyline	Elavil®, Endep®, Etrafon®	antidepressant
amoxapine	Asendin®	antidepressant
benzquinamide	Emete-Con®	anti-nausea/vomiting agent
bupropion	Wellbutrin®	antidepressant
buspirone	Buspar®	anti-anxiety
carbamazepine	Tegretol®	anticonvulsant
chlorpromazine	Thorazine®	neuroleptic
chlorprothizene	Taractan®	neuroleptic
clomipramine	Anafranil®	antidepressant
clozapine	Clozaril®	neuroleptic
desipramine	Norpramin®	antidepressant
diprivan	Propofol	anesthesia
doxepin	Adapin®, Sinequan®, Silenor®	antidepressant
droperidol	Innovar®, Inapsine®, Dridol®	anti-anxiety, anesthetic adjunct fluoxetine
	Prozac®, Rapiflux®, Sarafem®	antidepressant
fluphenazine	Permitil®, Prolixin®	neuroleptic
haloperidol	Haldol®	neuroleptic
imipramine	Tofranil®	antidepressant
lamotrigine	Lamictal®	neuroleptic
levodopa	Sinemet®, Parcopa®, Atamet®	antiparkinson agent
lithium	Eskalith®, Lithobid®	antimanic agent
loxapine	Loxitane®, Daxolin®	neuroleptic
mesoridazine	Serentil®	neuroleptic, gastrointestinal (unavailable in the US)
metoclopramide	Reglan®, Metozolv®	anit-nausea/vomiting agent
midazalam	Versed®	induction anesthetic agent
molindone	Lindone®, Moban®	neuroleptic
nortripyline	Aventyl®, Pamelor®	antidepressant
olanzapine	Zyprexa®	neuroleptic
perphenazine	Trilafon®, Triavil®	neuroleptic
phenytoin	Dilantin®	anticonvulsant
pimozide	Orap®	neuroleptic
prochlorperazine	Compazine®, Compro®	anti-nausea/vomiting agent
promazine	Sparine®	neuroleptic
promethazine	Phenergan®, Pentazine®,	antihistamine
protriptyline	Vivactil®	antidepressant
quetiapine	Seroquel®	neuroleptic
risperidone	Risperdal®	neuroleptic
thiethylperazine	Torecan®	anti-nausea/vomiting agent
thiothixene	Navane®	neuroleptic
trifluoperazine	Stelazine®	neuroleptic
triflupromazine	Vesprin®	neuroleptic
thioridazine	Mellaril®	neuroleptic
trazodone	Desyrel®	antidepressant
trifluoperazine	Stelazine®	neuroleptic
trimipramine	Surmontil®	antidepressant
ziprasidone	Geodon®	neuroleptic

BLEPHAROSPASM

The characteristics of benign essential blepharospasm (BEB) that set it apart from other conditions are as follows: The condition most commonly affects individuals over the age of 50 and becomes increasingly common with age. The squeezing of the muscles of eyelid closure occurs ultimately on both sides, even if it begins only on one side. If you have eyelid squeezing only on one side and it remains on one side for several years, it is very unlikely that you have benign essential blepharospasm. The converse is also true if the squeezing that you have is on both sides, it is very unlikely that you have hemifacial spasm, although bilateral hemifacial spasm has been described in a few patients.

Dr. Stanley Fahn has divided blepharospasm into four stages. **Stage 1**: Increased blinking only. **Stage 2**: Blinks that are more sustained, but not forceful. **Stage 3**: Forceful contractions of the entire orbicularis oculi with prolonged closure of the eyes. **Stage 4**: Powerful contractions of all the eyelid closing muscles, including accessory muscles of eyelid closure, such as those of the forehead, with prolonged and sustained closure of the eyes.

The spasms of benign essential blepharospasm are unpredictable and non-stereotyped. By this, I mean there is no definite trigger that will produce eyelid closure every time, such as there is with facial nerve regeneration after a Bell's palsy, where smiling may always lead to closure of the eyelid on that side. By saying that the movements are not stereotyped, I mean that on some occasions, an individual with this condition may feel and appear to have almost normal eyelid movements, whereas, at other times, there may be extremely forcible closure. This is in contrast to conditions such as hemifacial spasm, where almost the same pattern of movement abnormality will occur every time the twitch occurs, even though the frequency of twitching may change.

Patients with benign essential blepharospasm frequently report ocular symptoms prior to the onset of blepharospasm and during blepharospasm, such as sensitivity to light, dry eyes, various kinds of ocular pain, or excessive tearing of the eyes. This may be accompanied by signs of corneal drying that the ophthalmologist may be able to detect during an eye examination. Many patients report that bright lights, stress, fatigue, watching television, and driving all make the spasms more intense, whereas the intensity of squeezing is relieved by sleep and relaxation. Many patients discover that maneuvers, such as touching the eyelids, chewing, vocalizing, coughing, or rubbing the forehead may allow temporary suppression of the involuntary squeezing. These are sometimes referred to as sensory tricks. Patients with benign essential blepharospasm, by definition, do not have other symptoms of involuntary movement disorders, such as orofacial spasms involving the lower face, as is seen in Meige syndrome, involuntary eye elevation, neck muscle contractions, or involuntary movements of the arms or legs. Furthermore, patients with benign essential blepharospasm do not have an identifiable cause for the condition in contrast to patients with known degeneration of the basal ganglia, such as may occur in multiple sclerosis, strokes, and Parkinson's disease.

In addition to involuntary closure of the eyelids, patients with benign essential blepharospasm may have a feature called apraxia of eyelid opening, which describes an inability to initiate the opening of the eyes, usually following an episode of spasm, that is not associated with tonic contraction of the closing muscles of the eyelids, but rather an inability to activate the opening muscles. This reflects the central origin of the condition as a complex interplay between the muscles of closure and the muscles of opening and the higher brain level control of the coordination of these muscles.

Patients with this condition do not usually have evidence of facial weakness; however, with years of prolonged squeezing, secondary features that look like weakness may occur, such as drooping of the brows and drooping of excessive skin of the upper eyelids.

The recognition of benign essential blepharospasm (BEB) may be hindered by the fact that it has been given a complex and perhaps not very helpful name. Many patients and doctors have pointed out that there is nothing benign about the condition and it certainly isn't essential in the usual meaning of the word; most people feel that they could get along perfectly well without it. In this context the word essential means occurring with no other abnormalities. The word blepharospasm, when broken down into its roots, is fairly descriptive, but is in medicalese, rather than common language. Blepharo refers to eyelid and spasm the uncontrolled closing of the eyelids. Simplifying the word to the term blepharospasm alone is more satisfactory; however, it does not differentiate this particular condition from other forms of uncontrolled eyelid closure such as hemifacial spasm or even simple eyelid twitching (or fasciculations of the eyelid).

As noted above, the cause of benign essential blepharospasm is unknown. We hope that future research will lead us to appropriate treatments through a greater understanding of the origin of the condition.

Robert S. Baker, M.D., University of Kentucky, Lexington, Kentucky

Blepharospasm and Dry Eyes: Diagnosis and Treatment

Donald Faucett, MD

Many patients frequently call following BOTOX injections, complaining of dry eye symptoms. The intent of this brief article is to help you understand this problem and its treatment. The symptoms of a dry eye include: burning, stinging, scratchiness, increased light sensitivity, blurring of vision or stringy mucous secretions.

Paradoxically, patients also occasionally complain of excess tearing when the eye is actually too dry. To understand this last statement, one must be aware that we have small glands in the eyelid and on the surface of the eye that are responsible for the constant production of tears. The larger gland that most people think of works when one is in emotional or physical pain, if the eye has a foreign body, or is not being adequately protected by the glands in the lids and the eye. When the eye is not protected, one frequently experiences the burning, stinging, etc., and the lacrimal gland turns on resulting in excess tearing (epiphora). Epiphora can also be the result of improper drainage; however, this will not be discussed at this time.

