Disorders of Involuntary Facial Movement and Blepharospasm, Contemporary Evaluation and Management

Gary E Borodic, MD
Surgeon in Ophthalmology
Massachusetts Eye and Ear Infirmary
Assistant Professor of Ophthalmology
Harvard Medical School

Introduction, Overview and Definition of Terms

Prior to considering the subject of involuntary facial movement conditions, such as blepharospasm, it is useful to first define disease descriptive terms. Benign essential blepharospasm refers to isolated involuntary closure of the eyelids associated with increased frequency of blink, forceful spastic eyelid closure, or asymmetrical closures of the eyelids and periocular regions. The word “essential” was fashioned several generations ago, and refers to the absence of a primary disease of the structural eyeball. The eye examination is normal except for the involuntary movements. “Benign” refers to a condition that does not cause blindness in a conventional sense although this condition is highly visually comprising. Essential blepharospasm is a neurologic syndrome with many components and features that need to be distinguished from other ophthalmologic conditions, such as chronic allergy, uveitis, keratitis, dry eye, chronic blepharitis can cause secondary reactive blepharospasm. Essential blepharospasm is diagnostically grouped with more global involuntary facial movement disorders known as Meige syndrome (formerly Brueghel's syndrome), cranial facial dystonia, or upper facial focal dystonia. Meige syndrome is comprised of involuntary asymmetric contractions of facial muscles often involving blepharospasm, sometimes associated with tremors of the head, vocal cords or hand. Lower facial Meige syndrome does not have to involve blepharospasm but has same facial muscle contraction characteristics. Meige syndrome also includes other movement diseases including spasmodic torticollis, essential tremor of the hand or head, bruxism, tongue darting and in spastic dysphonia. The many combinations of these syndrome components may be observed in one patient or spread among the patient's family pedigree.

Hemifacial spasm is a synchronous contraction of one side of the face because of an ectopic excitation of the facial nerve. The movements are similar to that obtained by stimulating the facial nerve at the base of the skull or intra-cranial nerve segment which causes similar involuntary hemi facial contractions.

Aberrant facial nerve regeneration with lid closure synkinesis most commonly follows a well-defined episode of facial paralysis.

Apraxia of eyelid opening is a non-forceful involuntary closure. This type of movement configuration can be seen with essential blepharospasm or Meige syndrome. When apraxic movements of eyelids occurs without spastic movements, the syndrome is suggestive of central neurodegeneration such as progressive supranuclear palsy or Parkinson's disease.

Localized myokymia, (otherwise known as living flesh) often occurs as a normal variant on the lower lids. It can be associated with more wide-spread forms of myokymia.
Myoclonus represents bursts of facial jumping movements which may be asymmetric, short duration, non-synchronous and often asymmetric distributed. This is a fairly rare syndrome that is often associated with myoclonus of the soft palate.

The initial differential diagnosis of bilateral blepharospasm involves distinguishing between a localized essential blepharospasm, or neurologic blepharospasm associated with involuntary movements of the head and neck. Hemifacial spasm and aberrant regeneration look similar and have similar morbidity but distinguished by the temporal consistency. Constant involuntary contractions with blinking and facial movement are present with aberrant facial nerve regeneration. Hemifacial spasm is associated with moment to moment variations (period effect). Patients with hemifacial spasm have no symptoms for brief periods.

**Clinical Syndromes**

**Benign Essential Blepharospasm (Figure 1)**

Benign essential blepharospasm is a condition involving involuntary movement and closure of the eyelids, which causes visual loss. Its onset is anywhere between the ages of 40 and 80 with a slight increase predominance in females. By definition, this is a chronic disease that can be life altering and functionally blinding. Typically there are no structural lesions routinely found on routine MRI or CT scanning. The involuntary closure impacts the lids and surrounding structures. The involuntary eyelid closure impacts daily life, particularly driving and personal independence. The diagnosis often is initially confused with dry eye syndrome, blepharitis, various forms of eye irritating disease causing secondary blepharospasm. Photophobia exists in the majority of the patients which has no direct ocular explanation on diagnostic examination. Various emotional or inflammatory diseases of the eye can aggravate a pre-existing subclinical neurologic blepharospasm. With essential blepharospasm (in contrast to Meige syndrome), only a small number of patients have a genetic history of head and neck movement diseases within their pedigree. Emotional issues are important in this condition and need to be evaluated carefully to adequately provide competent management. Anxiety and depression are common, occurring in up to 50% of the patients. Sometimes obsessive compulsive personality traits have been noted (1,2). The cause-effect relationship of emotional conditions in all forms of facial movement disease is sometimes difficult to separate. The major life issues should be noted on first encounter, such as recent deaths, loss of job, and a living situation which may provoke stress, depression, insomnia, and general anxiety. These emotional traits will worsen the condition and in fact may play an endogenous role in generating the problem. The patient should be asked about frequent face touching to assess for sensory feedback tricks, a hallmark of true dystonia and movement disease. These feedback tricks are characteristic of the involuntary blepharospasm occurring both as essential blepharospasm and in combination with more generalized movement disease of the eyelids, head, and neck. Psychiatric history and use of past neuroleptic medications are important in the historic evaluation for both blepharospasm and Meige syndrome.

The examination should involve a complete analysis with slit lamp searching for keratitis, uveitis, and other inflammatory disease, which could render the patient's diagnosis as a secondary reactive blepharospasm. Neurologic blepharospasm's hallmark is the absence of primary eye diseases. Observations for involuntary movements of the lower face, head, and neck regions are important. Changes in voice or voice quality should be assessed. Rarely nystagmus can be part of the syndrome. In severe cases the author has seen advance rhytide patents and disfigurement in the glabellar area known as
Chvostek sign by prior generations of eye surgeons. The author has also observed one patient whose brow has been rubbed off by constant use of the sensory trick (figure 2). The nature of the involuntary movement could involve forceful lid closure, frequent pointing or apraxic type of nonspastic lid closure. The more apraxic movements present in the patient will make the condition more difficult to treat. Changes in lid structure, such as an elevated upper lid crease, involution ptosis, dermatochalasis, trichiasis, spastic entropion, and lower lid retractor disinsertions are co morbid components and further aggravate symptoms and need to be addressed in the treatment plan. Evidence of chronic allergy such as skin hyperpigmentation or chronic allergic changes at the lid margins and conjunctiva should also be assessed.

Photophobia is present in up to 80% of patients and most likely generated in the central nervous system (3,4).

Figure 1a

75 year old woman with isolated blepharospasm
And sever photophobia

Figure 2a:

85 year old man with Meige syndrome (blepharospasm associated with severe lower face oral dystonia and torticollis)

Figure 2b

Meige syndrome is often associated with abnormal lower facial movements as well as tremors in head
Hand, neck spasms. Abnormalities in facial expression are common.

