

## Nevada State Board of Dental Examiners



6010 S. Rainbow Blvd., Bldg. A, Ste.1 • Las Vegas, NV 89118 • (702) 486-7044 • (800) DDS-EXAM • Fax (702) 486-7046

THIS ADVISORY OPINION IS NO LONGER IN EFFECT.  
SENATE BILL 101 ENACTED IN THE 2017 LEGISLATIVE SESSION  
AMENDED CHAPTER 454 PERTAINING TO THE ADMINISTRATION OF  
BOTULINIUM TOXINS AND DERMAL FILLERS BY DENTISTS

**BEFORE THE NEVADA STATE BOARD OF DENTAL EXAMINERS**

Petition by Mark J Escoto, DDS for an Advisory )  
Opinion as to whether dentists may inject/administer ) AO-06-0518(C)  
Botulinum Toxin (BOTOX) to their patients. )  
\_\_\_\_\_)

At a public meeting of the Nevada State Board of Dental Examiners, held on September 21, 2006 at its offices located in Las Vegas with video-link to Reno.

Dr Tony Guillen-----PRESENT  
Dr. Rick Thiriot-----EXCUSED  
Dr. William O’Gara-----PRESENT  
Dr. Donna Hellwinkel-----PRESENT  
Dr. Michael Lloyd-----PRESENT  
Dr. William Pappas-----PRESENT  
Dr. Joel T. Glover-----PRESENT  
Mrs. Rosanne “Missy” Matthews-----PRESENT  
Mrs. Sharon Peterson-----EXCUSED  
Mr. James “Tuko” McKernan-----PRESENT  
Mrs. Bonnie Bryan-----PRESENT

**ADVISORY OPINION**

The Nevada State Board of Dental Examiners (“the Board”) makes the following findings of fact and conclusion of law:

**I. Procedural History**

1. On May 18, 2006, Mark J. Escoto, DDS filed a petition requesting that the Board issue an Advisory Opinion regarding whether dentists could administer/inject botulinum toxin (botox) to their patients for cosmetic purposes as well as dental treatment for bruxism. This petition has been designated by the Board as AO-06-0518(C).
2. Dr. Escoto stated that he was utilizing botox for strictly TMJ treatment in conjunction and neuromuscular therapy for his patients. He stated his treatments were not irreversible as the botox treatment wore off in three months. He stressed that he was not using botox for wrinkle clearing. Comments were made by Board member, Dr. William Pappas, that current literature identified dental uses of botox for trigeminal neuralgia and severe bruxism.
3. The petition is within the purview of the Board’s jurisdiction pursuant to NRS Chapter 631 and NAC Chapter 631; specifically, NRS 631.215 regarding the scope of practice for dentistry and NAC 631.279 as well as NRS 233B.120 issuing advisory opinions.
4. The Board issued a public notice of this petition for an advisory opinion in accordance with state law. Comments from Dr. Escoto were provided as well as Thomas Myatt, DDS, a licensed Oral & Maxillofacial Surgeon in Nevada on May 18, 2006.
5. The Board noticed a hearing on August 25, 2006 of the Legislative and Dental Practice Committee to review and deliberate regarding the use of botox by dentists. The hearing included comments from members of the Committee and staff regarding the FDA approved uses

of botox, the uses of botox for dental treatment, and the general use of botox for both circumstances by a general dentist as part of the scope of practice. Discussion of the cosmetic uses of dermal fillers by dentists also took place. The Committee issued a recommendation to the full board that dentists using botox or other like substances including dermal fillers for cosmetic purposes was not within the scope of practice for a dentist.

## **II. Comments of the Participants**

### **A. Staff's Comments**

5. Staff provided the newspaper article and described calls received regarding the known use of botox in the dental community for lip augmentations and temporary relief of facial wrinkles and frown lines. An article from the Journal of American Dental Association describing use of botox was confined to severe bruxism and was distributed to members, public attendees, and meeting speakers at the meeting held May 18, 2006.

### **B. Mark J Escoto, DDS' Comments**

6. On May 18, 2006, Dr. Escoto filed comments at the meeting; however correspondence was also filed with the Board prior to May 18, 2006. During live comments, Dr. Escoto indicated he was treating patients with extreme bruxism and neuromuscular dental disorders--TMJ. He indicated that patients were screened to diagnose extreme cases and that botox was not administered to just any patient and not for wrinkle relief or casual bruxism. According to his comments he has taken many continuing education courses regarding use of botox, head and neck anatomy, and dental education. He provided his criteria for diagnosing severe bruxism. He indicated he has not injected any patient with botox that did not have severe bruxism. Dr. Escoto was asking to continue the use of botox to treat patients in conjunction with his splint therapy. Dr. Escoto was asked about his submitted comments wherein he described his other uses of botox not related to dental procedures. When asked about whether he was performing lip augmentations, he responded that he was. He provided CE certificates for courses regarding botox use for lip augmentation. The issue was referred to the Legislative and Dental Practice Committee of the Board for review of submitted information hearing.

7. Dr. Thomas Myatt, a Nevada licensed Oral & Maxillofacial Surgeon, discussed the uses of botox for extreme cases of clenching, bruxism, and myofascial pain and dysfunction. Dr. Myatt is aware of botox use for Temporo-Mandibular Joint (TMJ) Disorder although he has not used it for that. Botox is an accepted 'adjunct' treatment for neuromuscular dysfunction.

8. Dr. Escoto did not attend the meeting on August 25, 2006 although noticed of the meeting.

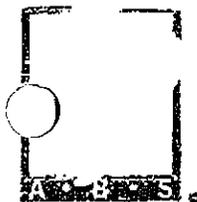
## **III. Board Decision**

9. Pursuant to NAC 631.279 through authority of NRS 631.190, and NRS 233B.120, the board having the discretion to issue an advisory opinion regarding the applicability and/or interpretation of any statutory or regulatory provision of Chapter 631.

10. The Board finds that administration of botox for cosmetic purposes is not within the scope of practice of a dentist. Further, the board finds that administration of dermal fillers and like substances for cosmetic purposes is not within the scope of practice of a dentist.

THEREFORE, based upon the findings and conclusions, it is hereby ORDERED on September 21, 2006 that:

1. The use of botox or other like substances including dermal fillers by dentists for cosmetic purposes is deemed a violation of NRS 631.3475 and NRS 631.215.



*A Beautiful Smile*  
Mark J. Escoto, D.D.S.

2471 Professional Court  
Las Vegas, NV 89128  
(702) 256-5853  
Fax: (702) 243-7581

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May 15, 2006

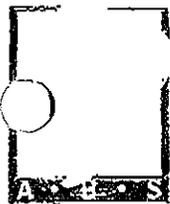
Dear Nevada Dental Board Members,

Attached are my credentials and a log of hours regarding my continuing education in the areas of Temporomandibular Disorder, orthodontics, botox and lip enhancement. My application of botox therapy is strictly medicinal. I treat my TMJ patients through splint therapy in conjunction with botox to help reduce their clenching cycles and muscle pain.

A dentist is the best choice for lip augmentation for the following reasons:

- Ideal oral esthetics are lost when an untrained professional attempts cosmetic dentistry and smile esthetics
- Dentist have better training and knowledge of lower facial, oral, and dental anatomy and proportions
- They are trained in the essential anesthesia techniques used for pain free lip augmentation
- They are comfortable with oral procedures involving filler materials
- The shape and volume of the lips are determined primarily by the support of the teeth, alveolar bone, vertical dimension and gums. These are the domain of the dentist
- A malocclusion like a deep overbite or an over-closed vertical dimension can decrease the size of both lips. Lip augmentation without dental correction is not satisfactory in this situation. This can only be diagnosed and treated by a dentist

I have completed over 600 hours of continuing education and have a residency in TMJ. I hold a Fellowship with the International College of Cranio-Mandibular Orthopedics and will obtain Mastership in 2007. I am also a member and Diplomat of the American Academy of Pain Management. I am well experienced and have extensive knowledge of the anatomy for the head and neck. I believe dentists are the best qualified to evaluate and treat the oral facial structures of a patient which include the lips and the muscles of the temporomandibular/craniomandibular complex.



*A Beautiful Smile*  
Mark J. Escoto, D.D.S.

2471 Professional Court  
Las Vegas, NV 89128  
(702) 256-5353  
Fax: (702) 243-7581

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My practice has been an outstanding member of the dental community for fifteen years. I stand behind my treatment and trust in my mentors who have given me the knowledge that I have been able to apply and successfully help my patients.

Sincerely,

Dr. Mark J. Escoto

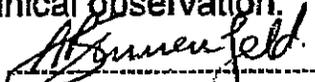
**Certificate of Achievement**

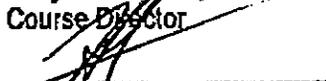
**Mark Escoto, DDS**

has attended a comprehensive course on  
**Botox® for Dentistry**

Given this 10<sup>th</sup> day of July, 2004  
Beverly Hills, California

This course included a comprehensive didactic session on dental treatments using Botulinum Toxin and a live clinical observation.

  
-----  
Andy Blumenfeld, M.D.  
Course Director

  
-----  
Howard Katz, D.D.S.  
Course Director

**CERTIFICATE OF ATTENDANCE**

**Dr Mark Escoto**

**has attended a comprehensive course in  
LIP AUGMENTATION FOR DENTISTRY  
WITH HYALURONIC ACID FILLERS**

**January 14<sup>th</sup> 2006, Beverly Hills, California**

**Course Director:**



**Howard Katz D.D.S.**

**CERTIFICATE OF ATTENDANCE**  
**Dr Mark Escoto**

**has attended a comprehensive course in the use of**  
**BOTOX® FOR DENTISTRY.**

**January 7<sup>th</sup>, 2006**  
**Beverly Hills ,California**

**Course Directors:**

  
**Howard Katz D.D.S.**

  
**Andrew Blumenfeld M.D.**

211 E. Chicago Avenue, Suite 900

Chicago, Illinois 60611-1999

(888) AGD-DENT ext 5300 Fax: (312) 440-0513

**Continuing Dental Education Transcript**

182262 Previous AGD/ADA # 163900246  
 Mark J. Escoto, DDS Member Since: 5/1/1989  
 2471 Professional Ct Status: Pre-Fellow  
 Ste 101 Passed Exam:  
 Las Vegas, NV 89128-0830 MAGD Accrual Date: 07/22/1997  
 PostGrad Work:

Current Maintenance Period: 06/01/2004 - 05/31/2007  
 Maintenance Credits Required: 75  
 Current Maintenance Credits: 148  
 Maintenance Credits Needed: 0  
 Current Grace Period:  
 Grace Period Credits Required:  
 Grace Period Credits:  
 Grace Period Credits Needed:

Date of Activity	Program ID#	Provider Organization Name	Subject / Discipline Code Description	Delivery Mode	Verify Code	Approved Hours	Maint. Hrs.
03/29/2005	210303	Straumann USA, LLC	690 Implants	Lecture		2.00	2.00
01/07/2006	218831	Meridian Center of Keller Laboratories,	180 Myofascial Pain Dysfunction/Occlusion	Lecture		7.00	7.00
01/23/2005	208518	Straight Wire Orthodontic Studies	370 Orthodontics	Participation		3.00	3.00
01/23/2005	208518	Straight Wire Orthodontic Studies	370 Orthodontics	Lecture		22.00	22.00
01/05/05	301313	EODO	370 Orthodontics	Participation		5.00	5.00
01/09/2005	208518	Straight Wire Orthodontic Studies	370 Orthodontics	Lecture		28.00	28.00
12/05/2004	208518	Straight Wire Orthodontic Studies	370 Orthodontics	Participation		3.00	3.00
12/05/2004	208518	Straight Wire Orthodontic Studies	370 Orthodontics	Lecture		22.00	22.00
10/23/2004	208518	Straight Wire Orthodontic Studies	373 Interceptive Orthodontics	Participation		2.00	2.00
10/23/2004	208518	Straight Wire Orthodontic Studies	370 Orthodontics	Lecture		12.25	12.25
10/16/2004	219258	NV Dental Association	180 Myofascial Pain Dysfunction/Occlusion	Participation		12.50	12.50
09/12/2004	301313	EODO	376 Functional Orthodontics	Participation		2.00	2.00
09/12/2004	208239	Discus Dental Impressions	376 Functional Orthodontics	Lecture		19.50	19.50
08/12/2004	218534	Academy of Laser Dentistry	135 Laser Therapy / Electrosurgery	Lecture		6.00	6.00
06/12/2004	218534	Academy of Laser Dentistry	135 Laser Therapy / Electrosurgery	Participation		2.00	2.00
05/01/2004	301313	EODO	138 Dental Photography	Participation		2.00	2.00
05/01/2004	218534	Academy of Laser Dentistry	138 Dental Photography	Lecture		18.00	18.00
02/08/2004	216102	Army-Fitzsimons Dentac	014 Biochemistry	Lecture		0.00 * P	4.00