One's tear film serves many functions: these include provision of a smooth surface for clear vision, protection and nutrition, just to mention a few. Following toxin injections, one's ability to blink decreases dramatically resulting in the above dry eye symptoms. This is why your doctor always recommends the use of artificial tears following toxin injections. Occasionally, one has to use these agents chronically. When patients require frequent use of one's natural tears, other treatment options are available to eliminate the use of artificial tears.

One of the most common options used by physicians to decrease the use of artificial tears is the use of the punctal plugs. These come in both dissolvable and permanent forms and are used to block the drainage of one's tears. Punctal plugs are inserted in the punctum which is the small opening in the eyelid next to the nose. This is the entry point into the tear drainage system. Frequently, physicians will start with a dissolvable plug to see if this improves or resolves the symptoms. If this does help, then permanent plugs or other surgical procedures are used to permanently close the puncta. When these procedures are used, one usually sees a dramatic reduction or elimination in the need for artificial tears.

The complete evaluation and management of the problem of dry eyes is often lengthy and requires patience and perseverance by both the patient and his physician.

GENETICS OF BLEPHAROSPASM

Mark Hallett, M.D.

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In order to truly understand blepharospasm and find the best treatment, it will be necessary to understand its cause. The cause of a disease is often not a single element but may be multiple elements. Moreover, the cause may differ in different people. Medicine is replete with examples of a single disorder resulting from several different etiologies.

It seems very likely now that one of the major etiological factors in producing blepharospasm is genetic. This means that a person's genetic makeup will be important in whether he or she develops blepharospasm or not. In some circumstances the genetic factor may be so powerful that it can produce blepharospasm by itself. In other circumstances it may provide a background on which another factor triggers and produces the blepharospasm.

What is the evidence that there is a genetic factor in blepharospasm? First of all, it has to be accepted that blepharospasm is a form of focal dystonia. Dystonia is a group of disorders characterized by involuntary muscle spasms. Common focal dystonias in addition to blepharospasm include: oral mandibular dystonia, spasmodic dysphonia, spasmodic torticollis, and hand cramps. We know that these focal dystonias are related to each other since many of them are seen in patients who have generalized dystonia or are early manifestations of generalized dystonia. Additionally, patients sometimes can have several different focal dystonias. Lastly, different family members can be affected with different types of focal dystonias. Already it is established that several types of generalized dystonia are produced genetically.

There is beginning to be strong evidence now that focal dystonias may also be caused genetically. The evidence comes from several fairly large epidemiological studies where families of patients with focal dystonia were examined. In these families, a number of other family members were found who had similar or different focal dystonias. For example, a patient with blepharospasm might well have another relative with blepharospasm or a relative with a different focal dystonia such as spasmodic torticollis. The frequency of other family members having focal dystonias is only about 5%, but this frequency is clearly more than what is seen in the general population and hence implies a genetic etiology.

The implication of this epidemiological information is that there is only a 1 in 20 chance of any relative of a patient with blepharospasm to also have a focal dystonia. This relates to children of patients with blepharospasm, for example. Hence, should you have blepharospasm, there is only a 1 in 20 chance for each of your children that they will have a focal dystonia like blepharospasm.

The possibility of finding a gene that causes blepharospasm is very exciting. Once a gene is found, this should lead to a much clearer understanding about blepharospasm. Such work is likely to take many years, but it should be a good start in the right direction. We are all hopeful that finding a gene relevant to blepharospasm will be a gateway to finding the final cure of this disorder.

Diagnosing Blepharospasm and Meige Syndrome: A Neuro-Ophthalmologist's Approach

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In a recent issue of Ocular Surgery News, a journal received by all ophthalmologists, one of my colleagues, Professor Alfredo Sadun at the University of Southern California in Los Angeles, emphasized that a good patient history and a systemized approach based on logic are the best diagnostic tools in neuro-ophthalmology. He points out that complicated instruments and laboratory testing are not nearly as important as a complete history followed by an examination that is based on that history. Nowhere is this truer than in the diagnosis of blepharospasm, Meige syndrome, and hemifacial spasm. As any patient with any of these conditions knows only too well, the main symptoms of all three conditions are involuntary eyelid and/or facial movements that may or may not be obvious when the patient sees his or her doctor.

In patients with benign essential blepharospasm, the movements are only of the eyelids on both sides without any abnormal movements of the rest of the face. In patients with Meige syndrome, the abnormal eyelid movements are also on both sides but are also associated with movements of both sides of the mid and lower face. In patients with hemifacial spasm, however, the movements are only on one side of the face. In many cases, particularly during a brief examination, the involuntary movements may not be apparent to the doctor who is examining the patient. Thus, it is crucial for the patient to explain as accurately as possible if the movements are on one side or both sides of the face, whether they affect only the eyelids or more of the face, whether they are constant or intermittent, whether anything makes them better or worse, any associated problems like light sensitivity, etc. It is also crucial for the doctor to LISTEN to the patient's history. Once the doctor has heard the history, he or she can look specifically for the findings that confirm his or her impression and can then discuss the treatment options and initiate treatment. Unfortunately, too many doctors do not take the time to listen to their patients and thus wind up either not making the diagnosis or performing a lot of needless tests. For example, patients with blepharospasm or Meige syndrome do not need blood tests, CT scanning, or MR imaging, but these tests are often performed by doctors who have not listened to the patient and do not realize that they have a condition for which such tests are not needed.

MEDICAL THERAPY FOR BLEPHAROSPASM

Stephen G. Reich, M.D.
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University of Maryland School of Medicine
Co-director, Maryland Parkinson's Disease and Movement Disorders Center

Prior to the introduction of botulinum toxin in the mid 1980s, oral medications were the mainstay of therapy for benign essential blepharospasm (BEB). With little knowledge of the cause(s) or changes assumed to be present in the brain responsible for blepharospasm, therapy was (and remains) largely empirical. That's a nice way of saying we put forward our best guesses and flew by the seat of our pants. As such, a diverse spectrum of medications was tried in succession hoping to hit on one, or a combination, that would strike a balance between reducing spasm and minimizing side effects. Next to those suffering from blepharospasm and their families, no one was more frustrated than we treating physicians. Medications alone generally do not provide acceptable treatment of blepharospasm. Yet, they do have a role and while many of my patients swear medications off, there are enough who swear by them, to encourage their use. What follows is my own approach for medical treatment of BEB. It is gleaned from a combination of the very few rigorous trials of medical therapy carried out for BEB, applying what we do know about brain changes in BEB, but mostly from flying by the seat of my pants trying to help people with BEB, ever mindful *to do no harm.*

The most effective and best-tolerated treatment for BEB and related disorders, is botulinum toxin, and I encourage all of my patients to start with it. I reserve medical therapy for patients who have an inadequate response to the toxin. What is an inadequate response? You and not your physician determine this. Simply, it is determined by how much BEB is interfering with your life, and this includes your occupation, your home life, pursuing hobbies and other pleasurable activities, or your psychological state. If you have had what you consider to be an inadequate response to botulinum toxin, then before going straight to medical therapy, it is essential to first determine why the response was inadequate, as the majority of people with BEB respond well. One of the most common reasons for "failure" of botulinum toxin is inexperience of the practitioner. Although injecting botulinum toxin is relatively straightforward, experience is everything, and if you have not had a good response, make sure you are seeing an experienced "injector." Other reasons for an inadequate response include atypical blepharospasm (such as eyelid opening apraxia), unrealistic expectations (it is not a cure), or the development of resistance, which is relatively uncommon. Once these factors have been considered, then it is reasonable to combine botulinum toxin with medication(s).