Figure 2c

This 66 year old man rubbed off a portion of the eyebrow by constant use of his sensory trick
Meige syndrome, craniocervical dystonia with facial, head, and neck involvement, Brugal syndrome, facial dyskinesia, focal and regional facial dystonia) (Figure 2)

Meige syndrome is distinguished from essential blepharospasm in that the involuntary movements and disease morbidity are not just limited to the eyelids but involve to varying degrees the lower face, neck (tremor, spasmotic torticollis, and voice) spastic dysphonia (5). Unlike benign essential blepharospasm, Meige syndrome is often associated with a family history of movement diseases of the head and neck. Careful family history is important particularly with respect to each element of the syndrome to assess genetic association. The full Meige syndrome involves blepharospasm, facial dyskinesia, essential tremor of the head and neck, spastic dysphonia, and involuntary movements of the tongue. It is rare to find all these components in one patient, but within a single pedigree multiple individuals may be affected with different aspects of the full syndrome such as involuntary lip smacking, asynchronous lower facial twitching, bruxism, vocal cord spasms. As is the case of essential blepharospasm, photophobia may be present; however, there are many cases where photophobia does not exist in a more generalized movement condition. As is in essential blepharospasm, sensory tricks are often present. Psychogenic factors can aggravate this syndrome but are less likely to be part of an initial etiology. In fact, the personality type associated with this condition is sometimes distinguishable from a focal essential blepharospasm in the author's experience. The condition can be progressive, visually incapacitating, and highly debilitating. Occasionally the syndrome can overlap tardive dyskinesia. It is particularly important in this syndrome to elicit history of prior use of neuroleptic drugs. Such neuroleptic drugs are listed in Table 1 (6). The need to distinguish this condition from a chemical lesion from the use of antipsychotic or neuroleptic drugs is important relative to anticipated prognosis. It is more difficult to treat the movement disease in cases with a drug induced facial or craniofacial dystonia (eg tardive dyskinesia).

The natural history is often progressive with a small subset of patients going into remission. If blepharospasm is untreated enormous impact on the quality of life can occur and disability can be forthcoming because of visual compromise. The complexity of this movement disease are not often well understood by family and friends and social isolation can occur. The abnormal facial movements impact driving, nonverbal communications, and overall quality of life. A very small number of patients can regress to a full neurodegenerative state such as Parkinson's disease, but fortunately this is rare. Apraxia of lid opening can occur and suggest a more malicious prognosis. Sometimes apraxia of lid closure that occurs in conjunction with the involuntary blepharospastic movements. Apraxic movements are more difficult to treat.

Table 1 Medications which can cause craniocervical dystonia:

<table>
<thead>
<tr>
<th>medication</th>
<th>other names</th>
</tr>
</thead>
<tbody>
<tr>
<td>trifluoperazine (Stelazine)*</td>
<td>perphazine (Trilafrom, Triavil)</td>
</tr>
<tr>
<td>promethazine (Phenergan)</td>
<td>trimeprazine (Temaril)</td>
</tr>
<tr>
<td>prochlorperazine (Compazine, Combid)</td>
<td>loxapine (Loxitane, Daxolin)</td>
</tr>
<tr>
<td>thioridazine (Mellaril)</td>
<td>fluphenazine (Permitil, Prolixin)</td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>haloperidol (Haldol)*</td>
<td>Navane triflupromazine (Vesprin)</td>
</tr>
<tr>
<td>chlorpromazine (Thorazine)*</td>
<td>Acetohenazine (Tindal)</td>
</tr>
<tr>
<td>thiethylperazine (Torecan)</td>
<td>molinndone (Lindone, Moban),</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>mesoridazone (Serentil)</td>
</tr>
<tr>
<td>metaclopramide (Reglan)*</td>
<td>amoxapine (Asendin)</td>
</tr>
<tr>
<td>promazine (Sparine)</td>
<td>piperacetazine</td>
</tr>
<tr>
<td>Respirodone*</td>
<td></td>
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</tbody>
</table>

* observed by author to produce a "Meige disease like" syndrome

### The Continuum between Essential Blepharospasm and Meige Syndrome

*Many patients with benign essential blepharospasm may progress to Meige syndrome. Such cases indicate strong evidence of an organic etiology of isolated benign essential blepharospasm. Essential blepharospasm may never progress to a more generalized form. Essential blepharospasm can be viewed according to the progressive vs non progressive nature in the individual patient. Subsets of each condition can have a sensory trick while others demonstrate no tactile sensory suppression. Certain cases a substantial history of depression, anxiety and compulsive behavior while other have no such history or tendencies.*

Although management is similar in both conditions, the impact of genetic relationships are quite different. 276 pedigrees from patients studied in the greater Boston area by the author, those with blepharospasm associated with generalized head and neck movement disorders were more likely to have a positive family histories of movement disease than isolated essential blepharospasm. Over 50% of the pedigrees were positive if the blepharospasm was associated with torticollis, essential tremor of the head, neck, or spastic dysphonia or lower face involuntary movements. Only 10% of the patients with focal isolated essential blepharospasm had a positive pedigree of movement abnormalities. In the author's experiences it is helpful to make some determination between benign essential blepharospasm and Meige relative to the use of systemic medications, such as Klonopin, Artane, or other anticholinergics. It also is important relative to genetic advising and perhaps studying the nature of these diseases and formulating treatment plans.

### Psychogenic Versus Organic Blepharospasm

In acute cases of blepharospasm (weeks to several months duration), the possibility of an emotional conversion reaction should be considered and psychiatric-type questioning should be instituted. In such cases the blepharospasm, prognosis can be self-limited and the condition may be a transient problem. By definition, neurologic blepharospasm is chronic. For chronic cases, a decisive label between psychogenic blepharospasm versus an organic blepharospasm is often not helpful in offering patients needed therapy but can have some impact on advice and approach to the problem. Notwithstanding this view, caution should still be used in recommending aggressive surgical procedures in which psychogenic etiology may be playing a major role. Figure 3 provides some important considerations and distinguish between
psychogenic and organic factors governing benign essential blepharospasm. Despite these guidelines, in some cases it is very difficult to determine with high confidence a purely psychogenic case versus an early organic form of the condition. *Patients thought to have a heavy psychogenic overlay should be referred to a psychiatrist or psychologist for evaluation and management of sleep disorders, anxiety, depression, which can be useful in providing a needed comprehensive multi-specialty approach.*

**Figure 3: Psychogenetic vs Organic**

Pathogenesis of Benign Essential Blepharospasm and Meige Disease

The cause of benign essential blepharospasm (BEB) and Meige Syndrome (MS) can be grouped together despite the distinctions made above. The research on these conditions comes from various investigational studies, including:

1. Lesion location analysis and postmortem or neuroradiology studies.
2. Studies of trigeminal facial reflex using electrophysiological analysis on facial muscles.
3. PET scanning on studies of the brain metabolism and possibly future neurotransmitters analysis.
4. Genetic analysis searching for specific polymorphisms and eventually with a gene-wide associated studies and the use of various computer protocols for DNA nucleotide sequencing searching for associated polymorphism relationships. Possible futures using molecular biologic testing such as gene specific PCR may be useful in genetic diagnosis.

The author believes these diseases are caused by *hyperactive brainstem interneurons governing rhythmic blink reflex, as well as interneurons that associate with different portions of the brain involving voluntary and involuntary facial movements.* Some of these facial movements could be involuntary relative to reactive emotional states and also functional relative to the eye with frequent blinking to maintain the continuous tear film over the cornea with preservation of the metabolism of the ocular surface.

The *hyper sensitization of these neurons* can be a result of:

1. Intrinsic changes in a neuron itself based on genetic or metabolic changes relative to receptors and interfacing with other portions of the central nervous system.
2. Intrinsic changes that alter and exaggerate responses to sensory input to the interneurons. Factors that increase sensitivity of the interneurons in turn worsen the symptoms of facial movements. Factors that suppress interneurons (raise response thresholds) mitigate the symptoms.

I. Anatomic Analysis in Lesions

Although lesions are to be rarely found in neurologic testing in forms of essential blepharospasm and Meige disease, there have been a number of cases reported where lesions in the basal ganglia and the brain stem have resulted in involuntary movement disease. The author remembers one patient in a deep coma from rupture of a top of the basilar artery aneurysm whose only spontaneous movements were fairly violent blepharospasm.

The incident of structural lesions causing “secondary neurologic blepharospasm” is very low (<1%). Most commonly lesions in the thalamus, midbrain, basal ganglia, cerebellum are found. Most common etiology is stroke, vascular malformations and benign cysts (7). This data is supportive of the brainstem pathology as being the most localizing brain region for the pathology.