**Exclusion Codes**

- Non-approved post-graduate program
- Program Provider not approved
- Provider - credit given elsewhere
- Discipline issue expired

Mark J. Escoto, DDS

182262

(ADA #) 163900246

Date Activity	Program Provider		Subject / Discipline		Delivery Mode	Verify Code	Approved Hours	Maint. Hrs.
	ID#	Organization Name	Code	Description				
06/22/2003	218833	Dr O' - Expert Resources, Inc	731	Radiology	Participation		4.00	4.00
06/22/2003	218833	Dr O' - Expert Resources, Inc	731	Radiology	Lecture		4.00	4.00
05/24/2003	218833	Dr O' - Expert Resources, Inc	376	Functional Orthodontics	Participation		4.00	4.00
05/24/2003	218833	Dr O' - Expert Resources, Inc	376	Functional Orthodontics	Lecture		4.00	4.00
04/26/2003	218833	Dr O' - Expert Resources, Inc	185	Appliance Therapy	Participation		4.00	4.00
04/26/2003	218833	Dr O' - Expert Resources, Inc	185	Appliance Therapy	Lecture		4.00	4.00
02/23/2002	208239	Discus Dental Impressions	780	Esthetics	Lecture		4.50	4.50
02/23/2002	208239	Discus Dental Impressions	550	Practice Management	Lecture		3.50	3.50
02/18/2002	218833	Dr O' - Expert Resources, Inc	376	Functional Orthodontics	Participation		4.00	4.00
02/18/2002	218833	Dr O' - Expert Resources, Inc	376	Functional Orthodontics	Lecture		4.00	4.00
11/19/2001	218833	Dr O' - Expert Resources, Inc	183	Occlusal Management	Lecture		2.00	2.00
11/19/2001	218833	Dr O' - Expert Resources, Inc	183	Occlusal Management	Participation		2.00	2.00
11/19/2001	218833	Dr O' - Expert Resources, Inc	370	Orthodontics	Participation		2.00	2.00
11/19/2001	218833	Dr O' - Expert Resources, Inc	370	Orthodontics	Lecture		2.00	2.00
01/19/2001	218642	BIOLASE TECHNOLOGY, INC	135	Laser Therapy / Electrosurgery	Lecture		6.00	6.00
02/05/2000	208518	Straight Wire Orthodontic Studies	182	TM Disorders	Lecture		6.00	6.00
12/15/1999	218833	Dr O' - Expert Resources, Inc	182	TM Disorders	Participation		8.00	8.00
12/15/1999	218833	Dr O' - Expert Resources, Inc	149	Multi-Disciplinary Topics	Lecture		8.00	8.00
10/09/1999	218833	Dr O' - Expert Resources, Inc	182	TM Disorders	Lecture		16.00	16.00
06/26/1999	218833	Dr O' - Expert Resources, Inc	182	TM Disorders	Lecture		8.00	8.00
06/26/1999	218833	Dr O' - Expert Resources, Inc	555	Dental Jurisprudence	Lecture		8.00	8.00
05/08/1999	218833	Dr O' - Expert Resources, Inc	555	Dental Jurisprudence	Lecture		16.00	16.00
05/01/1999	208518	Straight Wire Orthodontic Studies	370	Orthodontics	Participation		84.00	84.00
02/13/1999	214683	American Association of Orthodontics	373	Interceptive Orthodontics	Lecture		5.00	5.00
02/13/1999	214683	American Association of Orthodontics	182	TM Disorders	Lecture		5.00	5.00
02/13/1999	214683	American Association of Orthodontics	370	Orthodontics	Lecture		5.00	5.00
01/30/1998	214683	American Association of Orthodontics	370	Orthodontics	Lecture		5.00	5.00
01/30/1999	214683	American Association of Orthodontics	182	TM Disorders	Lecture		5.00	5.00
01/30/1999	214683	American Association of Orthodontics	373	Interceptive Orthodontics	Lecture		5.00	5.00
12/31/1998	218833	Dr O' - Expert Resources, Inc	370	Orthodontics	Lecture		8.00	8.00
12/19/1998	211859	DR ORDEN, ADAM	182	TM Disorders	Participation		0.00 * P	6.00
12/19/1998	218833	Dr O' - Expert Resources, Inc	182	TM Disorders	Lecture		16.00	16.00

## Exclusion Codes

- 3 Non-approved post-graduate program
- 4 Program Provider not approved
- 5 ( ) holder - credit given elsewhere
- 6 DART issue expired

Mark J. Escoto, DDS

182262

(ADA #) 163900246

Date of Activity	Program Provider ID#	Organization Name	Subject / Discipline Code Description	Delivery Mode	Verify Code	Approved Hours	Maint. Hrs.
12/18/1998	211859	DR ORDEN, ADAM	012 Anatomy	Participation		0.00 * P	6.00
12/18/1998	211859	DR ORDEN, ADAM	149 Multi-Disciplinary Topics	Participation		0.00 * P	6.00
11/16/1998	218833	Dr O' - Expert Resources, Inc	182 TM Disorders	Participation		16.00	16.00
11/10/1998	218833	Dr O' - Expert Resources, Inc	731 Radiology	Participation		8.00	8.00
10/17/1998	214683	American Association of Orthodontics	370 Orthodontics	Lecture		5.00	5.00
10/17/1998	214683	American Association of Orthodontics	182 TM Disorders	Lecture		5.00	5.00
10/17/1998	214683	American Association of Orthodontics	373 Interceptive Orthodontics	Lecture		5.00	5.00
10/11/1998	218833	Dr O' - Expert Resources, Inc	376 Functional Orthodontics	Lecture		12.00	12.00
10/11/1998	218833	Dr O' - Expert Resources, Inc	182 TM Disorders	Lecture		12.00	12.00
08/29/1998	214683	American Association of Orthodontics	182 TM Disorders	Lecture		5.00	5.00
08/29/1998	214683	American Association of Orthodontics	373 Interceptive Orthodontics	Lecture		5.00	5.00
08/29/1998	214683	American Association of Orthodontics	370 Orthodontics	Lecture		5.00	5.00
08/23/1998	208518	Straight Wire Orthodontic Studies	730 Oral Medicine, Oral Diagnosis	Participation		14.00	14.00
08/27/1998	218833	Dr O' - Expert Resources, Inc	180 Myofascial Pain Dysfunction/Occlusion	Lecture		8.00	8.00
06/27/1998	218833	Dr O' - Expert Resources, Inc	550 Practice Management	Lecture		8.00	8.00
06/07/1998	210235	Myotronics-Noromed, Inc	690 Implants	Lecture		14.00	14.00
06/07/1998	210235	Myotronics-Noromed, Inc	670 Prosthodontics-Removable	Lecture		14.00	14.00
11/05/1997	217153	Pride Institute	149 Multi-Disciplinary Topics	Lecture		7.00	7.00
10/19/1997	210235	Myotronics-Noromed, Inc	730 Oral Medicine, Oral Diagnosis	Lecture		18.00	18.00
07/24/1997	217153	Pride Institute	550 Practice Management	Lecture		14.00	14.00
07/22/1997	217153	Pride Institute	149 Multi-Disciplinary Topics	Lecture		21.00	21.00

**Es counting toward MAGD**

06/22/1997	210235	Myotronics-Noromed, Inc	180 Myofascial Pain Dysfunction/Occlusion	Participation		14.00	14.00
04/24/1997	217153	Pride Institute	550 Practice Management	Lecture		14.00	14.00
04/22/1997	210235	Myotronics-Noromed, Inc	730 Oral Medicine, Oral Diagnosis	Lecture		14.00	14.00
03/28/1997	209717	CNA Healthpro	555 Dental Jurisprudence	Lecture		4.00	4.00
03/22/1997	210235	Myotronics-Noromed, Inc	182 TM Disorders	Lecture		14.00	14.00
03/02/1997	210235	Myotronics-Noromed, Inc	180 Myofascial Pain Dysfunction/Occlusion	Participation		14.00	14.00
02/28/1997	210235	Myotronics-Noromed, Inc	180 Myofascial Pain Dysfunction/Occlusion	Lecture		7.00	7.00

**Exclusion Codes**

- G Non-approved post-graduate program
- P Program Provider not approved
- V  holder - credit given elsewhere
- X  issue expired

Mark J. Escoto, DDS

182262

(ADA #) 163900246

<u>Date of Activity</u>	<u>Program ID#</u>	<u>Provider Organization Name</u>	<u>Subject / Discipline Code</u>	<u>Description</u>	<u>Delivery Mode</u>	<u>Verify Code</u>	<u>Approved Hours</u>	<u>Maint. Hrs.</u>
02/26/1997	217153	Pride Institute	550	Practice Management	Lecture		14.00	14.00
12/16/1996	217153	Pride Institute	550	Practice Management	Lecture		14.00	14.00
08/16/1996	217153	Pride Institute	130	Electives	Lecture		11.00	11.00
05/30/1996	210804	STERI-OSS, INC	692	Reconstructive Phase Therapy	Lecture		2.00	2.00
10/10/1995	214267	American Dental Association	557	Patient Education/Motivation	Lecture		5.00	5.00
05/15/1994	208673	Zimmer Dental	690	Implants	Participation		20.00	20.00
07/30/1993	216555	Midwest Implant Institute	690	Implants	Lecture		16.00	16.00
05/13/1993	214204	Loma Linda University Denal School	610	Prosthodontics - Fixed	Participation		5.00	5.00
04/15/1993	214204	Loma Linda University Denal School	610	Prosthodontics - Fixed	Participation		5.00	5.00
03/11/1993	214204	Loma Linda University Denal School	610	Prosthodontics - Fixed	Participation		5.00	5.00
02/11/1993	214204	Loma Linda University Denal School	610	Prosthodontics - Fixed	Participation		5.00	5.00
01/14/1993	214204	Loma Linda University Denal School	610	Prosthodontics - Fixed	Participation		5.00	5.00
12/09/1992	214204	Loma Linda University Denal School	610	Prosthodontics - Fixed	Participation		5.00	5.00
11/12/1992	214204	Loma Linda University Denal School	610	Prosthodontics - Fixed	Participation		5.00	5.00
10/21/1992	214204	Loma Linda University Denal School	610	Prosthodontics - Fixed	Participation		5.00	5.00
05/04/1992	209877	SCRIPPS IMPL DENT ED/RES CTR	492	Soft Tissue Surgery	Lecture		84.00	84.00
02/16/1992	219290	AGD, CA	610	Prosthodontics - Fixed	Lecture		8.00	8.00
02/16/1992	219290	AGD, CA	550	Practice Management	Lecture		2.00	2.00
02/16/1992	219290	AGD, CA	490	Periodontics	Lecture		10.00	10.00
02/16/1992	219290	AGD, CA	310	Oral and Maxillofacial Surgery	Lecture		41.00	41.00
02/16/1992	219290	AGD, CA	180	Myofascial Pain Dysfunction/Occlusion	Lecture		6.00	6.00
02/16/1992	219290	AGD, CA	130	Electives	Lecture		6.00	6.00
02/16/1992	219290	AGD, CA	070	Endodontics	Lecture		2.00	2.00
02/16/1992	219290	AGD, CA	010	Basic Science	Lecture		40.00	40.00
02/16/1992	219290	AGD, CA	730	Oral Medicine, Oral Diagnosis	Lecture		36.00	36.00
02/16/1992	219290	AGD, CA	670	Prosthodontics-Removable	Lecture		9.00	9.00
10/28/1991	212136	San Diego County Dent Society	780	Esthetics	Lecture		6.00	6.00
06/29/1991	212136	San Diego County Dent Society	250	Operative Dentistry	Lecture		6.00	6.00
06/28/1991	212136	San Diego County Dent Society	690	Implants	Lecture		6.00	6.00
03/27/1991	212136	San Diego County Dent Society	690	Implants	Lecture		6.00	6.00