There are a variety of medications used for blepharospasm, but few have been subjected to rigorous clinical trials, and therefore, treatment is mostly a matter of trial and error. Therapy must be individualized – what works for one patient causes intolerable side effects in another. And, just like botulinum toxin, medications are also not a cure. Instead, the goal is to achieve improvement, evidenced by blepharospasm taking less of a toll on your normal, personal, and occupational activities. Unless a patient can tell me a specific way in which they are functioning better, then it is unlikely a medication is helping. Not uncommonly though, as a seemingly unhelpful medication is being tapered off, you may notice worsening of blepharospasm, proving that the medication was helping more than originally appreciated and therefore worth continuing. In addition to monitoring closely for beneficial effects, it is equally important to watch for side effects. A discussion about common and uncommon side effects should always proceed starting a medication. But, you cannot expect your physician to go over every single potential side effect, so you need to be responsible for learning about the medications yourself. By taking an active role in your treatment, the relationship with your physician becomes a *partnership* rather than a paternalistic one in which you play a passive role.

Aside from critically evaluating whether a medication is helping and being familiar with side effects, there are additional pharmacologic principles to understand. First, drugs for BEB should be started at a low dose and escalated gradually to improve tolerance. Second, when a high dose of a drug cannot be tolerated, it may be helpful to use low doses of several drugs at once. Third, most drugs should not be stopped abruptly, but instead, withdrawn gradually. Fourth, the more drugs you take, the greater the chance for interactions. This is particularly true for certain drugs such as the blood thinner coumadin, drugs for the heart, and seizure medications. Discuss potential interactions with your physician and pharmacist. Lastly, many side effects diminish or go away with time, so don't jump the ship too quickly before a drug has had a chance to work.

One of the more commonly used medications for dystonia, including BEB, is trihexyphenidyl (Artane®). This is an anticholinergic, meaning that it blocks the action of the neurotransmitter acetylcholine. A neurotransmitter is a chemical messenger that allows impulses (information) to travel between nerve cells. Other anticholinergics include benztropine (Congentin®), and the antihistamine, diphenhydramine (Benadryl®). These drugs are best tolerated in young people with dystonia but can occasionally be tolerated in the older adult. To be effective, a fairly high dose is required and side effects often limit its use. These include constipation, dry mouth, difficulty urinating, trouble concentrating, memory loss and confusion. If you have glaucoma, check with your ophthalmologist before using an anticholinergic. The second class of drugs to consider are the benzodiazepines, of which diazepam (Valium®) is the prototype. Others used for BEB include clonazepam (Klonopin® - my preference in this group), lorazepam (Ativan®), and alprazolam (Xanax®). How they work for BEB is not known, but in part, they function as muscle relaxers. If started at a low dose and escalated gradually, side effects are minimized, and many of them, especially sleepiness, go away with time. Other potential side effects include difficulty thinking, fatigue, and imbalance. These drugs, especially Xanax, can cause dependency, but this has been very uncommon in my practice, and fear of "getting hooked" should not preclude a cautious trial of a benzodiazepine.

The anti-spasticity-agents baclofen (Lioresel®) and tizanidine (Zanaflex®) are another class of muscle-relaxing drugs to consider for BEB. Like those mentioned above, they should be started at a low dose and escalated slowly. Although not an anti-spasticity-agent, cyclobenzaprine (Flexaril®) is also a muscle relaxant. Side effects of these agents are similar to the anticholinergics and benzodiazepines.

Prior to the introduction of botulinum toxin, BEB and other movement disorders were often treated with neuroleptics, sometimes referred to as antipsychotics referring to their primary use for serious psychiatric disorders. These include, among many others, haloperidol (Haldol®), thioridazine (Mellaril®), and trilafon/amitriptyline (Triavil®). The main chemical action of these drugs is to block the neurotransmitter dopamine. Although often effective for treating involuntary movements, their use is tempered by potentially serious side effects. This includes the ability to cause parkinsonism, which reverses when the drug is stopped. More importantly, they can also cause new involuntary movements, including spasm of the face and limbs, known as tardive dyskinesia or tardive dystonia, and unlike neuroleptic-induced parkinsonism, these complications may be permanent. With rare exceptions, this class of medications should be avoided today. But experience with neuroleptics demonstrated that dopamine plays a role in blepharospasm and other dystonias. A similar reduction in brain dopamine can be achieved with the drug tetrabenazine. Unlike the neuroleptics, which block dopamine, tetrabenazine prevents the release of dopamine from nerve cells and is much less likely to cause parkinsonism and only rarely causes involuntary movements. It is not available in the U.S. but can be obtained from Canada and other countries.

In light of the side effects of traditional neuroleptics, a new generation has emerged which, like tetrabenazine, are much better tolerated and less likely to cause movement disorders. These include risperdone (Risperdal®), olanzapine (Zyprexa®), quetiapine (Seroqel®), and clozapine (Clozaril®). There is relatively little experience using these agents for blepharospasm. I have had some success with risperdone and olanzapine. Clozaril can rarely lower the white blood cell count and therefore, very frequent monitoring is required. Additional side effects of the novel antipsychotics include, among others, sleepiness, insomnia, constipation, fatigue, and confusion.

The list of other potential agents used to treat blepharospasm is long and includes, among others, Parkinson's disease drugs such as carbidopa/levodopa (Sinemet®), seizure medications such as carbamazepine (Tegretol®), and the blood pressure medication Propranolol (Inderal®). In general, these are used infrequently since the introduction of botulinum toxin.

To sum up, if botulinum toxin has not provided enough relief for blepharospasm, it is worth considering adding an oral medication. Although in general, they provide only modest relief, the response is variable, and some people find them very helpful. It is a trial-and-error approach to hit on the appropriate drug or combination, all the while being vigilant about side effects. I am confident that research will eventually reveal the cause of blepharospasm, at which point we will no longer have to use guesswork and fly by the seat of our pants to choose drugs. Instead, we will roll up our sleeves and design rational, effective therapies.

ACUTE AND CHRONIC EFFECTS OF BOTULINUM TOXIN IN THE MANAGEMENT OF BLEPHAROSPASM

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Botulinum A toxin has been used in the treatment of blepharospasm since 1983. This substance has proven to be effective in controlling involuntary spasms of the eyelids in a number of neuromuscular disorders, most notably essential blepharospasm, Meige's Syndrome, and hemifacial spasm. While there is no cure for blepharospasm, botulinum toxin represents the most effective treatment with fewest overall complications. Although the long-term consequences of chronic botulinum toxin use are still not clearly understood, many short and long-term effects have been documented. These effects are generally mild and temporary in nature. They can be grouped as either acute (*immediate)* in nature in which the result becomes manifest within days, or chronic (*delayed)* where the effect may develop over some time and only after repeated exposure to the drug. Although most of these effects are seen locally near the sites of injection, some may occur distant to the area of treatment, and are therefore truly systemic in nature.

Acute effects of botulinum toxin

Certainly, the most important effect of botulinum toxin is its ability to block the action of some muscles. This neuromuscular blockade is the clinically desired effect in the management of facial spasms, and is the very reason for treatment. While the drug is acting, the eyelid muscles are weakened, resulting in reduced contraction and relief of spasms. The overall results of botulinum toxin therapy for blepharospasm have been gratifying; with more than 93% of treated patients reporting a noticeable decrease in spasm intensity. All patients experience recurrence of spasms over time, usually after about 12 to 13 weeks. Some individuals will not achieve control of spasms with the usual doses, but may respond to higher doses. It is important to understand that there is no *standard* dose or treatment pattern for all patients, and it may take several injection sessions to find a treatment pattern that works best. Nevertheless, about 3% of patients will not respond and another 4% may show decreasing effectiveness over time. It is not clear why some patients do not respond to toxin, and in at least some cases, the development of antibodies against the toxin may be responsible. The most important acute complications of toxin involve local effects that are always temporary. While often discouraging for the patient, these effects generally are preferable to the spasms they replace.