II. The Trigeminal Facial Reflexes (see figure 4)

The work of Tolosa, et al., and subsequent researchers have shown that the R2 wave in the trigeminal-facial nerve reflex is highly abnormal in many patients with Meige syndrome and benign essential blepharospasm (fig 4)(8-11). These studies involve stimulation to the trigeminal nerve with reflex contractions of the facial muscles, as measured with electromyography. Typically a stimulus will cause a short well demarcated contraction as measured by EMG. In patient with involuntary blepharospasm, a delayed R2 wave is widened indicating an abnormality in interneuron relay between the sensory trigeminal complex and the facial nerve nucleus. Further analysis of this phenomena revealed (figure 4) the sensory trick, a common characteristic in patients with blepharospasm and Meige syndrome, suppresses the prolonged R2 (trigeminal sensory movement suppression). The widened R2 wave has been interpreted as abnormal reaction of the blink interneurons to sensory stimuli. Blepharospasm is often understood to be a problem of movement, however, data from the trigeminal facial reflex studies give substantial credence to the sensory components of the condition.

Further, botulinum toxin has a suppressive effect shortening of prolongation of the R2 wave. These observations indicate that there are abnormalities in a neuron interpretation of sensory information or suppression of hyper excitable interneurons that result in involuntary firing of the motor nerves to the facial muscles.

It should be noted that the interneurons may be subject to other changes in the nervous system inclusive of neurodegeneration, abnormalities of mood and affect, sleep depravation, and possibly even hypersensitization of the trigeminal nerve/interneuron complex which occurs in such conditions as chronic thalamic pain, trigeminal neuralgia, chronic migraine and post inflammatory pain syndromes (12-14).

The reason why the interneurons become hyperactive should be a subject of further investigation.
Figure 4

Trigeminal Facial Reflex in Neurologic Blepharospasm

A. Elongated R2 wave (controls not shown)

B. Effect of Sensory stimulation on the R2 wave abnormality.
   a. R2 wave
   b. Sensory trick suppressing the R2 wave

III. PET Scanning

PET scanning is an effective way for looking at differential metabolism in the brain with labeled $^{18}$F glucose. Hyper metabolism of portions of the thalamus and other areas of the basal ganglia and possibly related areas of the gyri in the cortex (15-18) has been associated with blepharospasm. Thalamus and mid-brain appear to be the most consistent areas of highest metabolic activity. The use of PET scanning is rapidly evolving. A contemporary use of PET scanning relates to its use in glutamate metabolism (14). PET glutamate analysis has turned up interesting association with depression and mood disorders. Glutamate has been shown to be at high levels in patients with human depression. The glutamate is basically the most common neurotransmitter in the brain and its activity levels with respect to synthesis, release and receptor expression may be a factor in neuronal hyperactivity. Glutamate has also been linked to animal models of movement disease (19-20). Other neurotransmitters may be involved. Future studies of glutamate PET scans and related neurotransmitters may be useful in understanding the region of the brain which is dysfunctional relative to the neurotransmitters activity and receptor expression within hyperactive blink-related inter neurons.

IV. Genetic Studies /Polymorphisms

With the advancement of genomic testing, an accelerated interest has emerged to identify genes which segregate with various forms of movement disorders. Such studies could significantly advance knowledge of the cause of facial and lid movement disease based on a molecular and cellular basis, particularly relative to excitability of neurons and perhaps useful in disease classification.

An analysis conducted in the author’s practice reviewing 269 pedigrees was analyzed between 1983 -1998. Patients with primary essential blepharospasm (without involuntary movements in lower face, voice, neck or hand) had at least one other family member with a focal or regional dystonia in the head, neck or hand region in 20% of pedigrees. Patients with blepharospasm plus involuntary movement (Meige syndrome) in other regions of the head, neck or hand revealed about a 50 % positive pedigree for movement disease. The author’s experience indicated that patients with younger onset were more likely to show familial positivity.

Polymorphisms of genes encoding Torson A (DYT1) and D5 dopamine receptor genes have been associated with lifetime risk of focal dystonia (21-25).

A single mutation in TOR1A, the gene encoding torsin A protein, is responsible for most cases of early-onset generalized primary dystonia but has no significant role in primary late-onset dystonia which would...
be more characteristic of Meige syndrome (21-24). Recent case-control studies in Icelandic and Italian populations nevertheless raised the possibility that the 191G/T single nucleotide polymorphism (SNP) located at the 3_untranslated region of the TOR1A gene (SNP ID: rs1182) influences the risk of developing late-onset dystonia (23). However, these findings were not confirmed in other series from Germany or the United States of America (25).

In a recent study, 144 Italian patients and 257 US patients (all Caucasians) with essential blepharospasm were analyzed for the rs1182 SNP genotype by using real-time polymerase chain reaction and a site specific enzymatic cleavage for DYT1 to assess which patients progressed to more generalized head and neck movement disorder (23). In both series, females predominated; primary involuntary blepharospasm had its onset in the fifth to sixth decade and in most cases spread within the first 5 years. In both series, age of essential blepharospasm onset was greater in the patients who spread whereas duration of disease tended to be longer in those who did not. Essential blepharospasm spread to one body site in 40 Italian (28%) and 38 United States of America patients (15%). In both series, patients carrying the T allele (GT or TT) (polymorphism) were significantly more likely to experience spread than those without.

Polymorphism analysis is useful, however, and sometimes the translation and transcription of the particular gene does not give us a clear picture to what portions of the cell biology that are active. Such polymorphism analysis, however, is insightful with evaluations of different alleles in various genetic loci may allow insight into the diseases and physiology of hyperactive interneurons. With the addition of inexpensive genomic sequencing using rapid platform (Illumina Technologies), it may be possible now to establish and accelerate our knowledge in this particular area. Computer protocols could be useful in looking at the relationships of different polymorphisms and subsets in a way that would be beyond what could be imagined even 5 to 6 years ago. The author further believes such an analysis may be useful further to distinguishing organic- psychogenic disease basis.

Management of Essential Blepharospasm and Meige Syndrome

The management of essential blepharospasm in Meige syndrome involves controlling the degrees of involuntary movements so that vision is preserved and that distortions of the face are minimized (5).

The criteria to initiate therapy should be the presence of symptoms for at least 6 months and also some degrees of visual compromise, particularly such as driving, reading, or doing routine activities. Once it is decided when the treatment is going to be administered, botulinum toxin injections are the treatment of choice. At initial encounter, one can make some assessment of the psychosocial issues affecting the patient. Depression, obsessive compulsive personality traits, and anxiety disorders are particularly important in the initial evaluation and should be addressed. If the patient clearly has essential blepharospasm plus
involuntary movements and a family history with sensory tricks then the condition needs to be considered organic. And even in organic cases, symptoms can be aggravated by anxiety and sleep disturbances.

The treatment of botulinum toxin usually involves a Type A neurotoxin, Botox, Xeomin, and Dysport are available in the United States. These agents are not interchangeable with respect to dosing. Compositional analysis of the different properties of these materials should be by the knowledgeable injector. Diffusion potential, dose and unit potency of preparation vary between preparations. The industry has been active in trying to improve properties of agents to improve outcomes via duration, enhancement, and regional potency.

Additionally, therapy could involve the treatment of anxiety and sleep with the use of a benzodiazepine-type drug such as clonazepam (26). Benadryl can be used particularly as a sleep aid. Also the use of anticholinergics such as Cogentin and Artane can be helpful.

Filtered lenses are often helpful for blepharospasm and Meige disease if photosensitivity is present.