**Exclusion Codes**

- G Non-approved post-graduate program
- P Program Provider not approved
- V Observer - credit given elsewhere
- X DART issue expired

Mark J. Escoto, DDS

182262

(ADA #) 163900246

<u>Date of Activity</u>	<u>Program Provider ID#</u>	<u>Organization Name</u>	<u>Subject / Discipline Code</u>	<u>Description</u>	<u>Delivery Mode</u>	<u>Verify Code</u>	<u>Approved Hours</u>	<u>Maint. Hrs.</u>
03/06/1991	220322	WESTERN GNATH ST CL	690	Implants	Lecture		0.00 *P	3.00
02/13/1991	212136	San Diego County Dent Society	016	Pharmacotherapeutics	Lecture		6.00	6.00
02/12/1991	213686	PAUL REVERE ST CL-CA	253	Tooth-Colored Restorations	Lecture		2.00	2.00
02/03/1991	218203	INTERPORE INTL	690	Implants	Lecture		0.00 *P	14.00
05/16/1990	216208	Navy	250	Operative Dentistry	Lecture		2.00	2.00

**Exclusion Codes**

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- V  holder - credit given elsewhere
- X  issue expired

Mark J. Escoto, DDS

182262

(ADA #) 163900246

**FAGD SUMMARY OF TRANSCRIPT**

<u>DELIVERY</u>	<u>HOURS EARNED</u>	<u>MAX ALLOWED</u>	<u>USABLE HOURS</u>
EXAM STUDY GUIDE	0.00	25	0.00*
LECTURE	414.00	—	414.00*
MILITARY ROTATION	0.00	200	0.00*
PARTICIPATION	88.00	—	88.00*
POSTGRAD	0.00	250	0.00**
SELF INSTRUCTION	0.00	150	0.00**
TEACHING_PUBLICATION	0.00	150	0.00
	<u>502.00</u>		<u>502.00</u>

\* Total earned in these Delivery Modes: 502.00

Minimum combined hours required for these Delivery Modes: 350.00

<u>DISCIPLINE / DESCRIPTION</u>	<u>TOTAL HOURS</u>	<u>TOTAL ALLOWED</u>	<u>TOTAL USABLE</u>
010 BASIC SCIENCE	46.00	150.00	46.00
070 ENDOODONTICS	2.00	150.00	2.00
130 ELECTIVES	38.00	150.00	38.00
180 MYOFASCIAL PAIN DYSFUNCTION/OCLUSION	55.00	150.00	55.00
250 OPERATIVE DENTISTRY	10.00	150.00	10.00
310 ORAL AND MAXILLOFACIAL SURGERY	41.00	150.00	41.00
370 ORTHODONTICS	0.00	150.00	0.00
330 PEDIATRIC DENTISTRY	0.00	150.00	0.00
490 PERIODONTICS	94.00	150.00	94.00
550 PRACTICE MANAGEMENT	53.00	150.00	53.00
610 PROSTHODONTICS - FIXED	48.00	150.00	48.00
670 PROSTHODONTICS-REMOVABLE	9.00	150.00	9.00
690 IMPLANTS	50.00	150.00	50.00
730 ORAL MEDICINE, ORAL DIAGNOSIS	50.00	150.00	50.00
750 SPECIAL PATIENT CARE	0.00	150.00	0.00
770 SELF-IMPROVEMENT	0.00	10.00	0.00
780 ESTHETICS	6.00	150.00	6.00
820 POST GRAD EDUCATION	0.00	250.00	0.00
830 TEACHING FULL-TIME	0.00	150.00	0.00
855 FAGD EXAM STUDY GUIDE	0.00	25.00	0.00
860 FAGD EXAM PRE-1984	0.00	150.00	0.00
	<u>502.00</u>		<u>502.00</u>

**Exclusion Codes**

- 3 Non-approved post-graduate program
- 4 Program Provider not approved
- 5 Provider - credit given elsewhere
- 6 DART issue expired

Mark J. Escoto, DDS

182262

(ADA #) 163900246

**SUMMARY**

Hours Required for FAGD Award:	500.00
Hours Earned towards FAGD Award	502.00
Hours Remaining to achieve FAGD Award:	0.00

\*Congratulations! You may have met the 500-hour requirement for Fellowship. For information on Fellowship, to request a Fellowship application or to schedule the Fellowship Exam call 888-AGD-DENT or contact us online at [www.agd.org](http://www.agd.org).

**Exclusion Codes**

- Non-approved post-graduate program
- Program Provider not approved
- Folder - credit given elsewhere
- DART issue expired

Mark J. Escoto, DDS

182262

(ADA #) 163900246

**MAJSD SUMMARY OF TRANSCRIPT**

<u>Delivery</u>	<u>Earned Hours</u>	<u>Maximum Allowed</u>	<u>Total Usable Hours</u>
LECTURE	423.75	--	423.75
PARTICIPATION	181.50	--	181.50
EXAM STUDY GUIDE	0.00	25	0.00
MILITARY ROTATION	0.00	200	0.00
POSTGRAD	0.00	300	0.00
SELF INSTRUCTION	0.00	150	0.00
TEACHING_PUBLICATION	0.00	150	0.00
<b>Total All Delivery Modes</b>	<b>605.25</b>		<b>605.25</b>

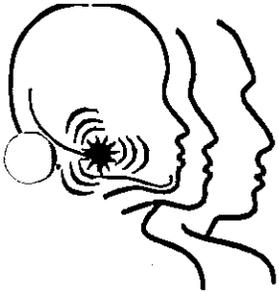
**DISCIPLINE SUMMARY**

<u>Discipline/Description</u>	<u>TOTAL PARTICIPATION</u>			<u>TOTAL OVERALL</u>		
	<u>Minimum Hours Required</u>	<u>Total Hours Earned</u>	<u>Hours To Go</u>	<u>Minimum Hours Required</u>	<u>Total Hours Earned</u>	<u>Hours To Go</u>
010 BASIC SCIENCE	12.00	0.00	12.00	12.00	0.00	12.00
070 ENDODONTICS	30.00	0.00	30.00	46.00	0.00	46.00
130 ELECTIVES	30.00	4.00	26.00	46.00	49.00	0.00
180 MYOFASCIAL PAIN DYSFUNCTION/OCCCLUSION	30.00	42.50	0.00	46.00	141.50	0.00
250 OPERATIVE DENTISTRY	30.00	0.00	30.00	46.00	0.00	46.00
310 ORAL AND MAXILLOFACIAL SURGERY	30.00	0.00	30.00	46.00	0.00	46.00
370 ORTHODONTICS	12.00	109.00	0.00	12.00	282.75	0.00
430 PEDIATRIC DENTISTRY	12.00	0.00	12.00	12.00	0.00	12.00
490 PERIODONTICS	30.00	0.00	30.00	46.00	0.00	46.00
550 PRACTICE MANAGEMENT	0.00	0.00	0.00	24.00	49.50	0.00
610 PROSTHODONTICS - FIXED	30.00	0.00	30.00	46.00	0.00	46.00
670 PROSTHODONTICS-REMOVABLE	30.00	0.00	30.00	46.00	14.00	32.00
690 IMPLANTS	30.00	0.00	30.00	46.00	16.00	30.00
730 ORAL MEDICINE, ORAL DIAGNOSIS	12.00	26.00	0.00	12.00	48.00	0.00
750 SPECIAL PATIENT CARE	12.00	0.00	12.00	12.00	0.00	12.00
780 ESTHETICS	30.00	0.00	30.00	46.00	4.50	41.50
		<b>181.50</b>	<b>302.00</b>		<b>605.30</b>	<b>389.50</b>
<b>Total Participation Hours Required:</b>	<b>400.00</b>			<b>Total Overall Hours Required</b>		<b>600.000</b>
<b>Minimum Participation Hours Still Required:</b>	<b>302.00</b>			<b>Minimum Overall Hours Still Required:</b>		<b>369.50</b>

Once you receive Academy Fellowship you may apply for Mastership. This chart shows how many of your credits will apply toward Mastership, based on the date you completed the hours for Fellowship. You will know you have completed the requirements for Mastership when this chart shows the following: 1) both 'To Go' columns are all zeros, and 2) both 'Total Hours Earned' columns reach the required numbers for Participation and Overall. Contact us at 888-AGD-DENT or www.agd.org for an application for Mastership.

**Exclusion Codes**

- Non-approved post-graduate program
- Program Provider not approved
- Holder - credit given elsewhere
- Issue expired



# Nevada TMJ Institute

Diagnosis and Treatment of Head, Neck,  
Facial Pain and Craniomandibular Disorders

## ***CURRICULUM***

## ***VITAE***



**MARK J. ESCOTO, D.D.S.**  
**F.I.C.C.M.O., Dpl. A.A.P.M., Dpl. C.F.O.**

**A Beautiful Smile**  
**2471 Professional Ct.**  
**Las Vegas, NV 89128**  
**702.256.5353**  
**702.243-7581 fax**

**Nevada TMJ Institute**  
**2471 Professional Ct.**  
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**702.259.4TMJ**  
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**Curriculum Vitae**

**BIOGRAPHICAL:**

Resident of Las Vegas, Nevada for more than thirty years.

Received all elementary and secondary education in Las Vegas, Nevada.

Graduated from Pre-Dental Program, University of Nevada at Reno with a Bachelor of Science in 1986.

Received a D.D.S. Degree from the University of the Pacific in 1989.

Maintained a private practice in Dentistry in San Diego, California from 1989 to 1991.

Has maintained a private practice in Dentistry in Las Vegas, Nevada from 1991 to present.

***Mark J. Escoto, D.D.S.***  
***F.I.C.C.M.O., Dpl. A.A.P.M., Dpl. C.F.O.***  
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**MEMBER:**

County Dental Society  
Nevada Dental Association  
American Dental Association  
Academy of General Dentistry  
International Association of Orthodontics  
American Association for Functional Orthodontics  
Functional Freedom Corporation  
American Academy of Pain Management  
The College of Forensic Orthopedics  
International College of Cranio-Mandibular Orthopedics  
North American Neuromuscular Study Club

**FELLOW:**

International College of Cranio-Mandibular Orthopedics  
(F.I.C.C.M.O.)

**DIPLOMATE:**

American Academy of Pain Management (Dpl. A.A.P.M.)  
Founder with Diplomate status in the College of Forensic  
Orthopedics (Dpl. C.F.O.)

**Mark J. Escoto, D.D.S.**  
**F.I.C.C.M.O., Dpl. A.A.P.M., Dpl. C.F.O.**  
Page 3

**CONTINUING EDUCATION:**

Advanced Surgical Techniques in Implantology

Branmark Prosthetic Course

Loma Linda Advanced Implant Study Club

Scripps Implant Dentistry Education and Research Center: Certification  
Received in 1992

Interpore IMZ Osteointegrated Implant System Seminar

Neuromuscular Orthopedic and Orthodontics

Midwest Implant Institute: Sinus Elevation

In the past five years, Dr. Escoto has concentrated his Continuing Education Studies in Clinical Orthodontics and TMD with a focus on:

Forensic Radiology (Analysis & Interpretation)

Tomographic Radiology

Temporomandibular Dysfunction (TMD)

Bio-instrumentation in TMD Diagnosis

Clinical Orthodontics : Diagnosis & Treatment

Orthodontic/TMD: Diagnosis & Treatment

Clinical Examination of Trauma Victims

TMD & Physical Therapy Treatment Specifically for Whiplash Victims

Neuromuscular Orthotic Treatment for Trauma Victims

**Mark J. Escoto, D.D.S.**  
**F.I.C.C.M.O., Dpl. A.A.P.M., Dpl. C.F.O.**  
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**PUBLICATIONS:**

Las Vegas Review Journal- May 14, 1999  
Article: Are You Suffering From Pain?