Ptosis

Although botulinum toxin is injected into the closing muscle of the eyelid, it can spread backward to the lifting muscle, resulting in a drooping of the upper eyelid. This is referred to as ptosis. Since the septum may be thinner on one side than the other, some patients may experience ptosis repeatedly in one eye only. Ptosis is seen in about 12% of treatments for blepharospasm. It is now well established that the degree of ptosis, as well as the incidence, is

related to the toxin dose. Therefore, those patients who require a higher dose for control of their spasms may experience more frequent episodes of ptosis.

Double vision

Placement of botulinum toxin into the deeper parts of the orbit can cause double vision. This results from weakening of the muscles that normally move the eyeball. As with ptosis, this may be seen more frequently in patients who have a severe thinning of eyelid tissues, or when the injection is placed too deep. Double vision has been seen in about 2% of treatments for blepharospasm. Recovery of these muscles is typical after several weeks.

Lower facial weakness

Below the eyelids, there are a number of very small muscles for facial movement. The spread of botulinum toxin to these muscles results in weakness of the lower face and mouth. Although usually only of minor consequence, marked mouth droop and drooling may sometimes be seen. The overall incidence of this complication is less than 1% when the injections are confined to the region around the eyelids. When injections are given into the middle and lower face for hemifacial spasm or for Meige's Syndrome, the incidence of facial weakness may climb to about 12%.

Dry eyes and tearing

These are common side effects of botulinum treatment for blepharospasm. Most treated patients will show a weak eyelid blink due to weakness of the eyelid closing muscles. This results in mild inability to close the eyes completely, and may be seen in as much as 65% of patients. Increased evaporation of tears causes dryness of the lower portion of the cornea, and symptoms of dry eyes. These symptoms include burning, scratchiness, and light sensitivity. The reported incidence of symptomatic dry eyes is about 2.5%. Most patients should be placed on artificial tears during toxin treatment. Dryness of the eye surface, combined with a weakening of the lower eyelid muscle, which is needed to move the tears into the drainage ducts, causes excess production of tears as a compensation. Excess tearing has been reported in 3.5% of treatments.

Chronic effects of botulinum toxin

The chronic effects of botulinum toxin distant from the sites of injection are more difficult to establish. Certainly, the most significant effect is generalized weakness reported in 1 out 10,000 treatments for blepharospasm. Generalized weakness or severe tiredness has also been reported at an even greater frequency following toxin administration for torticollis, with an incidence as high as 5% to 20%. Weakness of muscles as far away from the eyelids as the lower arms and legs has been seen. These neurologic disturbances slowly return to normal after discontinuing use of the toxin. Fortunately, this complication is exceptionally rare.

Botulinum toxin is a protein that is capable of inducing antibodies, and the formation of such antibodies in blepharospasm patients has been a matter of some concern. Most doctors who use botulinum toxin have seen a small number of patients (about 2%) who initially show effectiveness, in some cases falling to no response. It is likely that in at least some of these patients the formation of antibodies may be responsible. It is hopeful that the development of other forms of the toxin, such as B or F, might restore response in these individuals.

Clinical Features of Blepharospasm and Hemifacial Spasm

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Blepharospasm

Involuntary facial movements have been recognized for a long time and were depicted by artists who were fascinated by how these movements distorted the facial expression. For example, the 16th century Flemish artist Brueghel painted a woman with apparent blepharospasm and involuntary jaw opening. Although the eponym "Meige syndrome" sometimes has been used to designate idiopathic cranial-cervical dystonia, this term is not appropriate because Talkow in Germany and Wood in the United States described blepharospasm and orofacial dystonia several decades before the 1910 publication by the French neurologist's report. It was not until the 1970s that blepharospasm was recognized as a form of focal dystonia.

Before the development of sustained closure of the eyelids, about a third of the patients report increased frequency of blinking, suggesting that blepharospasm may be due to impairment of mechanisms associated with normal blinking. Although healthy individuals blink more frequently during conversation than at rest, in patients with blepharospasm the pattern is reversed, suggesting that conversation may act as a "sensory trick" or "*geste antagonistique"*. The increased blinking that precedes blepharospasm is commonly associated with a feeling of irritation in the eyes and photophobia (better termed "photosensitivity" or "photodynia"). It usually progresses to clonic and later tonic (sustained) contractions of the orbicularis oculi, leading to forceful closure of eyelids, often associated with involvement of the corrugator and procerus muscles and compensatory contractions of the frontalis muscles. Up to 20% of patients have unilateral involvement at the onset, but the opposite eye becomes involved later in all patients. Blepharospasm is seldom an isolated condition. This form of dystonia is often associated with dystonia in other facial cervical perioral and mandibular muscles (oromandibular dystonia). In addition, patients with blepharospasm may have dystonia in the limbs, trunk, and vocal cords (spasmodic dysphonia). Unlike idiopathic blepharospasm, which is most prominent when the patient is active, secondary blepharospasm often persists during rest. This distinction, however, is not reliable enough to differentiate primary from secondary blepharospasm.

Blepharospasm may vary from only a slightly annoying condition to a disabling disorder that interferes with daily activities such as reading, watching television, and driving. In our original study of botulinum toxin in patients with cranial dystonia, we used a rating scale, currently referred to as the Jankovic Rating Scale (Jankovic et al 2009a), to assess the severity and frequency of involuntary eyelid contractions. The self-rating response scale Blepharospasm Disability Index has been found to correlate well with the Jankovic Rating Scale. With the recent emphasis on quality-of-life outcome measures, there is a need to develop instruments that measure this domain. In this regard the cranio-cervical dystonia questionnaire (CDQ-24) will be helpful in evaluating the effects of botulinum toxin treatment on blepharospasm and cervical dystonia (Kenney and Jankovic, 2009).

Up to two thirds of patients are rendered functionally blind by their blepharospasm. Blepharospasm is usually exacerbated by bright light; as a result, many patients wear sunglasses both outside and inside. The spasms may be transiently alleviated by pulling on an upper eyelid or an eyebrow, pinching the neck, talking, humming, yawning, singing, sleeping, relaxing, reading, concentrating, looking down, and performing other maneuvers or sensory tricks (*geste antagonistique*). Although adult onset focal dystonias tend to remain focal, among the focal dystonias, the risk of spread was highest in patients with blepharospasm (31% past the head) compared to those starting in the upper extremities (16%), larynx (12%), or the neck (9%) (Weiss et al 2006). In most cases of blepharospasm, the spread occurs in the first 5 years after onset, as shown in several studies (Abbruzzese et al 2008). Another study, involving 124 patients presenting with blepharospasm (73 with cervical dystonia and 24 with focal hand dystonia; all with 10 years or more of symptom duration), showed that age at dystonia onset, age at initial spread, and the risk of initial spread were higher, and the time from onset to initial spread was shorter for the blepharospasm patients compared to other focal dystonias (Abbruzzese et al 2008). Similar findings were seen in a group of 132 patients followed for a mean of 7.5 years (Svetel et al 2007). Risk

factors for spread of blepharospasm include previous head or face trauma with loss of consciousness, young age at onset of blepharospasm, and female gender.