In rare situations, the use of anti-seizure medications, such as Neurontin (gabapentin), can be helpful.

Surgery is often used in these patients as adjuvant procedure and can be very effective. The type of surgical procedures advocated for essential blepharospasm and Meige disease not responding to medical therapy are listed in Table 2a (21-25).

The first surgical procedure to be considered is limited myectomy/and or ptosis-pseudoptosis repair (figure 5). This involves a blepharoplasty-type incision and stripping of pretarsal and preseptal orbicularis muscle sometimes associated with levator advancement. The chronic squeezing of the lids associated with both essential blepharospasm and Meige syndrome can lead to levator aponeurotic and lower lid retractor disinsertions. Disinsertions should be repaired placing the eyelid margin in normal position. Surgery should also be considered particularly for ptosis associated with lid crease and lid fold retraction.

Table 2a. Overview of Surgical procedures for

A. Essential Blepharospasm and Meige Syndrome.

1. Repair of pseudoptosis (dermatochalasis)
2. Ptosis repair with levator advancement
   Correction of lower lid retractor disinsertions
3. Limited myectomy associated with the above.
4. Frontalis slings
5. Direct brow lift with removal or preorbital orbicularis, glabellar and procerus muscle (aggressive myectomy).
6. Indirect forehead lift from endoscopic flap
7. Upper branch facial nerve transaction  
8. Total facial nerve trans section*  
9. Deep brain stimulator insertion*  
10. Chemoablation

**B. Hemifacial Spasm**

1. Repair of pseudoptosis (dermatochalasis)  
2. Ptosis repair with levator advancement  
   Correction of lower lid retractor disinsertions  
3. Limited myectomy associated with the above*.  
4. Microvascular decompression for hemi facial spasm

* uncommonly recommended as denervation weakness pre-exists in hemifacial spasm

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**Figure 5 Limited Myectomy with repair of levator aponeurotic disinsertion**

Note: Severely disinserted levator aponeurosis from spastic lid contractions.

The use of larger myectomies have been advocated (29-33). These procedures involve a more aggressive stripping of muscle both in the preorbital, preseptal, and pretarsal area associated with levator advancements. Such myectomies can be done in the upper and lower lid. The more aggressive procedures are more likely to be associated with lagophthalmos and exposure keratitis which can further aggravate the blepharospasm and photophobia making the condition more difficult to manage with both botulinum toxin and other methods. Additionally, the use of less invasive procedures have been advocated in recent years inclusive of levator sling procedures (29), use of a brow pin to enhance sensory trick suppression of blink (34), partial facial neurectomy (35) and use of various forms of chemo ablative agents (33). These methods have their place as they are tolerated better by most patients and do not run the risk of serious lagophthalmus and ocular surface abnormalities. Deep brain stimulation has been tried with variable results (36).

The author's approach to the therapy is given in priority diagram shown as Figure 6. The first priority is botulinum toxin Type A. Immunotype type B has been tried but associated with a greater diffusion, higher dose requirements, higher complication rates, and more pain because of a low pH formulation.
Surgical Procedures for Recalcitrant Blepharospasm and Meige Disease

Although botulinum toxin since the early 1980's has become the mainstay for therapy of benign essential blepharospasm, hemi facial spasm, and the Meige syndrome with involuntary eyelid closures, surgical therapy is unquestionably appropriate when medical therapy fails. Generally, surgical therapy should be considered when the patient has a chronic problem of at least 6 months duration and preferably over a year and has failed repeated botulinum toxin injections at varying doses, injection location strategies, and has at least failed one oral medication attempt to control the condition. The author believes a secondary non-responder to botulinum injections is more likely to respond well to surgical therapies. Patients with anatomic changes of the eyelids aggravating ocular surface area irritation, such as entropions, should be immediately and aggressively repaired as previously mentioned.

The classifications of surgical procedures used for the primary treatment of benign essential blepharospasm and Meige syndrome can fall into several categories, according to the relative risk/benefit ratio. Of course, the low risk/benefit ratio is a most acceptable starting point.

1. **Low benefit risk ratio procedures.**

This category involves levator advancements for patients with pseudoptosis or ptosis associated with the condition. Pseudoptosis with dermatochalasis should be considered a basic procedure for various reasons. The first is that there may be encroachment on the visual field and weight of the eyelid. Because of the constant squeezing, not only is the skin often lax but the levator aponeurosis often disinserts. Correcting the ptosis has a high yield and relatively low risk. It should be emphasized that no cure is given here but optimizing the botulinum toxin effectiveness is the goal. Capsulopalpebral fascia disinsertion from the
inferior tarsal commonly leads to involutional entropion. This problem is a relatively easily addressed with relief of surface irritation and aggravation.

2. Intermediate risk/benefit ratios

In this category, limited myectomy with ptosis procedures associated with stripping of the muscles along the pre-tarsal and pre-septal region is employed. The muscle stripping is a larger procedure and can sometimes be helpful in both reducing orbicularis closure strength. *It should be noted that this is done in a limited fashion, not requiring a large pre-orbital dissection and large en bloc resections of muscle. The approach is combined with levator aponeurotic advancements.*

The frontalis sling procedure has an intermediate risk/benefit rating. The author has not found this approach useful for spastic eyelid diseases, but *has found it more useful for the apraxia of eyelid opening.* In this situation there is not much squeezing as often as excessive of brow elevation. Major complications with this procedure are excessive elevation and irritation to the ocular surface. It is preferable to use reversible style procedures in the event this does occur, using either silicone tubing or with Supramid-TM, materials that can be removed. Tendon based materials are less useful as these could be more difficult to reverse even when direct cutting is attempted.

The upper branch facial neurectomies can be useful. This approach is helpful towards increasing the responsiveness to botulinum toxin. Upper branch facial neurectomies are generally well tolerated however a risk of asymmetric smile and reversibility of effect with time are the major issues. The procedure is done using a Montgomery nerve stimulator identifying lateral and medial branches of the facial nerves entering the orbicularis muscle for surgical transaction.

3. Higher risk/benefit procedures.

The higher risk procedures involve full facial neurectomies and the more extensive myectomy procedures. This category, although sometimes useful, requires a greater degree of surgical resection and sometimes can be associated with aggravating side effects. Large myectomy procedures can be effective but can result in exposure keratitis and aggravate dry-eye symptoms. Also, there can be appearance disfigurement. The problem with major facial neurectomy is the facial nerve regenerates and often there can be a return of full innervation. Full facial neurectomies can be disfiguring to the lower face. Deep brain stimulation should also be placed in this category.

4. New procedures.

The author has worked on the use of a titanium pin fixation procedure designed to tether the pre orbital orbicularis as well as stimulate the supra orbital nerve causing increased sensory input associated forceful contractions (34). In essence, the procedure is designed to produce an automatic surgically-generated sensory trick which suppresses hyperactive blink in the neurons (see figure 4), particularly with frequent forceful lid closure. The procedure is a small incision office based procedure and is minimally invasive (8-11). Figure 7 demonstrates pin placement and tethering of the orbicularis oculi. The procedure has had initially a good effect, however, over an extended period of several years of time
the effects do diminish. A discussion of the extended results of this procedure is given in Table 3). The initial response to converting a botulinum non responder to responder is 74%. Of those responding, 72% maintain a response in a three year follow up. Again, as in all surgical procedures, these are best used for the patients with *more organic forms of blepharospasm rather than patients who have had more of a psychogenic overlay.*

**Figure 6b Muscle fixation and Sensory Stimulation Pins**

![Muscle fixation and Sensory Stimulation Pins](image)

### Table 3a  Improvement to BTX response total sample over three years (28):

<table>
<thead>
<tr>
<th>Year</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>74%</td>
</tr>
<tr>
<td>Year 2</td>
<td>56%</td>
</tr>
<tr>
<td>Year 3</td>
<td>54%</td>
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### Table 3b: Maintenance of a favorable BTX response from subset initially responding (28)

<table>
<thead>
<tr>
<th>Year</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>100%</td>
</tr>
<tr>
<td>Year 2</td>
<td>84%</td>
</tr>
<tr>
<td>Year 3</td>
<td>72%</td>
</tr>
</tbody>
</table>
Surgical wounds, hyperactive brainstem inter-neurons and how surgical procedures work.