Las Vegas Review Journal – June 2, 1999  
Article: Why More Women Are Chronic Pain Victims

Las Vegas Review Journal – August 4, 1999  
Article: Splint/Orthotic Therapy for TMJ/TMD Patients

Picture This Journal – Winter/Spring 2000-1  
Article: Making the Best Smiles for Over a Decade

The Functional Orthodontist – Winter 2000  
Volume 17 \* No. 1 (Pages 32 to 34)  
Article: Removal of second molars to alleviate crowding and to  
Facilitate orthodontic treatment

**PROFESSIONAL LECTURES:**

14<sup>th</sup> Annual BioResearch Workshop Conference  
Presentation: Waterlase use in Dentistry

Las Vegas, Nevada Women's Fair, February 2003  
Presentation: Why More Women Are Chronic Pain Victims

## **A More Predictable Approach To Temporomandibular Dysfunction (TMD)**

**Howard Katz BDS**

Temporomandibular disorders often impair the quality of life of affected individuals. TMD's cause patient suffering and may "devastate its victim" 1 In advanced stages, the condition might be accompanied by tooth sensitivity, abrasion, fractures, mobility, or loss, 2 dental caries; alveolar bone loss; headaches; earaches and hearing loss 3,4 adverse, cumulative, irreversible effects on dental implants .5 6 and aesthetic restorations; diminished facial height which may in turn change one's appearance and cause mandibular over closure 7 ; hypertrophy of the masseter muscle, which in turn can adversely affect one's appearance. 8

As we enter the Twenty-first Century, dental experts are still searching for a non-aggressive preventative treatment for TMD and bruxism. TMD is not an acceptable diagnosis. It refers to a group of diseases with overlapping and similar signs and symptomatology. It is a generic disease like back problem or digestive disorder. It is not specific enough and limits one to treatment that is palliative and non definitive, such as analgesics, relaxation therapy and hot and cold packs. Virtually any other treatment relates to a more specific diagnosis.

The following is a list of etiologies of TMD's involving pain: trauma, capsulitis, neuralgia, neuritis, myalgia, myositis, myofascial pain syndrome, tension headache, cervicalgia, osteoarthritis, rheumatoid arthritis, hysterical conversion, hypochondriasis and hyperalgesia. A list of TMD's involving dysfunction includes: trauma, ankylosis, fibromyalgia, synovitis, disc-condyle adhesions, discitis, odontalgia, disc displacement with reduction, disc displacement without reduction, muscle trismus, neoplasia, infectious disease, osteoarthritis and rheumatoid arthritis. These disorders and dysfunctions do not have a common cause or common treatment. Each one has unique characteristics which must be addressed for optimal results. If dentists were to think of themselves as "physicians with a special interest in the diagnosis and treatment of orofacial pain," they are faced with making a differential diagnosis based on consideration of between 125-135 different possibilities, of which 18-23 would generally be considered within the focus of TMD experts. Epidemiology and double-blind controlled studies on TMD are being challenged. Normal has never been definitely defined and there are not two well-delineated states such as diseased and disease-free relative to TMD's. TMD is not one disease entity but a grouping of many different conditions. In virtually all epidemiologic research, TMD's have been studied as a group, so the results are meaningless. Pain as a gold-standard is unscientific. It is irrefutable having no testable observable or measurable phenomenology. Psychometric testing based on the patient's self-report of pain has never been proven to be more appropriate than objective physiologic measurement for the study of TMD phenomenology. No double-blind study based on pain can possibly be considered hard scientific evidence. (Allen Moses DDS)

Dr. Gordon Christensen states in an interview published in 'Dentistry Today' that "occlusion remains the major untreated disease in dentistry." We probably treat caries too much; we treat periodontal disease a little bit; *and we don't even talk about occlusion.* Occlusal disease affects at least one-third of the population. It is time that the profession becomes more involved in this area of dentistry. As long as untreated continues, the situation keeps getting worse. Thus, "by 40 or 50 years of age, most . . . have worn their teeth to the degree that extensive tooth restorations must be performed" 12. Despite almost one century of research, and despite well over one thousand publications on the subject, "no entirely satisfactory treatment has been identified" 13, 14. The American Dental Association has attempted to strongly encourage the profession to be more aware of TMD and to find a solution for TMD and bruxism, Dr. Christianson concludes: "Today's practitioners can avail themselves of various management strategies to control bruxism, but may not be able to stop it." 6. This approach will need to be supplemented by other therapies aimed at eliminating what by now is probably an ingrained behavioral pattern.

For almost a century dentists have relied on **splint therapy** for TMD and bruxism . 9 Splints have the ability to align the jaws to each other and to protect the teeth. Much current research on the treatment of TMD has been centered on the use of such dental appliances. In the United States alone, some 3.6 million splints are annually prescribed by dentists in an effort to combat bruxism (1.6 million splints), myofascial pain (0.9 million), and TMJ pain (1.1 million)--a \$1 billion industry. 10 Though covering or separating the teeth may be effective to prevent occlusal wear caused by bruxism, this treatment is often not effective for preventing and eliminating other symptoms of TMD. 11. Most splints are largely ineffective in treating TMD.

**Ice and heat** therapies are used to reduce the jaw pain and muscle tension. Application of moist warm towels directly to the jaw joints (5-15 minutes), followed by cold or ice applications (a few minutes), and then repeating this combination 2-5 times per day is sometimes helpful in the short term. Wrapping the jaw in a hot moist towel and **exercising** it through a range of motion has been recommended. 15. These jaw exercises may complement other approaches, but are not effective on their own. Pain from TMD has been related to depression or other emotional problems. **Drugs** are often prescribed for the stress and the brain malfunction etiological theories of TMD. These include anti-anxiety agents, muscle relaxants, and other drugs. They are of limited value in the treatment of the great majority of chronic TMD patients, and they often have untoward side effects. Commonly used antidepressants including Prozac, Paxil and Zoloft may cause bruxism (tooth grinding) and associated headaches. 16. Sufferers usually awaken in the morning with the headache and frequently have an accompanying sleep disorder. Although the pathophysiology of tension headaches are not well understood, it is probable that the headaches arise from afferent fibers in the pericranial musculature, and that sustained contractions of the pericranial muscle may cause tension headaches. 17 Dr James Boyd who developed the NTI-tss and the protocol for its use claims that prolonged nocturnal clenching contributes to migraines. 18

There are some schools of thought that TMD is a response to incorrect mandibular posture. In order for the masticatory system to function ideally the mandible has to be in a correct spatial (3 dimensional) relationship with the skull.<sup>19</sup> They suggest that treatment for bruxism and TMD may include major occlusal adjustments through full mouth rehabilitation sometimes in addition to orthodontics. This technique is irreversible, for it involves the grinding down most of the teeth (and artificially restoring others). The view of the majority of practitioners agreed that "occlusal equilibration is costly and relatively ineffective"<sup>20</sup>

Newer, more robust ceramic materials and better dental bonding with a gnathologically correct occlusion have shown promise in the treatment of TMD and bruxing. These procedures are very technique sensitive and costly. Not all dentists are competent in performing this treatment and a very small percentage of the TMD population can afford it. Moreover, even if malocclusion triggered the bruxing habit, there are no guarantees that its removal will eliminate or reduce bruxing, for the habit may have become an ingrained, self sustaining behavioral pattern. The majority of practitioners agree that "occlusal equilibration is costly and relatively ineffective" despite some spectacular claims in the older and more recent bruxism literature.<sup>21</sup>

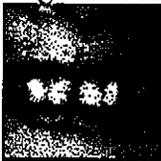
The most promising and exciting new addition to the dentists' arsenal against TMD is having **Botulinum Toxin A** injected into the painful muscles. A group of 46 patients with TMD were measured for subjective and objective responses to treatment with botulinum toxin A (BTX-A). BTX-A injections produced significant improvements in pain, function, mouth opening, and tenderness to palpation.<sup>22</sup> Many other studies have demonstrated similar benefits to TMD patients.<sup>23</sup> Botulinum toxin paralyzes or weakens the injected muscle but leaves the other muscles unaffected. The injections "block extra contraction [of the muscle] but leave enough strength for normal use," says Barbara Karp, M.D., deputy clinical director of the National Institutes of Health's National Institute of Neurological Disorders and Stroke. "Intra muscular injections of botulinum toxin re-establish the balance between masticatory closing and opening muscles. This relieves muscle pain, reverses masseteric hypertrophy with improvement of the face outline and restores normal kinetics of temporo-mandibular joints. Moreover, botulinum toxin injections eliminates habits of tooth grinding and clenching, and the consequences hereof. One single session of injections is curative for 2/3 of the patients. Injections of botulinum toxin in masseter and temporalis muscles are an efficient treatment of bruxism and TMJ dysfunction, cheap with no lasting side effect."<sup>24</sup> Local site-of-injection side effects from botulinum toxin injections are rare, assuming proper technique is used.

The novice should begin with injection of muscles he or she can inject with low risk of incorrect placement. The hard-to-find muscles should be avoided when starting out. It is recommended that the novice clinician attend an educational program covering injection technique, sites and doses. Improved injection technique can also be achieved by injecting and dissecting a few cadavers. The general latency for botulinum toxin type A is 1 week, its duration is 2 to 3 months, and it is recommended that injection be done no more than once every 12 weeks to avoid development of antibodies against the toxin. Depending on the target muscle, injection dose is 10 to 50 U of Botox type A per site

with a total dose of 200 U in the masticatory system. More than this can be used (400 U maximum) if other sites in the head and neck are included in the injection protocol. Most of the orofacial muscles are easily palpable muscles or have definitive bony landmarks to help with the localization process.<sup>25</sup>

Botulinum toxin has "an amazing safety record," says Bill Habig, Ph.D., the recently retired deputy director of FDA's division of bacterial products in the Center for Biologics Evaluation and Research. "Considering it's one of the most toxic materials known and there was a lot of concern about it, it's turned out to be very safe," he says.<sup>26</sup> In 2003, less than two years after it was approved by the FDA for wrinkles, the US consumer spent more than \$875MM dollars on Botox injections. This is to treat a condition that does not effect ones comfort or health. Many dental patients who are already being treated with Botox for wrinkles could be cured of their dentally related diseases with a slight modification in injection protocol.

Botulinum toxin's time to enter the field of dentistry has arrived. Despite the expense many patients will pay for Botox especially when it will make them feel better and look better. It will have its detractors like those who opposed cosmetic dentistry. Let us not forget that the elimination of pain is one of the noblest causes that dentists have!



Before

#### **A Case History:**

I'll always remember the first day I met Matti. The only thing sadder than her was the contents of her pink, blue and two green containers. They will filled with opaque, cracked, stained and ugly splints - the kind your patients are embarrassed to show you. Deep creases burrowed multiple parallel lines across her concerned forehead. Her eyes angled downwards at the corners, matching the shape of her lips and unhappiness. Swollen masseter muscles made her jaws seem wider than her upper face, almost like she had a mild case of mumps.

Her main reason for visiting my office was that she had heard that I had helped someone at a singles bar she frequented with a "jaw headache" problem. She had had episodic pain for many years in her temple, masseter and forehead. Other times it felt like it wrapped around her entire skull. Lately she carried large Costco containers of Advil and Tylenol in her purse. She took a cocktail of the two when the pain became so bad that she could not concentrate. Over the decades in dentistry I have seen many patients like Matti. Periodontally she had a couple of four's, and one five in the upper and lower molar region. Otherwise her gums looked good. No bleeding on probing. Her x-rays revealed that she had lost all her first molars and her upper left second molar - she said they were lost due to failed root canals. Her upper upper left molars were replaced fifteen years ago with a blade implant which failed after four and a half years. The other three quadrants had three unit bridges. Every tooth in her mouth, besides her lower cuspids and incisors were crowned with black margined PFM's, the kind most of us did before the Metal-free Age. Matti could have had a second career as a mobile porcelain shade guide. Every

tooth in her mouth was a different color. Some porcelain had sheared and chipped off the surfaces of 5, 12 and 13.