Psychiatric symptoms, such as anxiety, depression, and psychosis, may be present even before or at onset of blepharospasm and were identified in 18% of 264 patients. The prevalence of obsessive-compulsive symptoms, often attributed to basal ganglia dysfunction, in patients with blepharospasm was significantly higher than in those with hemifacial spasm, despite the clinical similarities. This coexistence with mild psychiatric symptoms may explain the tendency to label blepharospasm as a psychogenic problem. However, psychogenic forms of blepharospasm are extraordinarily rare, and there is usually little or no evidence of any psychopathology in patients with blepharospasm.

That blepharospasm represents a *forme fruste* of idiopathic (primary) torsion dystonia is now well accepted (Hallett et al 2008). In addition to the frequent coexistence of blepharospasm and dystonia in other body segments, the relatively frequent occurrence of family history of dystonia, essential-type tremor, or both supports the hypothesis that blepharospasm and other forms of dystonia may be genetically related. In our experience, one third of all patients with cranial-cervical dystonia have an action hand tremor similar to essential tremor or dystonia, and one third of patients have a first-degree relative with tremor or dystonia. Family history of blepharospasm has been reported to range between 9.5% and 27% among first-degree relatives of patients with blepharospasm. In a study of 56 families that included 436 first-degree relatives of probands, 233 of whom were examined, 27% of the index cases had at least 1 first-degree relative with blepharospasm, with estimated 20% penetrance if autosomal dominant transmission is assumed (Defazio et al 2006).

The study of blepharospasm due to some specific, identifiable cause (secondary blepharospasm) can provide insights into the pathogenesis of the primary, idiopathic disorder, sometimes referred to as "benign, essential blepharospasm." Although the most common cause of blepharospasm is adult-onset idiopathic torsion dystonia, there are many other less common causes (Table 1). Even though most patients initially consult ophthalmologists, ocular disorders probably only rarely cause blepharospasm (Martino et al 2005).

Table 1. Etiology of Blepharospasm

Primary dystonia

Sporadic

Inherited (all autosomal dominant)

- classic (Oppenheim) dystonia (DYT1-*TorsinA*)
- childhood and adult-onset cranial-cervical-limb dystonia (DYT6-*THAP1*)
- adult-onset cervical and other focal dystonia (DYT7-18p)
- adult-onset cranial-cervical dystonia (DYT13-1p36.13-36.32)

Associated with neurodegenerative disorders

Primarily sporadic

- Parkinson disease
- progressive supranuclear palsy
- multiple system atrophy
- multiple sclerosis
- central pontine myelinolysis
- juvenile parkinsonism-dystonia
- progressive pallidal degeneration
- intraneuronal inclusion disease
- infantile bilateral striatal necrosis
- familial basal ganglia calcifications

Primarily inherited

- dystonia-plus syndromes
- atypical autosomal dominant dystonia (not DYT1 gene)
- myoclonic dystonia
- dopa-responsive dystonia (DRD) (DYT5-GTP cyclohydrolase I 14q22.1)
- rapid-onset dystonia-parkinsonism
- early-onset parkinsonism with dystonia

- X-linked dystonia parkinsonism or Lubag
- paroxysmal dystonia-choreoathetosis
- Wilson disease
- Tourette syndrome
- Huntington disease
- Neurodegeneration with Brain Iron Accumulation (Hallervorden-Spatz disease)
- SCA3, SCA6, SCA16, SCA17, Friedreich's ataxia
- Machado-Joseph disease
- ataxia telangiectasia
- neuroacanthocytosis
- dentato-rubral-pallidoluysian atrophy
- hereditary spastic paraplegia with dystonia
- Fragile-X syndrome
- Mohr-Tranebjaerg syndrome

Associated with metabolic disorders

Amino acid disorders

- glutaric academia
- methylmalonic academia
- homocystinuria
- Hartnup disease
- tyrosinosis

Lipid disorders

- metachromatic leukodystrophy
- ceroid lipofuscinosis
- dystonic lipidosis ("sea blue" histiocytosis) gangliosidoses
- hexosaminidase A and B deficiency

Miscellaneous metabolic disorders

- mitochondrial encephalopathies
- Leigh disease, Leber disease
- Lesch-Nyhan syndrome
- triosephosphate isomerase deficiency
- vitamin E deficiency
- biopterin deficiency
- pseudohypoparathyroidism

Due to a specific cause

Perinatal cerebral injury and kernicterus

- athetoid cerebral palsy
- delayed onset dystonia

Infection

- viral encephalitis
- encephalitis lethargica
- Reye syndrome
- subacute sclerosing panencephalitis
- Jakob-Creutzfeldt disease
- AIDS
- other: tuberculosis, syphilis, tetanus

Other disorders

- collagen vascular disorder

- paraneoplastic brainstem encephalitis
- cerebral vascular or ischemic injury (stroke)
- brain tumor
- arteriovenous malformation
- head trauma and brain surgery
- peripheral trauma
- toxins: MN, CO, CS2, methanol, disulfiram, wasp sting
- drugs: levodopa, bromocriptine, antipsychotics, metoclopramide, fenfluramine
- flecainide, ergot, anticonvulsants, certain calcium channel blockers

Due to an ophthalmologic cause

Reflex blepharospasm

- blepharitis, conjunctivitis, “dry eye syndrome," keratitis, iritis, uveitis
- albinism, achromatopsia, maculopathies
- lesions in the nondominant temporoparietal lobe (Fisher sign)

Peripherally induced

- hemifacial spasm
- tic convulsif
- Bell palsy
- aberrant facial regeneration with facial synkinesis
- hemimasticatory spasm
- facial myokymia
- Schwartz-Jampel syndrome
- amyloidosis
- oculomasticatory myorhythmia (Whipple disease)

Tardive dystonia is probably the most common cause of secondary dystonia, including blepharospasm. Tardive dystonia consists of a persistent dystonic movement involving chiefly the face, jaws, neck, trunk, and arms. Blepharospasm may be the initial presentation of tardive dystonia. In addition to dopamine-receptor blocking drugs (neuroleptics), other drugs that can cause blepharospasm are lithium, lamotrigine, and others.

A variety of CNS lesions involving the rostral brainstem, thalamus, and the basal ganglia (eg, stroke, multiple sclerosis, thalamotomy, hydrocephalus) have been reported in association with blepharospasm and other forms of cranial dystonia. These reports of lesions producing blepharospasm, oromandibular dystonia, or both support the notion that in addition to the basal ganglia, other subcortical and brainstem structures play an important role in the pathophysiology of cranial dystonia.

Peripheral trauma is increasingly recognized as a cause of dystonia, and peripheral trauma may trigger dystonia in carriers of the idiopathic torsion dystonia gene (Jankovic 2009b). Up to 12% of patients with blepharospasm report the occurrence of ocular trauma prior to the onset of their movement disorder. About 11% of otherwise healthy individuals have dry eyes, but most patients do not have dry-eye syndrome as seen in Sjögren disease, although they may have dry-eye symptoms. Many patients experience symptoms of “dry eyes” and other ocular symptoms shortly before the onset of blepharospasm, suggesting that disorders of the anterior segment of the eye may actually trigger blepharospasm. Whether dry eye syndrome is the cause or result of blepharospasm is not known. People with dry eyes blink more frequently than those without dry eyes, presumably to reduce the chance of holes developing in the tear film and blink oscillations help thicken the lipid layer of the tear film. The production of proteins, particularly lacritin, normally secreted by the lacrimal glands is markedly reduced in some patients with blephritis, which reduces the lipid laye. Although blephritis often precedes blepharospasm, it is not clear that it is a risk factor for blepharospasm as blephritis is a frequent symptom in otherwise normal individuals. It is possible that some form of injury to the anterior segment of the eye causes trigeminal sensitization leading to photophobia, increased blinking, and blepharospasm. The mechanisms of photophobia and dry eyes are complex and may be due to an ocular problem as well as a central effect. Furthermore, dryness may be more related to the make-up of the tear film and its dynamics than the actual amount of tears produced.