Ironically, most of the thoughts and the use of surgical procedures is to limit the contractility of an orbicularis muscle, either by resecting the protagonist muscle to lid closure or cutting the innervation to the muscle. Although this makes great anatomical sense, this may not be a compelling and most comprehensive way to treat the diseases, as the disease is sensory generated. Further, the author has noted improvement of the involuntary movement out of proportion with the weakness created by many advocated published procedures such as myectomies.

The sensory impacts of the healing wounds should be carefully considered as having a possible beneficial effect with respect to central sensitization and inter-neuronal excitability. Although a great void exists in the written medical literature on the effect of healing wounds of the central nervous system, the central nervous system clearly is involved in the wound healing process. Disease processes involved with healing wounds includes reflex sympathetic dystrophy, which inherently generates a dystonia. Healing wounds can have an effect on motor control interneurons and even sensory pain adaptation in the central nervous system at the brain stem level. Adaptation occurs during the healing process with less pain noted after several days with respect to most facial wounds. The central nervous system adaptation process can interplay with motor neuron excitability.

The physiology of surgical wound healing created in all of the above procedures may be playing a role in the effectiveness of the procedures. This has never been really addressed in oculoplastic literature, however, there is a high likelihood that this is playing a mechanistic role. Recently, the effect of blepharoplasty has been advocated as an adjunctive procedure to the treatment of migraine headache (37). Migraine headache is responsive to surgical procedures and there have been advocates of using forehead lifts, glabellar myectomies, as well as blepharoplasty as a way of relieving the chronic migraine. Some authors give "nerve entrapment glabellar muscles" as the effective mechanism(38-39). The author believes the physiology of the surgical wound healing process to be a more likely reason for these observations. A sensory/motor CNS effect produced by surgical wounds may be a mechanism contributing to the functional anatomic effect on muscle and nerve produced by many of the aforementioned procedures. With the use of increased imaging studies using neurotransmitters, a better understanding of CNS effects produced by surgical wounds can be better characterized with future research.

It is of historic interest that Dr. Parkinson in 1813 described surgical wounds as being therapic for muscle spasms of the head and neck region. In fact Dr. Parkinson tried to place cork within the wound to enhance the intensity and duration of this effect for the treatment of movement disease. The phenomena described in this section may not be so novel (40) but needs further characterization.

Hemi- facial Spasm (see Figure 7a):

Hemifacial Spasm is an involuntary contraction of muscles on one side of the face supplied by the ipsilateral facial nerve. The involuntary movements are synchronous and vary from time-to-time (period effect)(41). Usually the condition begins with involuntary twitching of the eyelid with closure of the
palpebral fissure. In early stages, myokymic type movements can be seen in the upper or lower portion of the face. Involuntary contractions of the eye lids is associated with zygomaticus muscles pulling the angle of the mouth up accentuating the nasolabial fold. Often in more advanced cases there is lip ectropion during the contractions (see Figure 7). The condition is often chronic, however remissions can occur but are uncommon. With the involuntary contractions, occasionally there is a thumping sound in a minority of patients due to involuntary contraction of the stapedius muscle in the middle ear.

The condition often progresses with age and with increasing frequency and amplitude of the involuntary contractions. The involuntary contractions are the same as one would elicit by stimulating a proximal end of the facial nerve with a nerve stimulator.

The morbidity of this condition has to do more with nonverbal forms of facial communication. The patient’s ability to conduct a conversation using natural facial expression is severely impaired. Morbidity questionnaires on this condition indicate that communication in face-to-face social interaction had the highest degree of impairment. In a study on hemifacial spastic disease (Table 3)(42,43) social communication was associated with the highest degree of morbidity relative to other components of the syndrome. Vision is also impaired by involuntary closure but not as severely involved as an essential blepharospasm and blepharospasm associated with involuntary dystonia of the head and neck (Meige syndrome). The condition can be associated with some degree of depression and impact on psychosocial type of interactions which prove to seriously impair life.

If a patient's occupation requires a substantial amount of communication, the condition is particularly pernicious. Hemifacial spasm is a form of facial neuropathy as the patients have a decrease in the amplitude of contractions. In more advanced cases, substantial weakness can be noted on the afflicted side. Hemifacial spasm rarely can be associated with trigeminal neuralgia (tic convulsif) which, like hemifacial spasm is usually caused by nerve route compression at brainstem exit zones. Hemifacial spasm is not uncommon occurring in about 1 in 10,000 - 20,000 persons.

<table>
<thead>
<tr>
<th></th>
<th>Baseline (SD)</th>
<th>Postinjection (SD)</th>
<th>Wilcoxon (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life</td>
<td>5.01 (1.81)</td>
<td>3.12 (2.94)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Social</td>
<td>39.51 (10.5)</td>
<td>29.34 (13.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Personal appearance</td>
<td>50.13 (4.6)</td>
<td>15.55 (2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Visual</td>
<td>15.06 (5.77)</td>
<td>11.15 (7.06)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Severity</td>
<td>10.73 (3.2)</td>
<td>7.66 (3.6)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

* Points: The lower score reflects improvement, closer to normality. n = 50, control/treatment ratio (1:1). None of the placebo groups demonstrated any statistically significant differences and there were no differences between baseline and subsequent values for control or active drug groups.

4b. Correlation of Severity of Deformity with Morbidity:

<table>
<thead>
<tr>
<th></th>
<th>Pearson Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life</td>
<td>0.583</td>
</tr>
<tr>
<td>Social interaction</td>
<td>0.637</td>
</tr>
<tr>
<td>Visual function</td>
<td>0.502</td>
</tr>
<tr>
<td>Severity</td>
<td>0.566</td>
</tr>
<tr>
<td>Personal appearance</td>
<td>0.507</td>
</tr>
</tbody>
</table>

* p < 0.001 for all domains.

Aberrant Facial Nerve Regeneration:

Aberrant Facial nerve regeneration *most commonly occurs after Bell’s palsy but may occur after Ramsey Hunt syndrome, intracranial sub occipital craniotomy for cerebral pontine angle tumors (eg acoustic neuroma), or penetrating trauma to face or skull base.* Weakness is associated with various patterns of involuntary movement. Eyelid closure occurs with facial expression or use of facial and jaw muscles. Table 3 covers morbidity associated with the syndrome based on large scale studies linking the degree of disfigurement associated with morbidity. Unlike hemifacial spasm, frank weakness is obvious in most cases and the condition does not show moment to moment variation. Reflex tearing so called *crocodile tears* is common. More uncommonly, reflex sweating can occur (*Frey's syndrome*). Patients may suffer co
existing neurotrophic keratitis if fifth cranial nerve was injured which complicates management. Occasionally facial tightness and discomfort is associated with the increased resting tone associated with the synkinetic movements.

Treatment usually involves the use of botulinum toxin injection in similar regions as hemifacial spasm but usually at lower doses. The surgeon should be mindful that in this syndrome, increasing the weakness of closure is more likely to create exposure keratitis from lagophthalmos. The author recommends about 10 units as a total starting dose with no more than 2.5 U locations depicted in Figure 10).