Matti awoke most mornings with a ringing in her ears and a severe pain on both sides of her head. Her jaws clicked and popped as she struggled to open her mouth. At best she could open wide enough to fit two fingers vertically between her teeth. Over the years her psycho-therapist had prescribed Zoloft and Prozac for her depression. The pills often seemed to make her headaches worse. Her physician had informed her that he could find nothing wrong with her and her headaches were a symptom of her depression.



Her previous dentist had made her three or four splints, both in hard acrylic and thermoplastic material. She had either chewed through them after her dentist had made them too thin after equilibrating them, or did not fit after new crowns were seated. The discoloration and smell of the stale saliva-old acrylic combo discouraged her from wearing them. She had tried thermoplastic splints but the taste made her nauseas. After dental visits she was more inclined to wear them with professional motivation from her hygienist or dentist; but if she did not see him for some time she wore them less and less. Her previous dentist had asked her to wear them as much as possible both during the night and day.

The best to she could was to attempt to wear them part of the time to satisfy him but was not comfortable while eating or speaking with them in her mouth. She ultimately wore them part of the time to satisfy her conscience and her dentist. However she would often awaken with the splint in her mouth and still have severe pain on the sides of her head and jaw. It was obvious that duplicating the same splint again would duplicate the existing outcome- supervised, perpetuated masticatory muscle spasm!

My treatment plan for Matti went as follows: my first goal was to relax the masticatory muscles. The fastest relief I could give her was to place a NTI-tss into her mouth. This would bring some immediate relief to her tired muscles by inhibiting her clenching reflex, and confirm my diagnosis. I was reluctant to perform any minor adjustments on her old crowns because I wanted her jaw muscles out of spasm and thereafter I anticipated the jaw would re-align itself differently. Her clenching habit to care of the occlusal equilibration by shearing off most interfering cusps. Once the jaw muscles relaxed I intended following with a functional orthotic which would allow her chew, bite and relax in a more comfortable posture. On mentioning this to her, she immediately

shook her head from side to side. She also objected to wearing anything in her mouth during the day, including a smaller, daytime NTI-tss. Her job involved speaking all day. This prevented her from wearing the device while at work. I explained that the goal of ideal treatment was to restore all the teeth in such a way that they looked natural and that when the opposing teeth met, the mandible would be re-positioned in a more comfortable position. Otherwise the treatment would perpetuate her pain. The teeth would eventually break again.

After a week Matti returned to my office. She had experienced a huge improvement on awakening and the jaw ache was not as severe as before. But by late afternoon the TMJ and the muscles around it were painful.

When I recommended augmenting the effects of the NTI-tss with Botulinum neurotoxin, she was apprehensive. Her first concern was having poison injected into her. I assured her that it was a safe, natural protein with minimal side-effects. But this wasn't her main concern. Despite her extensive history of dental treatment she was petrified of needles. Her muscles were also tender. She was scared that injecting them would be painful and she would possibly faint. It was decided that we would place her in a recumbent position in the dental chair and would use nitrous oxide to relax her while we gave the Botox. On the day of treatment Matti was given a disclosure form to sign after the pro's and con's of Botox treatment was covered. Correct nitrous oxide protocol was followed. I decided to inject the masseters, temporalis and frontalis muscles. The tender spots and hypertrophied areas were easy to locate with finger pressure. After five minutes she was adequately less anxious to begin injecting. We used a .031 gauge ultra-fine needle that was almost unnoticeable to her during the injections. BTX-A was injected into two areas of both masseter muscles (5 U at each site) and 3 equidistant spots on both temporalis muscles (5 U at each site). Eight areas were injected with 2.5U at each site across the upper forehead avoiding the outside of the pupils. Immediately after the injections there was some skin tenderness at the injection sites. The one side of her forehead had a tiny bruise visible at another injection site not covered by hair.

I followed up with Matti every two weeks for the following 4 months. After 8 days Matti was pain free, she could almost fit four fingers vertically into her mouth, and the muscles were no longer tender to touch. The deep forehead furrows had disappeared off most of her forehead. The sad individual tormented by pain had been replaced by a happy, smiling person. She remained pain free for about 14 weeks. When the tenderness returned it had a lot less of a vengeance than before. However we decided to follow the same dose protocol as we had done 4 months previously. Matti's pain relief lasted 6 months before she requested more BTX A injections. We timed this to coincide with her hygiene visits. We also reduced the dose to each site by fifty percent. Each temporalis site was injected with 2.5 U. Each masseter site was injected with 2.5 U. The entire procedure did not take longer than five minutes.

Matti considers my office trendy because we offer state of the art treatments like cosmetic dentistry and Botox. She is seriously considering having a full mouth rehabilitation.

1. Goldman, J. R. (1992). Soft Tissue Trauma. In A. S. Kaplan & L. A. Assael (Eds), *Temporomandibular Disorders* (pp. 191-223). Philadelphia: Saunders.

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6. Christianson, G. The Journal of the American Dental Association, February 2000.
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8. Rijdsdijk, B. A., Van Es R. J., Zonneveld, F. W., Steenks, M. H., & Koole, R. (1998). Botulinum toxin type A treatment of cosmetically disturbing masseteric hypertrophy. *Nederlands Tijdschrift voor Geneeskunde*, 142, 529-32.
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12. Christensen, 1999 Christensen, G. J. (1999). Destruction of human teeth. *Journal of the American Dental Association*, 130, 1229-30.
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## **CAN BOTULINUM TOXIN A (BOTOX) SAVE YOUR TEETH AND ENHANCE YOUR SMILE?**

**Howard Katz DDS**

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Modern dentistry has trained the general public to demand and accept innovative treatments from their neighborhood dentist. There was a time when you had a toothache you would go to a dentist to pull your tooth out - that is all they were trained to do. Dentists have not always performed the specialized, sophisticated treatments that they do today like restore and replace teeth with implants, root canal treatments, crowns and cosmetic dentistry, straightening teeth with invisible braces. As successful treatments became more predictable and acceptable more and more general dentists performed them.

Dental disease is caused by two predominate causes. Treatments have been designed to combat the effects of these:

A) micro-organisms that destroy dental hard tissue and provoke the immune system to destroy gums and bone

B) excessive muscle forces that predispose to wear and breakdown of the teeth, gums, bone and the tissues of the TMJ. In this article the methods of using Botulinum Neurotoxin A as an adjunctive treatment used to control muscle function that cause and contribute to disease are discussed.

The damage caused by excessive biting forces and dental trauma is being treated with intra-oral appliances, occlusal adjustments, sophisticated dental restorations and/or surgery. These are all excellent treatment options but they are not for every patient. While occlusion used to be regarded as the main cause of disease affecting the masticatory system, muscular and psychological factors are as important. Precise differentiation of the individual causal etiological factors is generally not possible. The term Temporomandibular Dysfunction is used to cover every disease effecting the normal masticatory function. Unfortunately there is no common treatment for every cause of TMD because it encompasses too many different disease entities. These separate diseases have to be isolated and then treated.

The dental profession has always prided itself in that the focus of oral healthcare has been based on prevention. The focus of treatment should be in the prevention and reduction of these destructive habits. Extra-capsular TMD is often transient and the least invasive treatment options are usually best used to begin treatment. Orthognathic surgery, orthodontics and a neuromuscular rehabilitation of the occlusion are invasive, irreversible and expensive for the majority of patients. There is no guarantee to the patient that these major treatments will be effective. Sophisticated restorations are not only very technique sensitive, they involve the removal of additional healthy tooth material. The most esthetic, conservative restorations may not withstand the forces applied to them. There is also a reluctance to have perfectly healthy teeth prepared for ceramic or gold restorations when the teeth are esthetically pleasing and asymptomatic.

Intra-oral splints can be very effective in preventing excessive wear and enabling the jaw to function in the most relaxed posture. Yet there is a very low compliance with intra-oral splints and other protective removable appliances worn over the teeth even when they are effective. Patients do not like to have appliances in their mouths impeding normal function like eating and speaking. Less than one in five patients will wear a prescribed appliance as prescribed by their treating dentist.

Many dentists have bleach trays and comfortable intra-oral devices for their own mouths that they do not use as often as they should. Why should our patients be any different.

The continued use of analgesics, narcotics, steroids and anti-inflammatories for associated dento-facial symptoms is not ideal, nor conducive to health. There are many unwarranted side-effects. Certain patients like airline pilots, air-traffic control personnel, surgeons, military personnel and anyone else operating heavy machine equipment should not be taking narcotics. Yet patients will opt for this despite the inherent risks and danger because of their ease of use.

An extremely effective way to prevent damage and to enhance treatment to dental hard tissue and restorations would be to de-program the muscles responsible for excessive destructive forces and other gnathologically related diseases.

#### THE NEW PARADIGM:

There is clearly a pronounced need to improve the options available for preventive treatment of muscle generated dental disease, which requires effective, safe agents that have minimal side effects, are well-tolerated for long-term use, and that eliminate or reduce the need to use other irreversible treatments or medications. Intramuscular injections of Botulinum toxin type A (BTX-A) have been increasingly used throughout the US as a novel approach to preventive treatment that may provide effective, safe, and well-tolerated long-term relief of intractable symptoms in patients who have failed conventional approaches to treatment. The public does not yet associate Botulinum neurotoxin A with their dentist but they very soon and enthusiastically will. Dentists are skilled in the anatomy of the lower facial anatomy and chewing apparatus. They are also prolific injectors. Dentists have the advanced training in recognizing and treating force related dental problems. This reduces the risk of side-effects associated with unskilled injectors and injection technique.

#### Background

##### Botulinum neurotoxins

There are seven botulinum neurotoxin serotypes (A, B, C, D, E, F, and G), produced by

*Clostridium botulinum*, all of which inhibit acetylcholine release, though their

intracellular target proteins, the characteristics of their actions, and their potencies vary substantially.<sup>2</sup> At the neuromuscular junction, the inhibition of acetylcholine release by BTX-A blocks or reduces contraction of muscles, an effect which has been used therapeutically in disorders characterized by overactive muscle activity such as cervical dystonia (CD), blepharospasm,<sup>3,4</sup> and spasticity.<sup>5</sup>

Botulinum toxin A (Botox) is the muscle relaxant that has been popularized in the elimination of facial lines.<sup>6</sup>

Botulinum toxin type A (BOTOX<sup>®</sup>; Allergan, Inc.; Irvine, CA) is currently approved for the treatment of blepharospasm, strabismus, and CD.<sup>7</sup> Binder and colleagues, treating patients for facial lines, noted improvement of migraine symptoms after BTX-A injections.<sup>8</sup> This discovery led to further investigation in clinical trials of BTX-A preventive treatment of migraine and other dento-facial diseases including TMD.

Btx A has been proven to successfully eliminate or reduce excessive clenching by desensitizing spindle cells within tense muscles, the main cause of force related dental disease, when injected into the chewing muscles. Parafunctional clenching to the extent that it effects oral function causes damage to oral tissues is usually transient. For this reason aggressive irreversible treatments should be avoided. Particularly where compliance is a problem, Botulinum toxin A (Botox) offers this option.

Preventative control of biting parafunctions and excessive forces on the chewing apparatus will be the most significant paradigm in dental treatment since local anesthetic and the dental drill. Dentists will have the ability to reduce the need for major aggressive treatments that involve surgery or drilling many teeth. "Surgical procedures that alter anatomic relationships without addressing factors contributing to pathogenesis may be more prone to failure and recurrence of [TMD] symptoms. It is clear that excessive loading on articular tissues is one of the causative factors that must be identified and addressed by all clinicians treating patients with TMJ pathology" <sup>2</sup>

The public does not yet associate Botulinum neurotoxin A with their dentist but they very soon and enthusiastically will. Dentists are skilled in the anatomy of the lower facial anatomy and chewing apparatus. They are also prolific injectors. Dentists have the advanced training in recognizing and treating force related dental problems. They are also very familiar with facial anatomy. It will be possible to teach dentists fairly easily how to treat their patients with BTX A and how to avoid the major side-effects. These are caused predominately by incorrect injection technique. This reduces the risk of side-effects associated with unskilled injectors.