In addition to dystonia, other conditions can lead to closure of the eyelids. Ptosis may result from

weakness or paralysis of the levator palpebrae muscle or the smooth muscle of Müller. Some patients are unable to open their eyes because they cannot "activate" the levator palpebrae muscles. This is analogous to the motor blocks or the freezing phenomenon experienced by some, and the terms “apraxia of eyelid opening. Progressive supranuclear palsy is the most common cause of eyelid freezing seen in the Parkinson clinic, but other parkinsonian syndromes, Huntington disease, hemispheric cerebral vascular disease, and neuroacanthocytosis are occasionally associated with this phenomenon. Apraxia of eyelid opening, however, can occur in isolation without any other motor deficits, and it may improve with levodopa and recur when levodopa is reduced as may be the case after deep brain stimulation (Umemura et al 2008).

Hemifacial Spasm

Hemifacial spasm, a form of segmental myoclonus, is characterized by *unilateral*, involuntary, paroxysmal tonic or clonic contractions of the muscles innervated by the 7th cranial nerve (Wang and Jankovic 1998). The presumed pathophysiologic mechanism of hemifacial spasm involves the generation of ortho- and antidromic impulses by a damaged area of the facial nerve. The constant antidromic stimulation may result in "kindling," causing neuronal discharge in the facial motor nucleus, leading to hemifacial spasm. Typically, at onset the patients experience occasional twitches in the eyelids, but with progression the spasms and twitches become more constant and involve the lower facial musculature. The clonic and tonic contractions are triggered by action (smiling, talking, eating, blinking). Hemifacial spasm is easily distinguished from blepharospasm caused by dystonia because it is virtually always unilateral, although there are rare exceptions (Tan and Jankovic 1999). Furthermore, in contrast to blepharospasm, patients with hemifacial spasm often exhibit paradoxical raising of the eyebrow as the eye closes (the “other” Babinski sign) (Stamey and Jankovic, 2007). The term "tic convulsif" describes the rare coexistence of painful trigeminal neuralgia and hemifacial spasm. The phenomenology of aberrant facial regeneration or facial synkinesis is similar to hemifacial spasm, but the onset usually follows facial palsy. Studies in macaque monkeys show that following facial nerve injury, the orbicularis oculi motoneurons innervate the perioral muscles causing co-contraction (synkinesia) of eyelid and perioral muscles. In one series of 164 patients with hemifacial spasm, 9 (5.5%) were thought to have coexistent blepharospasm (Tan et al 2004). Blepharospasm also has been reported after Bell palsy, but prospective studies could not demonstrate an association between Bell palsy and subsequent blepharospasm. Hemimasticatory spasm is a rare disorder whose underlying mechanism is similar to hemifacial spasm, but the trigeminal rather than the facial nerve is involved. The spasms of the masticatory muscles may or may not be associated with hemifacial atrophy. Facial myokymia, a rapid undulation and flickering of the facial muscles from the frontalis to the platysma, is thought to be due to an intramedullary lesion close to the facial motor nucleus. Multiple sclerosis is probably the most common cause, but intra-axial tumors and Guillain-Barré syndrome have also been described as associated with this movement disorder. Tetanus is caused by tetanus toxin, a product of *Clostridium tetani*, and it is characterized by hyperactivity of motor neurons, which causes forceful closure of the eyelids. Although rare in the United States, it still remains a major public health problem in underdeveloped areas. Amyloidosis V and Schwartz-Jampel syndrome (autosomal recessive disorder manifested by combination of blepharospasm, blepharophimosis, dwarfism, muscular hypertrophy, generalized muscular stiffness and myotonia) represent additional causes of blepharospasm.

Blepharoclonus refers to rhythmic contractions of the orbicularis oculi closely resembling tremor, present during gentle closure of the eyelids. Although no apparent cause can be identified in many cases, blepharoclonus is occasionally associated with multiple sclerosis, obstructive hydrocephalus, and Arnold-Chiari malformation. Blinking, the most common motor tic present in 70% of patients with Tourette syndrome, is characterized by bursts of rapid, nonsustained contractions of the orbicularis oculi. On the other hand, dystonic tics of the eyelids, found in 15% of patients, can cause diagnostic difficulties because they are transiently sustained and may resemble blepharospasm.

An important cause of facial movements is Whipple disease. In addition to gastrointestinal symptoms, patients with Whipple disease typically exhibit supranuclear ophthalmoparesis and rhythmic contractions of the eyelids, face, and mouth in synchrony with convergent eye oscillations. This oculomasticatory myorhythmia is usually associated with contractions of neck as well as the pharyngeal and proximal and distal musculature.

The phenomenology of blepharospasm is usually the same regardless of its cause. The presence of associated findings, however, may suggest a specific etiology. The recognition of stereotypies (repetitive, patterned, seemingly purposeful but purposeless movements), for example, suggests the diagnosis of tardive

dystonia, whereas corneal Kayser-Fleischer ring and evidence of hepatic failure indicate Wilson disease (Svetel et al 2001).

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Botulinum Neurotoxins in the Management of Blepharospasm

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Introduction to blepharospasm

Blepharospasm is a focal dystonia characterized by excessive involuntary contraction of the orbicularis oculi muscles, leading to repetitive blinking or sustained closure of the eyelids. In severe cases, tonic eyelid closure can lead to functional blindness and can have significant negative impact on the patient's quality of life (Langlois et al, 2003; Hallett, 2002). Inability to open the eyes can also occur as a result of failure of levator palpebrae muscle activation ("apraxia of eyelid opening"). Primary, essential, or idiopathic blepharospasm, often referred to as benign essential blepharospasm, is not associated with any known etiology (Hallett, 2002). Blepharospasm occurs spontaneously but can be triggered by exposure to bright lights, watching television, reading, driving, or fatigue. Contractions may be ameliorated with sensory tricks such as touching the forehead or the eyebrow or talking (Langlois et al, 2003; Defazio and Livrea, 2004). Blepharospasm may occur alone or it may be accompanied by dystonia of the lower face and jaw (Meige syndrome) or other focal dystonias such as cervical dystonia (spasmodic torticollis) (Hallett, 2002).

Blepharospasm is chronic, progressive, and frequently disabling, with age of onset typically in the fifth or sixth decade (Hallett, 2002; Defazio and Livrea, 2004). In their review of published epidemiologic data, Defazio and Livrea concluded that the crude estimates of prevalence range from 16 to 133 per million (Defazio and Livrea, 2002). Women are more than two times more likely to be affected than men and are typically older at onset (Hallett, 2002; Defazio and Livrea, 2002). Prior head trauma with loss of consciousness, family history of dystonia, and prior eye disease may also increase the risk of developing blepharospasm (Defazio and Livrea, 2002). Older age at onset, female gender, and prior head/face trauma are also thought to be risk factors for the spread of dystonia to other muscles (Defazio and Livrea, 2002). Causes of secondary blepharospasm include acquired conditions (eg, brain-stem lesions of inflammatory or vascular origin) or, less frequently, inherited metabolic/neurodegenerative conditions, such as Wilson's disease, Huntington's disease, and parkinsonian disorders in which blepharospasm may be a neurological sign of either the disease or treatment with dopaminergic drugs (Defazio and Livrea, 2004).