**Apraxia of Eyelid Opening**

The syndrome of *apraxia of eyelid opening involves* closure of the eyelids without spasms, but with increased frontalis tone. Brows are usually high but lids are closed, with no squeezing.

Isolated apraxia suggests a neurodegeneration which is often progressive such as Parkinson’s disease, Progressive Supra nuclear Palsy, Alzheimer’s disease, or other forms of neuro degeneration.

The author has seen occasional cases of Parkinson’s disease with blepharospasm and apraxia of lid opening. Further, some cases of essential blepharospasm/Meige can have apraxic type movements occasionally but the predominant movement is a spasm.

Maintaining eyelid control with botulinum toxin is more difficult for this condition predominantly as the spasms are not a major component. If a patient with blepharospasm/Meige has a high frequency of apraxic movements, botulinum toxin would most likely be less effective.

The management needs to be customized with botulinum and possible surgical procedures, such as levator advancement and, reversible frontalis sling procedures. Attention should be given to not creating any aggravating keratitis from exposure.

**Hemifacial Spasm Treatment**

**Botulinum Toxin:**

Botulinum toxin is the most convenient, safe, and effective therapy for the treatment of hemifacial spasm. With respect of efficacy, there has been clear evidence of improvement including quality of life assessments, social interactions, vision, and self-perception (see Table 3). The therapy addresses impairment in non-verbal communication and disfigurement associated with distortions of muscles of facial...
expression. The distortions carry over to misinterpretations in social interactions from involuntary winking and facial movement. Peripheral vision to a lesser extent is also impaired.

Botulinum toxin dosing for this condition needs to be lower in the periocular area over other forms of facial movement disorders, such as essential blepharospasm and Meige syndrome. The pre-existing denervation of the muscle, because of the facial neuropathy, makes the botulinum toxin more effective at a lower dose. Generally, a maximum periocular combined dose should not exceed 20 Unit for BOTOX-TM (oncobotulinum). Higher doses can cause lagophthalmos, exposure keratitis, and ocular pain, as well as excessive hemi facial paralysis. The injections are generally given in the upper face. For lower face injections it is necessary to avoid the zygomaticus muscles along their mid and lower inferior regions to reduce the paralysis of the lateral angle of the mouth. Injections can be given into the platysmal muscle if banding occurs, or even over the mentalis muscle if lip ectropion and lip disfigurement is present. Mid-face injections must be approached with care. Additionally, the author has found a method of managing mid-face disfigurement involving the use of fillers, such as Restylane and Perlane to the zygomaticus area (43). This improves the disfiguring accentuation of the nasolacrical crease seen with the involuntary spasms (figure 8), as well as creates a weight deferential on the face with lower face ballasting, which can be useful in camouflaging the involuntary movement. In a series of 20 patients, 16 (approximately 80%) noticed improvement over botulinum using combined therapy (43). Anti-seizure medicines have been tried. Such medicines have included Tegretol, Neurontin, and clonazepam. Generally side effects and inconsistent efficacy of these medications make them poor choices for the treatment of hemifacial spasm.

Fig 8: Nasolabial fold accentuation in a case of hemifacial spasm before and after use of filler

In the event that a complete cure is desired, and patients are willing to take the associated risks of a craniotomy and microvascular decompression, the Jannetta operation can be effective therapy and provide a complete cure in many situations (44-49). The procedure involves a brain stem approach through a sub-occipital craniotomy, identification of the intracranial seventh nerve, separating tortuous blood vessels from the nerve trunk, and placing insulating gel film placed around the 7th cranial nerve. The procedure is similar to that used to treat trigeminal neuralgia, which can be associated with hemifacial spasm in a small fraction of patients. The efficacy is given in Table 4. The side effects include hearing loss, vestibular symptoms, lack of effect in a considerable number of patients, and the worse possible case, bleeding in the operative field, brain stem vasospasm, and potentially serious stroke in the region of the brain stem. These side effects and the ordeal of craniotomy are often unacceptable to patients, who more frequently prefer safer convenient medical therapy with botulinum toxin the preferred initial approach. In situations in which there is tissue resistance to botulinum or a frustrated patient because of lack of satisfactory results, the use of microvascular decompression can be considered. This procedure should be conducted by a surgeon with considerable experience with this approach who performs the procedure on a consistent basis.
The long-term management of hemifacial spasm can be effective with botulinum toxin, as the dosing is low, the risk of long-term resistance is extremely small, and the efficacy can be quite good.

**Neuro Surgical Treatment for Hemifacial Spasm (44-49):**

As mentioned, microvascular decompression (MVD) of the 7th cranial in the vicinity of the nerve root exit zone via posterior craniotomy is the only definitive cure for the condition. The early work of Dr. Peter Jennetta has been expanded within the past three decades to multiple centers worldwide for the management of hemi facial spasm. Many of the variations of vessels compression on the 7th cranial nerve including anterior inferior cerebellar artery, posterior inferior cerebellar artery and vertebral artery are implicated as targets for the facial nerve irritation, possible demyelination causing ectopic and ephaptic transmission accounting the symptoms of bursts of generalized and segments firing.

The results obtained with microvascular decompression in experienced tertiary care neurosurgical centers have been quite favorable generally ranging from 85-90% (see table 4). Most common complication relates to hearing loss induced by the procedure at a rate reported between 5-10%, worsening of facial paralysis, and in very rare cases brainstem stroke and hemorrhage. Long term cure rates have been commonly obtained with recurrence less likely. The results have been reported to be best in centers conducting a higher volume of microvascular decompressive procedures for hemifacial spasm, intractable trigeminal neuralgia or glossopharyngeal neuralgia.

The author notes that in cases of “tic convulsice” due to tortuous compressive vessels can represent an uncommon but significant subset of patients with hemifacial spasm. The combination of trigeminal neuralgia and hemifacial spasm may be a more compelling indication for neurosurgery, particularly if the facial pain syndrome is poorly controlled.

Hemifacial spasm in rare circumstances in adults can be the result of a compressive tumor or other intracranial pathology. AV malformations, epidermoid tumors, meningiomas, vestibular schwannomas, pontine glioma are examples of lesions reported to cause the syndrome in adults. The author has noted two cases in which removal of epidermoid resulted in permanent cure. The condition has been reported in moyamoya disease and secondary to arachnoid cysts.

Cases of tic convulsice may be more likely to show a mass lesion.

Children with hemifacial spasm represent a distinctive subset as intracranial tumors are more likely. Careful radiologic evaluation of the posterior cranial fossa/fourth ventricle should be pursued.
Table 4: Summary of Neurosurgical Results using Microvascular decompression

<table>
<thead>
<tr>
<th>Authors</th>
<th>Journal</th>
<th>Sample size</th>
<th>Success rate based on at least 6 months follow up</th>
<th>Hearing complications</th>
<th>Mortality</th>
<th>Hematoma Brainstem stroke</th>
<th>Facial palsy</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalkanis Eskandar et al</td>
<td>Neurosurg 2003 52:1251-61</td>
<td>237</td>
<td>N/S</td>
<td>N/S</td>
<td>.3%</td>
<td>.5%</td>
<td>1%</td>
<td>Higher vol hospital better result</td>
</tr>
<tr>
<td>Barker, Jenneta et al</td>
<td>J Neurosurg 1995</td>
<td>782</td>
<td>85%</td>
<td>3% “deaf”</td>
<td>.1%</td>
<td>.4%</td>
<td>1%</td>
<td>Second op less effective</td>
</tr>
<tr>
<td>Shah et al</td>
<td>Clin Neurol Neurosurg 2012</td>
<td>150</td>
<td>N/S</td>
<td>7% “Non serviceable”</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Miller et al</td>
<td>Br Journal of Neurosurgery 26: 438-44 2012</td>
<td>5685 (combined)</td>
<td>91%</td>
<td>3.2% (2.3% permeant)</td>
<td>.1%</td>
<td>10%</td>
<td>Meta analysis</td>
<td></td>
</tr>
<tr>
<td>Rhee et al.</td>
<td>Acta Neurochir 2006 148:839-43</td>
<td>410</td>
<td>N/S</td>
<td>N/S</td>
<td>N/S</td>
<td>N/S</td>
<td>5.4% (most transient)</td>
<td></td>
</tr>
<tr>
<td>Yuan et al</td>
<td>Chin Med Journal 2005:118, 833-6</td>
<td>1200</td>
<td>88%</td>
<td>2.6%</td>
<td>N/S</td>
<td>N/S</td>
<td>N/S</td>
<td></td>
</tr>
</tbody>
</table>