### **ADMINISTERING BTX-A FOR PREVENTIVE DENTALLY RELATED CONDITIONS**

Patient selection: BTX-A therapy is appropriate for patients for whom other preventive treatments and medications are poorly tolerated or contraindicated, for those refractory to other treatments, for those in special patient populations, as well as for those who simply prefer this treatment. Contraindications to the use of BTX-A include sensitivity to toxin or neuromuscular disorders such as myasthenia gravis or Eaton-Lambert syndrome.

## **Pretreatment Procedures**

### **Informed consent**

Once an appropriate patient is selected for BTX-A treatment, the dentist should set reasonable treatment goals. Patients should first be told that the use of BTX-A as preventive treatment is off-label use; that while there is clinical evidence to support its use as a preventive agent, investigation is ongoing. Patients should also be told that the optimal effects of BTX-A treatment may not be experienced for at least 1 week and will begin to wear off after approximately 3 months, and that multiple treatment cycles may be needed to achieve an optimal therapeutic effect.<sup>22a</sup> Galvez-Jimenez N, Lampuri C, Patino-Piccinillo R, Hargreave M. Dystonia and headaches: the response to botulinum toxin therapy. [Abstract] Cephalalgia. 2003;23:760.

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The known side effects of BTX-A treatment should also be made clear; these include possible injection-site pain, headache, rash, bruising, or ptosis. Informed consent should be obtained.

**Identifying injection sites:** Once treatment is ready to commence, patients should indicate the anatomical locations of the head most frequently affected by pain or muscles tender to touch. The treating dentist should be able to identify the anatomical areas of tenderness and sites that produce pain on palpation (including the frontalis, temporalis, masseter, pterygoids, posterolateral neck and shoulder regions) and examine the face and neck to assess symmetry.

#### **Preparation of BTX for Injection**

One neurotoxin type A (BOTOX<sup>®</sup>) and one type B (MYOBLOC<sup>®</sup>; Elan Pharmaceuticals) are available in the United States. The majority of the evidence has been based on using the type A toxin. Lyophilized BTX-A, available in vials containing 100 U, should be diluted with 2 or 4 mL of preservative-free 0.9% saline, which yields a preparation of 5.0 or 2.5 U per 0.1 mL, respectively. **BTX Injection Sites**

The injection sites commonly used for BTX-A treatment of dental related conditions are the glabellar and frontal regions, the temporalis muscle, the masseter, the depressor anguli oris, the pterygoid muscles, and the cervical paraspinal region. Blumenfeld AM, Binder W, Silberstein SD, Blitzer A. Procedures for administering botulinum toxin type A for migraine and tension-type headache. *Headache*. 2003;43:884-891 Patients should be placed in a sitting or supine position for injection of the frontal and temporal regions, and a sitting position for injection of the posterior neck region and trapezius. It appears most of the adverse events associated with BTX-A injections are related to the technique and skill of the injector. Correct injection technique helps minimize adverse events and optimize treatment outcomes. The precise anatomical location, optimal choice of injection site within a particular muscle, dosages, and volumes used should all be considered carefully. Bilateral injections are advisable in the case of unilateral headache or TMD pain as unilateral injection can lead to the development of symptoms on the other side of the face.

#### **Safety and Tolerability of BTX-A**

BTX-A has an excellent safety and tolerability profile. There are generally no systemic effects from treatment. The reported effects, which are usually minimal and transient, include blepharoptosis (droopy upper eyelid) and muscle weakness at

**injection sites.**<sup>16</sup> Evers S, Rahmann A, Voilmer-Hasse J, Husstedt I-W. Treatment of headache with botulinum toxin A - a review according to evidence-based medicine criteria. *Cephalalgia*. 2002;22(9):699-710.

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## **Postinjection Procedures**

### **Instructions to patients**

Patients should be informed that wheals or blebs at the injection sites will disappear within approximately 2 hours. They should not massage these wheals especially in the forehead as this may cause ptosis. BTX-A-induced relief of headache and TMD symptoms may take several weeks to reach its maximal benefit and the response to injection may change over time. Patients should be informed that they may achieve a greater therapeutic effect with repeated treatments. Blumenfeld A. Botulinum toxin type A as an effective prophylactic treatment in primary headache disorders. *Headache*. 2003;43:853-860. Troost BT. Botulinum toxin type A (BOTOX®) in the treatment of migraine and other headaches. *Exp Rev Neurotherapeutics*. 2004;4:27-31.

The effects of BTX-A injections wear off typically by 3 to 4 months and repeat injections will be necessary.

### **Approaching insurers**

BTX-A use for dental disease treatment is off-label. Discussion should take place with insurers regarding reimbursement. An example of the types of patients typically deemed appropriate for BTX-A preventive treatment by insurers is given in the list below. To build a case that a specific patient is suitable for BTX-A preventive treatment, a letter explaining the need of specific patient to receive BTX-A together with published clinical data will need to be sent to the insurer.

### **Patients Typically Deemed Appropriate by Insurers for BTX-A Preventive Treatment of Headache**

- Intractable migraine headaches and /or TMD at least twice a month
- Chronic daily headaches of 15 headache days per month
- Headache causing disability lasting three or more days

- o 3 or more failed trials of at least 3 preventive pharmacological therapies and other dental treatments with or without concomitant behavioral and physical therapies
- o Abortive medications are required more than twice a week.
- o Abortive medications and treatment are contraindicated due to coexisting medical conditions
- o The occupation or physical health of the patient contra-indicates conventional treatment

#### **POTENTIAL DENTAL USES**

The following are dental conditions that may be successfully treated using Botulinum toxin A (Botox): Teeth, gum, cartilage and bone do not regenerate, and, a full complement of teeth is essential for overall health. Damage to these tissues can be prevented and the success of reparative dental therapies can be predictably enhanced using Botulinum toxin A (Botox)

Patients suffer from facial pain <sup>4</sup> caused by muscle spasm when the relaxed posture of the mandible does not match the occlusion This is one of the many causes of Temporomandibular Disorder TMD. This pain is exacerbated with parafunctional clenching (when the patient forces their teeth for long periods of time for no apparent reason.) When Botulinum toxin A (Botox) is injected into the muscles of mastication and forehead, this clenching reflex (theoretically initiated by sympathetically innervated spindle cells) is often eliminated.<sup>5, 6</sup> This allows the muscles to relax appropriately and the pain dissipates as the freeway space re-appears. The forces created by excessive grinding and clenching of the teeth without food in the mouth are many times greater those the forces required to masticate food. These excessive forces damage the teeth, bone, joints and gums .<sup>7</sup> Because a very small percentage of available force is required to masticate food, muscle function is not weakened sufficiently to have any effect on chewing and swallowing.

Tooth decay is more prevalent in clenchers because excessive forces cause micro-fractures and abfraction of enamel especially around existing restorations. This may be followed by accelerated decay and gingival recession.<sup>s</sup> Botulinum toxin A (Botox) can be used to reduce these very common dental conditions especially with patients who brux or clench excessively while not being able to maintain ideal dental hygiene.

Excessive parafunctional forces created by clenching the jaws impede healing and re-attachment of gum and bone in the mouth following trauma. Low doses of Botulinum toxin will limit the parafunctional clenching. Reduction in clenching intensity will allow traumatized tissue to heal.

Higher doses can be used as a 'pharmaceutical splint' limiting muscle contraction before resetting and during rehabilitation after fracture of the facial bones e.g. when the condyle of the mandible is broken.

Parafunctional clenching contributes to periodontal trauma. Limiting the clenching before and after periodontal surgery will benefit healing. The use of a splint is often contraindicated when the teeth should be functional during healing. However with significant bone loss excessive forces may jeopardize dental stability and contribute to additional tooth loosening. The use of Botulinum toxin may be used to control these potential destructive forces. The same applies in the patient with bone loss associated with either advanced periodontal disease or osteoporosis, and a strong bite. Bite force is not diminished with reduced alveolar bone support.

Implant patients will benefit from pre-surgical Botulinum toxin A (Botox). After multiple implants or immediate loaded implants are placed osseointegration can be prevented or impeded by excessive functional and parafunctional forces. Overloading the implants results in implant failure by loosening of the implant components or prevention of osseointegration. Nishimura, R. D., Beumer, J, 3rd, Perri, G. R., Davodi, A. (1997) 9,10,11

Occlusal rehabilitation patients will benefit from Botulinum toxin A (Botox). Botulinum toxin A can be used to verify that the correct diagnosis has been made. This will also convince patients that their toothache is muscular and not pulpal in origin. This should be done before rushing into a major irreversible treatment "At best, we are only managing signs and symptoms to the best of our ability within the framework of the patient's ability to cope with the disorder" <sup>12</sup> The best thing we can do for our clenching patients, then, is to help them control parafunctional habits and thereby minimize the chances of temporomandibular and dental complications.

Long-term temporization or a functional oral orthotic is used before occlusal reconstruction to ensure that the treating dentist has positioned the mandible comfortably, reset the occlusion correctly and that vertical dimension is maintained. Often the ideal

position varies vastly from the desired position in all three dimensions. These prostheses will be better tolerated and the patient will be more compliant with the use of Botulinum toxin A (Botox).

Orthodontic treatments on patients that are clenchers, have a deep bite or crossed bite are prolonged if the vertical component of muscular force is greater than the force of the fixed or removable appliance. 13 These cases often require the use of removable functional retainers in combination with regular fixed braces in an attempt to control the component of vertical force. Orthodontic treatment time will be reduced and the patients will be far more comfortable and functional (eating, speaking, swallowing) with the use of Botulinum toxin A (Botox) especially if clenching is reduced.

An overactive genioglossus muscles protrudes the tongue between the teeth while swallowing, referred to as a tongue thrust. The force of the tongue prevents the front teeth from erupting into occlusion or separates the teeth so that they don't meet when the jaw closes. Low doses of Botulinum toxin A (Botox) into these muscles will prevent a tongue thrust and allow the teeth to erupt into occlusion. 14

Gummy smiles may be caused by over-contraction of the upper lip muscles, obicularis oris and levator anguli oris. This cannot always be corrected with osseus and gingival recontouring. The upper lip muscles can be proportionately weakened with Botulinum toxin A (Botox) so as not to expose the upper gums when smiling. 15

Overactive depressor anguli oris muscles tend to give individuals a sad or annoyed expression weakening these muscles allows these individuals to appear to have a happier disposition.

The depressor muscles of the lips together with an overclosed vertical dimension of the bite pulls the outer corners of the mouth downwards and creates a deep skin fold or crease. Patients with vitamin deficiencies and those that drool into these creases develop angular cheilitis. Botulinum toxin A (Botox) can be used to weaken the depressor muscles allowing the deep skin fold to dissappear. The elimination of this skin fold prevents saliva pooling and allows the saliva to rapidly evaporate This allows the skin to dry eliminating the angular cheilitis caused by the prolonged moisture.