Current therapeutic approaches

The goal of blepharospasm treatment is to reduce or prevent unwanted, repeated, forced closure of the eyelids. Approved in 1989 for the treatment of blepharospasm, botulinum neurotoxin (BoNT) is now the treatment of choice for this disorder (Hallett, 2002; Defazio and Livrea, 2004). BoNT therapy is highly effective in patients with spasm of the orbicularis oculi muscles and can be used for many years without loss of efficacy (Hallett, 2002; Defazio and Livrea, 2004). Apraxia of eyelid opening is more difficult to treat than blepharospasm, but some patients with apraxia of eyelid opening improve with BoNT injections, particularly if the apraxia of eyelid opening is triggered by blepharospasm (Forget et al, 2002). Patients with involuntary levator inhibition, alone

or in combination with blepharospasm, are less responsive to BoNT (Aramideh et al, 1994; Aramideh et al, 1995; Forget et al. 2002).

For the minority of patients refractory to BoNT therapy, treatment alternatives include trihexyphenidyl, clonazepam, baclofen, and tetrabenazine (Balash and Giladi, 2004; Defazio and Livrea, 2004), although these are generally not very efficacious. Patients who are unresponsive to these medications are candidates for myectomy of the eyelid protractors (Hallett, 2002; Defazio and Livrea, 2004).

Mechanism of action of BoNT in blepharospasm

The effect of BoNT in blepharospasm is largely attributable to the muscle relaxation produced as a result of the inhibition of acetylcholine release at the neuromuscular junction. The first use of neurotoxins to treat eye movement disorders was reported in an animal study in the early 1970s showing that injection of low doses of neurotoxic agents into the extraocular muscles, under electromyographic control, reduced the activity of hyperactive muscles (Calace et al, 2003). This finding prompted subsequent human studies of BoNT type A (produced as BOTOX® by Allergan, Inc., Irvine, CA, and Dysport® by Ipsen, Slough, UK) in ocular motility disorders including blepharospasm. Early studies explored the activity of BoNT in patients with blepharospasm using single-fiber electromyography, compound motor action potential of the orbicularis oculi muscle (measured by stimulation of the facial nerve), blink reflex, and blink reflex recovery curve (Girlanda et al, 1996). These measurements were carried out before injection and at 1, 2, and 4 weeks after unilateral BoNT injection. Postinjection facial compound motor action potential decreased bilaterally and single-fiber electromyography indicated abnormal neuromuscular junction function bilaterally. The excitability curve of blink reflex was not altered by therapy. These results confirmed the actions of BoNT at the neuromuscular junction and provided evidence of bilateral clinical and neurophysiologic effects following unilateral administration, presumably as a result of local toxin spread (Girlanda et al, 1996).

Clinical data

The safety and efficacy of BoNT in the treatment of blepharospasm has been demonstrated by a small number of double-blind studies and a considerable number of open case-control studies. A double-blind, placebo-controlled study by Jankovic and Orman demonstrated the beneficial effects of BoNT type A (BOTOX®, then known as Oculinum), in 11 patients with blepharospasm (Jankovic and Orman, 1987). This study found that all patients with blepharospasm improved after a total of 14 series of BoNT injections, with 72% improvement over baseline on severity rating score (0 = absent, 4 = most severe) and a mean duration of beneficial effect of 12.5 weeks. There was no improvement in patients who received placebo.

As noted by Jost and Kohl, the total number of patients studied in randomized controlled trials is small; however, results were consistent across trials and concordant with the positive findings of open-label studies (Jost and Kohl, 2001). One weakness noted in some of these clinical trials is the inclusion of patients with blepharospasm and patients with hemifacial spasm without a clear delineation between the two disorders. Although Jost and Kohl concluded that blepharospasm qualified for evidence-based medicine Ia classification (systematic review of randomized clinical trials with homogeneity among trials), there are only 3 Class I studies involving only 22 patients (Table 1).

Table 1. Class I studies indicating the efficacy of treatment of blepharospasm with BoNT type A.

Reference	Study design	Treatment/ Cohort size	Outcome
Fahn et al, 1985(abstract only)	Prospective, double-blind; compared eyes of each patient, one treated with BoNT, the other with saline control	BOTOX®*10 U/eye(N=5)	Significant patient- and observer- assessed improvement with BoNT; duration of results not specified
Jankovic and Orman, 1987	Prospective, placebo-controlled crossover design; blinded observers	BOTOX®*25 U/eye; if ineffective, then 50 U/eye(N=11)	Significant patient- and neurologist-assessed improvement with BoNT only; mean duration of efficacy, 12.5 weeks
Girlanda et al, 1996	Prospective, double-blind; compared eyes of each patient, one treated with BoNT, the other with saline control	BOTOX®20 U/eye(N=6)	Subjective scale, improvementwith BoNT

U=units.

*The BOTOX® formulation was known as Oculinum at the time these studies were conducted.

A recent systematic review by Costa and colleagues found no randomized controlled trials with sufficient numbers of patients to fit the inclusion criteria. The authors therefore concluded that no high-quality data support the use of BoNT for treatment of blepharospasm, but that studies have indicated that BoNT type A is effective and safe for treatment of blepharospasm, benefiting 90% of patients. They further note that this considerable effect size makes placebo-controlled trials of blepharospasm treatment with BoNT type A impractical and perhaps unethical (Costa et al, 2005).

Several studies have assessed the dose of BoNT required for efficacy in blepharospasm. In an open-label, uncontrolled study, 115 patients with cervical dystonia, blepharospasm, or facial hemispasm were treated over a period of 2 years to evaluate the effects of low-dose BoNT treatment (Rollnik et al, 2000). BOTOX® was diluted in 20 mL of 0.1% albumin solution to arrive at a concentration of 25 MU/mL. The mean duration of beneficial effects was 11.7 weeks and patient-evaluated clinical global improvement was 2.7 points on a 0 to 4 scale. A study that examined the qualitative changes from BOTOX® treatment over time found that the mean interval of symptom relief was longer with a low dose (4.0 months, 16 U) than with a high dose (3.2 months, 24.2 U) (Snir et al, 2003). In a hospital-based study comprising 215 injections of BoNT type A in patients with focal dystonias, the lowest dosages of Dysport were required for patients with blepharospasm (122 U) and writer's cramp (92.5 U), whereas a dosage of over 500 U was required for patients with generalized dystonia. The best treatment response was observed in patients with blepharospasm (>98%) and hemifacial spasm (97%), whereas patients with generalized dystonia showed the poorest response (Gupta et al, 2003).

The long-term efficacy of BoNT in the treatment of blepharospasm has also been examined. Jankovic and Schwartz analyzed the long-term effects of repeated BoNT (BOTOX®) treatments in 42 patients with blepharospasm who underwent at least 5 different treatment sessions. The total treatment dose and peak efficacy rating were constant over time, but the duration of action increased and the frequency of side effects diminished over time. They concluded that chronic treatment was not associated with any decline in benefit, and that efficacy may improve slightly with repeat treatments (Jankovic and Schwartz, 1993).

A more recent long-term follow-up study analyzed data from 235 patients treated with BoNT (BOTOX®) for a variety of different movement disorders and dystonias, including blepharospasm, over a 10-year period (Hsiung et al, 2002). After 5 years and a total of 2616 treatment cycles, substantial clinical benefit was noted in 90% of patients with blepharospasm, 88% with hemifacial spasm, 63% with cervical dystonia, 100% with jaw closing and lower limb dystonia, and 56% with writer's cramp. There was an increase in patient satisfaction after 5 years of treatment, with a benefit of 75.8% and with efficacy maintained for over 10 years in some patients. The most common reasons for discontinuing treatment were development of primary resistance (defined as less than 25% improvement after 2 or 3 consecutive trials with increasing doses of BoNT type A) in 9.1% of patients and development of secondary resistance (defined as achievement of at least 50% improvement for at least 2 treatment cycles followed by less than 25% improvement after 2 or more subsequent treatment cycles) in 7.5% of patients. Adverse effects, mostly minor, included dysphagia, pain, and bruising, and were the cause for discontinuation in 1.3% of patients. The results demonstrated that efficacy and tolerability were well maintained after long periods of treatment.