NS =not stated in reference

How Botulinum Toxin Works for Benign Essential Blepharospasm/Meige Syndrome and Perhaps Other Forms of Blepharospasm

Classic Mechanism:

Botulinum toxin, since its introduction in 1982, by Dr. Alan Scott (51), has become the mainstay of the therapy for essential blepharospasm, facial dystonia, hemifacial spasm, and aberrant facial nerve regeneration, and many other forms of movement diseases, inclusive of cervical dystonia and oral
mandibular dystonia. During the 1980's the basic teaching of how botulinum toxin mechanism of action involved binding at the neuromuscular presynaptic membrane followed by cleavage and internalization of the L chain resulting in blocked vesicular release of acetylcholine causing partial flaccid paralysis along the injection sites with associate neurogenic muscular atrophy (52-54). Further, the botulinum toxin spread was controllable by unit doses quantized by using sharply defined LD-50's in the 20 to 30 grams Swiss-Webster mouse. This effect is still a major mechanism and is governed by a diffusion gradient away from the injection site that is a dose dependent function (52-54) (Figure 9). Injection sites and dosage are critical to both efficacy and reduction of regional side effects such as ptosis, diplopia. While excessive weakness and undesirable spread to non targeted muscles can be a problem for blepharospasm treatment, the problem is even greater for higher dose paradigms such as used for spasticity, neck dystonia (52). In high dose administrations, spread to critical muscles involving swallowing and mechanical respiration have been reported. Dosing should be used cautiously with neuromuscular diseases such as myasthenia gravis (55) and other neuromuscular conditions.

On an average, the author believes the use of 40-60 units total dose for essential blepharospasm and Meige syndrome about 15-20 units for hemifacial spasm (using BOTOX)-TM. With hemifacial spasm syndromes secondary aberrant facial nerve regeneration, 15 units or less injected in multiple locators should be used with the surgeon cognizant of induced lagophthalmos and induced exposure from excessive weakness.

**Figure 9a:**
Botox induced neurogenic atrophy as compared to controls

**Figure 9b:**
Demonstration of a dose dependent diffusion gradient

### Injection Strategies

During the first decade of use botulinum injection publications covered the distribution of neuromuscular junctions within muscles and various formats of injection. As documented by the classic work of Wolf and Coers in the 1950's (56), sphincter muscles such as the orbicularis oculi have been shown to have a wide and homogenous distribution of neuromuscular junctions along the entire body of the muscle. This diffuse innervation arrangement has been the reason extensive surgical reconstructions of the eyelids often has little effect on lid closure. The extensive innervation from multiple directions offer resiliency to motor nerve damage from large lid resections and reconstructions (57). Further, given this wide distribution multiple injection sites along the muscle are often advocated. Further, multiple small injection dose controls diffusion.

 Attempts have been made to try to enhance the effect on the protagonists of lid closure (52). Using multiple well placed injection sites at lowest effect dose mitigates ptosis from spread into the levator
palpebrae superioris muscle. Given the lid retractor muscular is remote from the orbicularis muscle, the anatomic regional orbicularis denervation is possible without usually causing ptosis. Figure 10 demonstrate the typical injections sites. These sites allow for 1. Spread of toxin across orbicularis 2. Maximizing distance to upper lid retractor muscle and 3. Avoidance of spread to inferior oblique, lateral rectus and superior rectus which can result in diplopia. With these injections paradigms efficacy has been categorically documented at about 80% with complications rate of about 2% ptosis and diplopia (1%) using equivalent doses of type A botulinum toxin (BOTOX-TM, XEOMIN-TM). The author believes the chemical formulations of botulinum toxin impacts the diffusion characteristics with DYSPORT being more likely to diffuse at equivalent potency LD 50 dosing paradigms (47).

**Figure 10a:**

![Usual Injection Points](image)

**Figure 10b:**
Recently, lower dose injections have been described the mid-lid way from the usual sites at lower doses with demonstrated efficacy (58). Mid-lid injections because of a shorter distance to the diffusion into levator and superior rectus muscles and runs an increased risk of ptosis/diplopia, the most common complications of botulinum toxin use for blepharospasm. However, in a recent review, with lower doses in the mid lid (2.5 U), similar ptosis complication rates were noted, however diplopia rates were increased over the conventional 1%. There is a mechanical advantage in giving the mid lid injections based on muscular weakness at the furthest distance from the lid closure fulcrum. If Whitnall's ligament is considered a fulcrum to lid closure based on a sagittal orientation (Fig. 10B), than the mid lid would be furthest distance from the physical fulcrum and the weakness produced would have greater torque effects on lid closure. The author believes mid lid injections best reserved for difficult management cases, and because of higher diplopia rates. The segmented effects on muscle atrophy may allow maximal effect on eyelid closure with minimal dosing.

Botulinum Formulations (BOTOX-TM, XEOMEN -TM, MYOBLOC-TM, DYSPORT-TM)

All botulinum toxin preparations produce regional titratable denervation which disseminates with higher doses. Type A immunotypes toxins produce more denervation at lower LD 50 (BOTOX, DYSPORT, XEOMEN) than type B (MYOBLOC). Immunotype A is preferred because of high potency, excellent stability, low diffusion and favorable denervation properties. Various type A toxins have different formulations and different concentrations of bulking agents. BOTOX contains 500 mcg/100 U whereas DYSPORT contains 125 mcg/500 U. There is a clear relationship in vitro between botulinum potency upon dilution and albumin concentration in diluents (59). Although many of the type A products state on packet inserts that fermentation derivatives of the Hall strain, the strain emanated in laboratory works almost 100 years ago with multiple poorly documented divisions and maintenance. Dr. Hall may have distributed
several strains (Andy Pickett). Zinc is a well-known cofactor in the enzymatic activity of the light chain endopeptidase activity acting on cytoplasmic SNAP-25 target which facilitates vesicular acetylcholine secretion in myoneural junctions. Yet, Zn concentration has never been characterized within the albumins or the reconstituted injection solutions despite albumin being the major binding transport protein for Zn. Only several differentiating points are covered, however strain derivation today is of interest with some preclinical studies suggesting the botulinum A2 strain may have higher intrinsic neuromuscular denervating properties (60). Further studies of different preparations are in progress (61). The most ideal botulinum toxin preparation should have the following characteristics:

1. greatest regional denervation potency per LD 50 unit
2. the lowest LD 50 dosing paradigm per indication
3. lowest diffusion
4. suitable immunologic characteristics so the protein based drug can be used repeatedly over many years
5. the longest duration of action
6. be least painful on injection (eg, physiologic pH, isotonic)

Although it is beyond the scope of this chapter to discuss compositional pharmacology further, it most certainly will be a subject of further studies and journal article in the future.