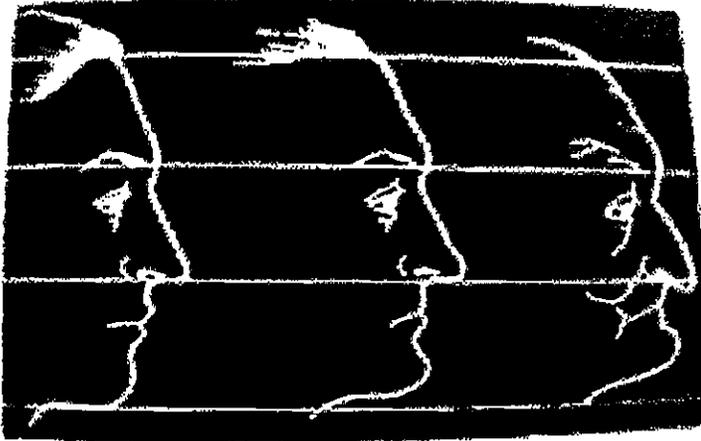
The jaw closing muscles are much stronger than the jaw opening muscles. When the closing muscles remain semi-contracted or in spasm, mouth opening is limited. 17

This limits:

Oral hygiene: neither the patient, dentist or hygienist is able to perform necessary hygiene to prevent oral disease

Dental treatment: necessary dental treatment including x-rays cannot be done

Eating: the teeth cannot be separated sufficiently to bite an apple or a sandwich



The use of Botulinum toxin A (Botox) combined with a multitude of health and cosmetically beneficial therapies will place the dentist in a unique position to provide comprehensive functional and cosmetic maintenance.

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# Botulinum Toxins in Dentistry — The New Paradigm for Masticatory Muscle Hypertonicity

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A variety of factors, such as stress, hormones, diet, drugs, trauma, and certain neuromuscular diseases, can lead to an increase in sympathetic muscle tone, which results in masticatory muscle hypertonicity and parafunction. Dentists have traditionally attempted to treat and prevent this transient disease with methods that are expensive, risky, irreversible, and not evidence-based. There is a need for a conservative reversible noninvasive treatment that is quick, easy, relatively inexpensive, long acting, and effective. Botulinum toxin, a natural protein, is one of the most potent biological substances known. Masticatory muscle relaxation can be reliably achieved by injecting measured doses of botulinum toxin into specific sites in the major muscles of mastication. A reduction in dystonia and pain with optimization of function is easily achievable with a site- and dose-specific injection protocol. The use of botulinum toxin offers the dentist an extremely effective tool to add to the armamentarium for treating conditions that derive from masticatory and other pericranial muscular conditions, and offers the general dentist who is not an expert in gnathology and occlusion a safe, effective treatment for controlling the symptoms of masticatory muscle hypertonicity. [*Singapore Dent J* 2005;27(1);7-12]

**Key Words:** botulinum toxin, masticatory muscle hypertonicity, parafunctional clenching

The use of botulinum toxin in the dental office for the treatment of dentally related conditions including parafunctional clenching, extracapsular myogenic temporomandibular disorder (TMD), trismus, and the associated headaches is a new option for symptom relief in patients in whom conventional treatments are not effective. Used appropriately and with a fully informed patient who understands that no treatment is guaranteed, botulinum toxin injections represent a different treatment protocol for patients who visit their dentists seeking relief from these conditions.

To understand the effects of botulinum toxins on extracapsular myogenic disease in the masticatory system, the non-diseased state should be recognized. In the non-diseased state, the masticatory system functions to preserve all the tissues in the entire system. In the non-diseased, semi-relaxed state, the teeth remain separated by the freeway space. This space is maintained by a balance

in force between the opening and closing muscles of the jaw. The jaw-closing muscles are not truly relaxed to prevent gravity from allowing the mandible to drop and the mouth to gape open. As the teeth make contact, there is a reduction in contractile force by the mandibular elevators, particularly the temporalis, medial pterygoid, and masseter muscles, in order to reduce sustained force between opposing teeth.<sup>1</sup> The jaw-opening muscles, particularly the lateral pterygoid muscles, are activated just before teeth-to-teeth contact.<sup>2</sup> These muscles act like an air brake to limit the force of the teeth in opposing jaws from biting too hard into each other. As the bite opens, the lateral pterygoid relaxes. Tooth-to-tooth contact initiates a swallowing reflex to remove the bolus from between the teeth and to eliminate the reason for mastication.<sup>3</sup> These basic functions prolong the life of the periodontium and the health of the entire system.

Certain conditions can cause an increase in sympathetic muscle tone. These conditions include stress, hormones, diet, drugs, trauma, and certain neuromuscular diseases.<sup>1</sup> The increased tone affects the trigeminal centre in the brain, which stimulates the masticatory closing muscles causing masticatory muscle dystonia recognized as masticatory muscle hypertonicity and parafunction.<sup>4</sup>

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This is most evident in the anterior aspect of the temporalis muscles. Dystonia in the masticatory system is a disorder characterized by involuntary sustained muscle contractions resulting in repetitive movements or abnormal postures. It is also recognized as parafunctional clenching.

If the temporalis muscles do not relax when the teeth come together, the lateral pterygoid in an attempt to separate the teeth remains contracted and is unable to relax. The lateral pterygoid muscles are unable to open the mandible because of the superior strength and tenacity of the temporalis. As lactic acid accumulates in the muscles, they start to cramp. Lateral pterygoid muscular pain symptoms are usually secondary to temporalis hypertonicity. When the temporalis is able to relax, symptoms from the lateral pterygoid in spasm usually disappear without any other specific treatment to the lateral pterygoid.

The pathological conditions attributed to masticatory muscle hypertonicity and parafunction<sup>2</sup> are shown in Table 1. Patients who are not susceptible to muscle hypertonicity and parafunction maintain freeway space. These patients are less likely to exhibit any of the conditions listed in Table 1 that are associated with hypertonicity and parafunction. This is why patients with malocclusion and missing teeth are often symptomless as these factors are not synonymous with muscle pain and other conditions listed.

**Table 1.** Pathological conditions attributed to masticatory muscle hypertonicity and parafunction

- 
- Abfraction
  - Alveolar bone loss
  - Cervical pain
  - Cervical erosion
  - Chipped anterior teeth
  - Delayed healing to periodontium after trauma<sup>4</sup>
  - Difficulty chewing
  - Dysphagia (difficulty swallowing)
  - Facial and pericranial muscle pain (nonspecific)
  - Flared upper anterior teeth
  - Fractured cusps and restorations<sup>7</sup>
  - Gingival recession
  - Limited mouth opening
  - Locked upper buccal cusps
  - Loss of molars
  - Masseteric hypertrophy
  - Open interproximal contacts
  - Painful teeth
  - Scalloping of lateral border of tongue
  - Tender, sensitive teeth
  - Thermal sensitivity (hot and cold)
  - Tinnitus (ringing in the ears)
  - Tooth mobility
  - Wear facets gums<sup>5</sup>
- 

Many of the symptoms, especially pain, may be transient. Accurate scientific observations combined with astute clinical observation of masticatory physiology and pathology using noninvasive objective electronic measurement may be useful for identifying the precursors to extracapsular muscle disorders and susceptibility characteristics of patients. Parafunction can be measured using electromyography, electrosonography, and electrokinetic tracings analysed properly in retrospective studies. These diagnostic tools also demonstrate what effect a specific treatment may have on this disorder.

Traditionally, dentistry has attempted to treat and prevent this transient disease with methods that are expensive, risky, irreversible, and not evidence-based. These include analgesics, splints, moist heat, exercises, transcutaneous electrical nerve stimulation, muscle relaxants, low-dose tricyclic antidepressants, local anaesthetics, alpha adrenergic receptor antagonists, occlusal adjustments, full mouth rehabilitation, orthodontics, orthognathic surgery, or a combination of these treatments.<sup>8</sup>

Ideal dental procedures and restorations will not have any affect on sympathetically innervated muscle hypertonicity. An ideal intraoral device or splint made with the greatest of intentions will not work if the patient has poor compliance, which includes the majority of patients when it comes to wearing orthotics or most other intraoral devices.<sup>9</sup> Many dentists are not comfortable with prescribing medication that has severe, unwarranted side effects. Major occlusal adjustments are risky, expensive, and have no guarantee of success.<sup>9-11</sup>

## Botulinum Toxin

The profession obviously has a need for a conservative reversible noninvasive treatment that is quick, easy, relatively inexpensive, long acting, and effective. A longer acting, more reliable method of obtaining masticatory muscle relaxation can be achieved by injecting measured doses of botulinum toxin (BTX) into specific sites in the major muscles of mastication.<sup>12-14</sup> These doses are sufficient to shut down the efferent response from spindle cells within the muscles that are implicated in initiating and potentiating the sympathetic dystonic cycle. The effect of BTX is to act as a governor on sympathetically driven trigeminal innervation to the masticatory muscles. The obvious treatment goal is to reduce spasm but not to interfere with normal function.<sup>15</sup> A reduction in dystonia and pain with optimization of function is easily achievable with a site-specific and dose-specific BTX injection protocol.<sup>16</sup>

BTX, a natural protein, is one of the most potent biological substances known. The toxin inhibits the release of acetylcholine (ACH), a neurotransmitter responsible

for the activation of muscle contraction and glandular secretion. Administration of the toxin results in a reduction of tone in the injected muscle. Some nerve terminals are not affected by the toxin, allowing the injected dystonic muscle to contract, but with less force. This weakness allows for improved posture and function of the hypertonic muscle. The degree of weakening depends on the dose, and the duration of weakness is further dependent on the serotype of BTX employed.

The seven distinct serotypes, A, B, C, D, E, F and G, differ in their potency, duration of action, and cellular target sites.<sup>17,18</sup> BTX-A is marketed worldwide under the name Botox® (Allergan Inc, Irvine, CA, USA), and in Europe as Dysport® (Speywood Pharmaceuticals Ltd, Maidenhead, UK). Botox® has been approved by the US Food and Drug Administration (FDA) for the treatment of strabismus, blepharospasm,<sup>19</sup> focal spasms including hemifacial spasm,<sup>20</sup> cosmetically for the facial glabellar lines,<sup>21</sup> and more recently for the treatment of cervical dystonia<sup>22</sup> and axillary hyperhidrosis. BTX-B has been approved by the FDA for the treatment of cervical dystonia, and will be marketed under the name Myobloc® in the United States and Neurobloc® in Europe (Solstice Neurosciences Inc, South San Francisco, CA, USA).

### Structure

BTX is synthesized as a large single-chain peptide. Activation requires a two-step modification in the tertiary structure of the protein. This process converts the single-chain neurotoxin to a di-chain neurotoxin comprising a 100,000-Da heavy chain (HC) linked by a disulfide bond to a 50,000-Da light chain (LC). BTX acts at the neuromuscular junction where it exerts its effect by inhibiting the release of ACH from the presynaptic nerve terminal.

ACH is contained in vesicles, and several proteins (vesicle-associated membrane protein [VAMP], synaptosome-associated protein 25 kDa [SNAP-25], and syntaxin) are required to release these vesicles through the axon terminal membrane. BTX binds to the presynaptic terminal via the HC. The toxin is then internalized and the HC and LC are separated. The LC from BTX-A cleaves SNAP-25, the LCs from serotypes B and F cleave VAMP, and that from serotype C cleaves syntaxin.<sup>23</sup>

This disrupts ACH release and subsequent neuromuscular transmission, resulting in weakness of the injected muscle.

### Potency

The potency of BTX is expressed as mouse units, with 1 mouse unit equivalent to the median lethal dose (LD 50) for mice. Botox® is dispensed in small vials containing 100 U, while a vial of Dysport® contains 500 U. The relative

potency of Botox® units to Dysport® units is approximately 1:4.

The lethal dose of Botox® in humans is not known, although it has been estimated to be about 3,000 U. The usual maximum total recommended dose at an injection session in the dental office is about 80–100 U. This means that the injector will have to inject 30 vials before a potentially lethal outcome. There is such a huge disproportion between the clinical dose and the lethal dose that a fatal overdose is almost impossible.

### Preparation

The toxin is produced by the Gram-negative anaerobic bacterium *Clostridium botulinum*. It is harvested from a culture medium after fermentation of a toxin-producing strain of *C. botulinum*, which lyses and liberates the toxin into the culture. The toxin is then extracted, precipitated, purified, and finally crystallized with ammonium sulfate. In this form, BTX-A should be stored in a refrigerator but not frozen. BTX-A should be diluted with preservative-free saline and the preparation used within 4 hours of reconstitution. Conditions for stability of the toxin in solution include pH 4.2–6.8 and temperature less than 20°C. The large molecule is very fragile and is inactivated easily in solution by shaking.