Another study that examined the long-term effects of BoNT type A (BOTOX®) in blepharospasm followed 168 patients from 1980 to 2001 (Calace et al, 2003). A total of 1264 treatment cycles (range,1-41 cycles per patient) were conducted during the study period. A total of 93% of patients reported improvement after treatment, with a mean duration of improvement of 3.6 months (range, 0-16 months). Three patients (1.7%) had a total remission of spasm. Twelve patients (7%) who underwent more than 14 treatments and were followed for 10 years or more (range, 10-18 years) showed no reduction in duration of relief over time, demonstrating that BoNT therapy is effective over the long term. All side effects were local in nature.

Clinical considerations

Injection procedures

The position of the injection sites around the orbicularis oculi muscle is thought to influence the efficacy and side effects of BoNT type A (Cakmur et al, 2002). A wide range of injection techniques have been reported, but there is no standard treatment protocol. Typically, injections are made in the upper eyelid above the eyebrow, medially and laterally, and in the lower eyelid laterally to weaken the orbital preseptal part of the orbicularis oculi. To weaken the pretarsal part of the orbicularis oculi, BoNT is injected subcutaneously into the mid upper eyelid close to the eyelash line (Defazio and Livrea, 2004) (Figures 1 and 2). A study by Cakmur and colleagues compared the impact of different injection sites on BoNT type A (BOTOX®) treatment of involuntary eyelid closure. Patients with blepharospasm who received pretarsal injections of BoNT type A experienced a higher response rate and longer duration of maximum response (97% response, 11.4-week duration of maximum response) than did patients who received preseptal injections (90% response, 8.2-week duration of maximum response). Moreover, major side effects (eg, ptosis) were less frequent with pretarsal injections than with preseptal injections. This study

was limited by the fact that it was not prospective or blinded; nevertheless it clearly supports that the location of the injection site can impact BoNT efficacy (Cakmur et al, 2002). Because BoNT can diffuse from the site of injection into surrounding tissue, it is recommended that injection dose and volume should be adequate to weaken specific portions of the orbicularis oculi muscle while limiting diffusion to nearby muscle (Defazio and Livrea, 2004).

Fig. 1 Location of injections for preseptal BTX-A treatment. Arrows indicate orientation of the tip of the needle.

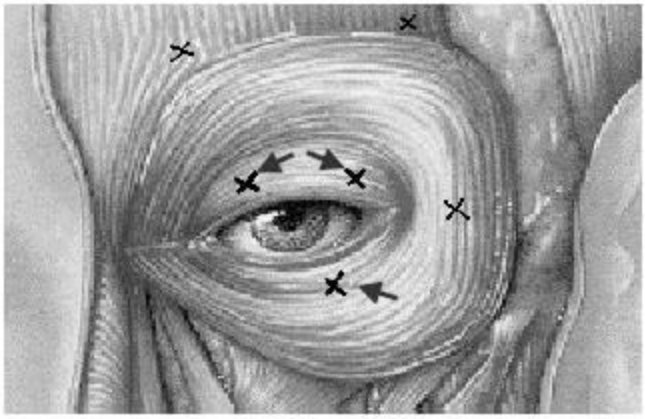

Fig. 2 Location of injections for pretarsal BTX-A treatment. Arrows indicate orientation of the tip of the needle.

Figures used with permission from Cakmur et al. *J Neurol.* 2002;249:64-68.

BoNT serotypes

The vast majority of studies of the effect of BoNT in blepharospasm have been with the A serotype, with similar efficacy and duration of action noted with different type A preparations. The ratio of units of Dysport to BOTOX® for similar efficacy is 4:1, as concluded by the authors of two studies that examined the two available formulations of BoNT type A for the treatment of blepharospasm (Table 2).

Table 2. Comparison of BoNT type A formulations for treatment of blepharospasm.

Reference	Study design	Treatment/ Cohort size	Outcome
Nussgens and Roggenkamper, 1997(Class I)	Double blind, prospective, crossover	BOTOX® 44 U average (range, 25-85 U) *or* Dysport 182 U average (range, 100-340 U) (N=212)	Mean duration of efficacy similar for both formulations: BOTOX® 7.98 weeks (range, 0-16 weeks); Dysport® 8.03 weeks (range, 0-22 weeks)(*P*=NS). Significant difference in number of patients experiencing adverse effects (17% vs 24%; *P*<0.05) and ptosis (1.4% vs 6.6%; *P*<0.01) with BOTOX® vs Dysport, respectively
Sampaio et al,1997 (Class II)	Unblinded observer, blinded patient, prospective, parallel	BOTOX® 12.5 U/eye (n=21)*or* Dysport 50 U/eye(n=21), booster dose permitted at1 month	*Primary:* NS difference in mean duration of effect of BOTOX® vs Dysport (11.2 vs 13.3 weeks) and number of booster doses needed (4 [19%] vs 9 [43%], respectively). *Secondary:* latency of effect, clinical efficacy, adverse reactionsalso equivalent

U=units; NS=not significant.

A limited number of studies have examined the efficacy of other BoNT serotypes. Colosimo and colleagues recently reported an open-label pilot study of BoNT type B (Myobloc®; Solstice Neurosciences, Malvern, PA) in 13 patients with blepharospasm who had positive responses to BoNT type A (Colosimo et al, 2003). Of 13 patients, 5 rated the efficacy of BoNT type B as greater than that of BoNT type A, and chose to continue type B treatment. BoNT type B was generally well tolerated, with pain during injection reported as the most common side effect. BoNT type B is not approved for treatment of blepharospasm. Further studies are needed to establish its efficacy and safety.

Antibody production

A potential consequence of long-term therapy with BoNT is the development of an immune response against the toxin. The literature regarding the frequency of antibodies in patients treated with BoNT contains conflicting reports on this subject. Comparison of studies is difficult owing to variability in methods used to titrate antibodies (Calace et al, 2003), but it does seem that antibodies are more likely with higher doses and regimens where injections are more frequent than every 3 months (Langlois et al, 2003). Since the dose for the treatment of blepharospasm is relatively low, the impact of antibody development on clinical effectiveness of the treatment for this indication is virtually nil (Defazio and Livrea, 2004). It appears that with the new formulation of BOTOX®, antigenic protein content is reduced and antibodies to botulinum toxin are less problematic (Scott, 2004; Langlois et al, 2003).

Recent advances and future directions

Blepharospasm is clearly linked to other dystonias, and many patients with blepharospasm have other involuntary spasms that appear to be dystonias. The contribution of genetic background to the etiology of blepharospasm is an area requiring further investigation, particularly in view of the increasing epidemiological evidence that adult onset focal dystonia is likely the result of an

autosomal dominant genetic disorder with markedly reduced penetrance (Defazio and Livrea, 2004; Defazio and Livrea, 2002).

In a recent investigation to clarify the role of abnormalities in dopamine neurotransmission in the generation of dystonic movements, case-control allelic associations were studied in patients with blepharospasm, using polymorphisms in the dopamine receptor and transporter genes as markers (Misbahuddin et al, 2002). Allele 2 of a DRD5 dinucleotide repeat was found to be significantly associated with blepharospasm, suggesting a possible role for this receptor in its pathogenesis.

In addition to increased understanding of the pathophysiology of blepharospasm, other areas for ongoing study include strategies to reduce the risk of antibody production, which can lead to treatment failure, and evaluation of the efficacy and safety of other botulinum toxin serotypes, including type B, which is currently approved for treatment of cervical dystonia.

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