Non Neuro Muscular Effects of Botulinum Toxin:

Although blockage neuromuscular transmission is the major effect, it clearly does not explain the whole picture for the treatment of blepharospasm. The weakness or closure of the lid can increase tear drying, sometimes producing a small degree of keratitis. Keratitis with surface drying should worsen blepharospasm and make the eye more light sensitive. The opposite actually happens which is counterintuitive (3), indicating deficient understanding on mechanisms. The improvement in blepharospasm is often out of proportion to the degree of weakness both in the facial muscles and other regions of the body where the botulinum toxin is used for dystonia therapy. An even more interesting observation is the relief of photophobia after botulinum toxin injections is also not easily explained in blepharospasm patients (3). These observations cannot be explained by neuromuscular weakening. Other mechanisms are operative. In the early 1990's, the discovery of the effect of the toxin on pain (3, 62-65), tension headache, migraine headache, and other forms of head and neck pain, indicated there are other biologic mechanisms. Botulinum toxin has clearly been documented over decades to block the autonomic nervous system function. Autonomic nerve system interacts with blood vessels capable of generating neuropeptides, substance CGRP and substance P. Histamine, possibly serotonin, nitric oxide, and other locally active substances which are affected. These effects are clearly noted with such conditions as involving vasospasm, such as Raynaud's disease associated with scleroderma, sweating, cholinergic urticaria, and forms of peripheral pain sensitization. The effect on migraine is also thought to be at least in part due to effect on vessels. The vascular structure is rich in potentiators of local sensitizing tissue substances sensitive to autonomic neurogenic interactions, such as mentioned both at the level of the endothelium and adventitial accumulations of mast cells and associated with blood vessels. Figure 11 demonstrates effects on histamine release in patients with cholinergic urticaria, atopic eczema, and lid inflammation in blepharitis (66). Others have made similar observations (67, 68).
Beyond effect on local vessels and sensory nerves, there is evidence that the toxin influences relays in the central nervous system. Desensitizing sensory nerves via autacoid interactions may influence afferent sensory input, and cause functional CNS changes. However, even this mechanism is probably not complete with respect to CNS affects. In recent research, benign essential blepharospasm and Meige disease has been associated with excesses in CNS glutamate neurotransmitters in animal studies (69). Botulinum toxin has clearly been known to block glutamate within the central nervous system cells when directly injected (70), as well as neuronal cell cultures (71). A consideration in not only having the effect on sensory input to the brain stem but actually diffusing it to the brain stem should be seriously considered. In Figure 12, my research team analyzed the CNS effects of a large dose of botulinum toxin around the face of a 30 g mouse in the corresponding anatomic areas that usually are given to patients with blepharospasm/cosmetic application. In Frame A one can see at large pre lethal doses, trophic effects on the brain with increasing atrophy in the region of the neostriatum of the brain covering many of the relays involved in blink. Further, the effect on glutamate receptor expression is seen on Figure 12 B, and GABA receptors on Figure C. Such depression of neuroreceptors possibly could be secondary to sensory relay. However, when the botulinum is fused to an alexia protein tracing system and diluted and injected, the dye was directly found in the brainstem at 6 hours (figure 12 D) (74). Others have shown the possibility of penetration of botulinum toxin into the central nervous system.

The mechanism by which botulinum toxin works for chronic headache is thought to involve a decrease in sensitization of thalamic pain neurons, which would be consistent with the central effect of the toxin on
blepharospasm and related movement disease. At the time this chapter was written, botulinum toxin has been investigated for application for mood and affect disorders such as human depression and anxiety. The CNS effect on neurotransmitters would be consistent with the notion that botulinum toxin may have psychotropic effects and may be benefitting blepharospasm patients not only by movement modulation, sensory modulation but by direct psychosocial effects acting as an anti-depressant, anti-anxiety agent.

Fig 12

a. Forehead Injection of 8 LD 50 U, Trans-cutaneous

b. 

c. GABAergic Receptor Activity Botex Injection

- Nootonin: PBS-treated Mouse
- Nootonin: Botox-treated Mouse
- Nootonin: PBS-treated Mouse
- Nootonin: Botox-treated Mouse

- Alexa Dye Studies / Botex
- PBS-injected mouse
- PBS-injected mouse
- Nootonin-injected mouse
- Botox-injected mouse
Human Longevity Assessments after Repeated Botulinum Injections in Peri-Ocular Area (Figure 13)

In concluding, a comment on the effect of repeated botulinum toxin injections over many years with respect to safety. As blepharospasm has been the longest indication for botulinum toxin use on a regular basis, some unique analysis can be done from patients who have been treated since 1982 who have treated the medication for decades. Botulinum toxin has had notorious history prior to 1982, and many patients were concerned about whether there can be long term side effects adversely effecting heath. Side effects have been local and known to be limited to short intervals (eg. ptosis, diplopia). Systemic effects after exposure have related to critical diffusion with attendant respiratory paralysis. Effects after decades of reinjections have suggested no serious side effects, however, longevity has never been addressed to the best of the author’s knowledge. Others have noted safety after long term exposure (73,74).

The author of this chapter has retrospectively looked at 54 patients from his 33 years of practice who have received at least 10 years of botulinum toxin injections repeatedly. In this group, all injections were started after the age of 60 years old. Most patients were diagnosed with either hemifacial spasm, Meige syndrome or benign essential blepharospasm

Figure 13 is an analysis of duration of life after injections have been started compared with longevity analyses produced by the most recent US census (2007). Data was analyzed both categorically and linearly based on a virtual person’s longevity presenting at the time of first injection (based on the census).

The long term recipient of the injections actually exceeded the Social Security death rate curve prediction. Stated differently, the analysis suggests that this patient population appears to be living actually longer than the average American during the time period the analysis was conducted.

There are many variables in interpreting this information, but this is reassuring that the repeated use of the toxin does not seem to have a long-term deleterious effects on survival. In fact, there may be some benefits. Theoretically, if botulinum toxin is effective in treating human depression, or sleep disorders, or chronic axillary states, as is being investigated currently, this could be a heavily modulating effect on duration of life. Certainly, sleep patterns and circadian rhythm synchronization has been linked to effect on mood and affect and longevity. The author has noted that the patients not only benefit from improved vision but have distinct improvement in sleep, depression and anxiety, conditions that collectively aggravate and may in fact be center in many cases of benign essential blepharospasm (74). Disorders of mood and affect have been linked to longevity. Botulinum toxin appears to be active in brainstem structures modulating sleep, mood and affect. Further studies are currently on to analyze scientifically with large numbers to analyze the efficacy of the toxin in many of these indications.
Fig 13a Longevity Analysis for long term Botulinum Injections

Figure 13 B  Statistics

Categorical

<table>
<thead>
<tr>
<th>Age at first injection</th>
<th>Beat the 2007 Census Life Expectancy</th>
<th>Died Prior to Average Life expectancy</th>
<th>Chi Sq P value Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>39</td>
<td>15</td>
<td>P&lt;0.02</td>
</tr>
<tr>
<td>&gt;65</td>
<td>27</td>
<td>9</td>
<td>P&lt;0.03</td>
</tr>
<tr>
<td>&gt;70</td>
<td>26</td>
<td>6</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>&gt;75</td>
<td>16</td>
<td>4</td>
<td>P&lt;0.04</td>
</tr>
</tbody>
</table>

Linear t test vs predicted longevity at first injection (virtual twin life expectancy based on 2007 census):

<table>
<thead>
<tr>
<th>Living patients</th>
<th>Living Patients Student t test P&lt;0.03 significant one tailed, P&lt;0.05 two tailed, P=0.01 matched statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deceased Patients</td>
<td>Student t test P&lt;0.03 significant one tailed, P&lt;0.05 two tailed, P=0.01 matched statistic</td>
</tr>
</tbody>
</table>


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