### Dentofacial applications of BTX injections

Patient education and counselling are essential components of a comprehensive therapeutic approach to all patients with masticatory parafunctional conditions. Dentists and physicians administering BTX must have a good understanding of both the anatomy of affected muscles and the resultant movement disorder. BTX can be used as sole therapy or as an adjunct to oral medications. Oral disclusion devices may also play a role as a supplement to BTX. The ideal of BTX treatment is to achieve a balance between weakness sufficient to reduce spasm but insufficient to interfere with function. The dental applications of BTX injections are shown in Table 2.

### Treatment protocols

The treatment techniques involve the use of a 100-U vial of BTX diluted with 4 mL of unpreserved sterile saline. With this dilution, each 0.1 mL contains 2.5 U of BTX-A. The BTX is aspirated into and injected using a 1-mL tuberculin syringe and a 0.30-gauge half-inch needle.

The applications of BTX evolved serendipitously from the original ophthalmic indications. Blepharospasm patients (unable to open eyes) who had BTX injected around their eyes reported that their forehead lines disappeared. Patients injected for their brow lines reported that their headaches disappeared. Other patients injected for brow lines and crow's feet reported that the pain

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**Table 2. Dentofacial applications of botulinum toxin injections**

- Extracapsular myogenic pain caused by masticatory muscle hypertonicity
- Secondary dental pain
- Trismus<sup>24</sup>
- Adaptation to rapid change in vertical dimension associated with oral prostheses
- Elimination of bruxism<sup>25</sup>
- Masseter hypertrophy<sup>13,14,22</sup>
- Increased success with immediate loaded implants<sup>26</sup>
- Gummy smiles (injecting levator anguli oris alaeque nasi)
- Limit muscle forces during orthodontic treatments<sup>13</sup>
- Limit clenching after periodontal treatments
- Limit muscle hypertonicity after orthopaedic and orthognathic surgery; postoperative muscle pull on the periosteum is responsible for pain
- Sialorrhoea associated with stroke or Parkinson's disease
- After trauma to oral tissues<sup>6</sup>

associated with migraines and extracapsular myogenic temporomandibular joint caused by masticatory muscle hypertonicity improved or disappeared. The treatment protocol for masticatory muscle hypertonicity became more predictable with injections into the masseter and temporalis muscles.

The current treatment protocol ranges from one injection of 7.5 U bilaterally into the anterior vertical fibres of each temporalis muscle. In more severe cases, additional injections of 2.5 U are given into the middle and posterior third of the temporalis muscles. Treatment begins with lower doses because it is always possible to titrate up to a higher dose if necessary.

The masseteric component of pain is treated with 5 U injected into the belly of the masseter below an imaginary line joining the tragus of the ear and the corner of the mouth. Pain relief from the tendon of temporalis is achieved with multiple injections of 2.5 U equidistantly spaced in the temple area outside the orbital rim of the eyes.

The side effects of botulinum toxin injections are site and dose related. Any injections given within 1 cm above the eyelid and outside the midpupillary line will cause eyelid ptosis.<sup>27</sup> Additionally, any injections given below the eye and inside the midpupillary line may cause diplopia (double vision). When injecting above the tragus-labial commissure line, the zygomaticus muscles are weakened and the corner of the mouth will droop. The rules governing cosmetic injections should be followed while treating all masticatory muscle hypertonicity-related disorders to avoid cosmetic side effects, for example eyelid ptosis or a droopy corner of the mouth. For this reason, the dentist should be familiar with the cosmetic treatment protocols. The sites and doses for BTX therapy are shown in the Figure.

### Contraindications

No absolute contraindications to the use of BTX-A are known. Relative contraindications for clinical application of BTX are pregnancy and lactation, neuromuscular disease (e.g. myasthenia gravis, Eaton-Lambert syndrome), motor neuron disease, and concurrent use of aminoglycosides.

### Conclusion

The use of BTX in dentistry offers the dentist another extremely effective tool to add to the armamentarium for treating conditions that derive from masticatory and other pericranial muscular conditions. Most dentists are familiar with the oral anatomy and are comfortable injecting into the oral musculature. The treatment protocols and injection techniques require essential, yet minimal training for the general dentist. BTX in dentistry will offer the general dentist who is not an expert in gnathology and occlusion a safe, effective treatment for controlling the symptoms of masticatory muscle hypertonicity.

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• **Botox for TMD:** I was diagnosed with TMD 3-4 years ago by an ENT. I have been seeing an ENT in a clinical study for the use of Botox in treating TMD pain for 2 years. I was part of the study, so the treatments were free, but to continue them will cost me roughly \$1800 every 5-6 months (that's how long the Botox lasts). The Botox temporarily paralyzes the targeted muscles in the jaw and head that trigger TMD symptoms, clenching, grinding, etc, which in turn cause a host of problems from migraines, to aching teeth, backs, necks, ear pain. This treatment has been the ONLY thing that has worked, and I want to know what you know about the use of Botox for TMD? It's been used for CP and eye spasms LONG before it was being used by Hollywood for beauty. I'm hoping that more ENTs look into this treatment for their patients. Suffering with TMD is so terrible because of the pain, and because of the ignorance of the disorder by doctors. It's not mental, and no amount of a liquid diet is going to cease the grinding that takes place when we sleep. And valium and xanax will only make us drug addicts. Any information you can provide on this disorder becoming more recognized by the otolarongologists and dentists of the world would be greatly appreciated! ...Visitor from New York [\(answer\)](#)

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### Key Benefits of Botox Injections

- "Botulinum toxin type A produces prolonged muscle relaxation which is dose dependent and can be easily targeted to affected muscles,"
- Botox blocks the excessive release of a neurotransmitter called acetylcholine from the terminal where the nerve transmits signals to the muscle. The affected terminals are not able to cause muscle contraction. Clinical effects are usually seen within one week of injection and typically relief endures for three to four months or more.

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### Botox Effective For Relief Of Incapacitating Chronic Pain

ORLANDO, FL -- November 19, 1999 -- People who suffer from a variety of chronic pain syndromes may obtain relief with injections of Botox(R) (botulinum toxin type A), a product of Allergan, Inc., according to a group of clinical studies presented at the International Conference 1999: Basic and Therapeutic Aspects of Botulinum and Tetanus Toxins held in Orlando, Florida.

"Chronic pain whether it is migraine, whiplash or back pain, can significantly interfere with the activities of daily living," said Dr. Mike Royal, Department of Anesthesiology/Pain Management, University of Oklahoma, Tulsa OK, who presented his study on the use of botulinum toxin type A (BTX-A) in patients suffering from back pain. Treatment with Botox provides an alternative therapy that is effective when these debilitating conditions do not respond to conventional treatment."

"Botulinum toxin type A produces prolonged muscle relaxation which is dose dependent and can be easily targeted to affected muscles," said Dr. Marvin Schwartz, from the University of Toronto, Pickering, Ontario, Canada, who presented data on whiplash at Toxins '99.

Myofascial pain syndrome is a chronic, painful condition associated with areas of increased muscle tone, which are clinically felt as tight bands punctuated by small areas that are very tender to pressure, often called trigger points. Myofascial pain is often treated with

conventional therapies such as non-steroidal anti-inflammatories, analgesics and physical therapy. These therapies however, have limitations and are associated with side effects.

In a retrospective study conducted at the Pain Evaluation & Treatment Center in Tulsa, OK, 70 percent of patients with myofascial pain in the back and extremities who received BTX-A injections over a two-year period reported good (15.5 percent) to excellent (54.5 percent) pain relief lasting an average of 2.5 to 3.6 months. Ten percent were free of pain at the one-year follow up. Patients experience relief from symptoms within one week after the first injection. The treatment was well tolerated with only a few patients having mild and very transient reactions. With the BTX-A injections, patients were able to tolerate more aggressive therapeutic exercise.

In addition, according to a randomized double-blind placebo controlled study conducted at the University of Toronto, Canada and presented at the Toxins '99 meeting, 26 patients suffering from whiplash associated disorder (WAD) treated with BTX-A demonstrated a significant improvement ( $p < 0.01$ ) in total range of neck motion and subjective pain compared to the placebo group. No side effects were reported in this study.

Additional studies on BTX-A indicated that:

- Low back myofascial pain can be safely and effectively treated with BTX-A injections even when the pain does not respond to conventional therapies.
- The efficacy of BTX-A is superior and longer lasting than conventional steroid therapy for myofascial pain.
- BTX-A may be more effective than lidocaine in the treatment of myofascial pain.
- In patients with TMJ, BTX-A showed statistically significant improvement in pain experience, function, mouth opening and tenderness to palpation in TMJ patients.

Botox blocks the excessive release of a neurotransmitter called acetylcholine from the terminal where the nerve transmits signals to the muscle. The affected terminals are not able to cause muscle contraction. Clinical effects are usually seen within one week of injection and typically relief endures for three to four months or more. Repeat injections of Botox may be required to maintain the desired clinical effect.

Migraine is a condition that affects some 25 million Americans (three times as many women as men). The condition is characterized by moderate to severe pain, generally localized on one side of the head and exacerbated by movement or physical activity. Attacks, which may last as long as four to 72 hours, are often accompanied by nausea, vomiting, and sensitivity to light and sound. While new treatments have been developed to manage

migraine, there have been few developments in the therapies to prevent migraine. New data, however, suggests that Botox may be effective as prophylactic therapy for migraine.

A multi-center, double-blind, placebo-controlled trial of BTX-A showed that injection of 25 U BTX-A provided significantly reduced the frequency and incidence of migraine and associated vomiting for at least three months following injection. The 25 patients that received BTX-A measured significantly better on frequency of migraines, number of migraines, reduction in migraine severity, reduction of vomiting and reduction in the number of days in which acute migraine medications were used.

Other studies on treatment of migraine with BTX-A indicated:

-- Intramuscular injections of BTX-A are effective in preventing chronic tension-type headache when standard therapy fails.

-- Headache severity was significantly decreased following intramuscular injections into the most tender pericranial muscles with BTX-A.

Botox works by blocking the excessive release of acetylcholine from the peripheral nerve terminal at the neuromuscular junction (where the nerve transmits signals to the muscle). The affected terminals are inhibited from stimulating muscle contraction, resulting in muscle relaxation. Over a period of several months the beneficial effects gradually fade. Side effects of treatment with Botox are usually transient and mild to moderate in nature.

A highly stable, purified form of botulinum toxin type A is currently marketed in the U.S. under the brand name Botox(R) by Allergan, Inc. for the treatment of strabismus and blepharospasm associated with dystonia (disorder of the eye muscle that controls blinking). Researchers across the country are also studying its uses in a number of other disorders including cervical dystonia (involuntary muscle spasms in the neck and shoulders), post-stroke spasticity, back pain, migraine and tension headache

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**Practical Advice for Administering Botulinum Toxin Type A for the  
Preventive Treatment of Migraine and Tension-Type Headache**

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## **PART I: RATIONALE FOR THE USE OF BOTULINUM TOXIN AS PREVENTIVE HEADACHE TREATMENT**

### **Introduction**

Approximately 45 million Americans have chronic recurring headaches, with 17% of all American women and 6% of men suffering from migraine.<sup>1</sup> Chronic daily headache (CDH), defined as a headache which occurs more than 15 days per month with a duration of at least 4 hours per day, occurs in 4% to 5% of the US population.<sup>2</sup> This disease burden is associated with considerable cost. Direct medical costs of migraine treatment in the US have been estimated at \$9.5 billion (1993), over \$2.7 billion of which is incurred for acute medications expenditures<sup>3</sup> and \$13 billion in indirect costs, including missed workdays and impaired productivity.<sup>4</sup>

Acute therapies, such as triptans, offer rapid symptomatic relief of headaches but do not prevent future attacks. In addition, the overuse of acute medications can exacerbate headache symptoms. Headache prevention strategies are therefore essential for many headache patients. Effective preventive drug therapy reduces the use of other medications, and appears to lessen the overall burden of the illness in terms of the patient's need for medical attention.<sup>5</sup>

Unfortunately, commonly used preventive agents are associated with side effects<sup>6,7</sup> that may limit the extent to which patients adhere to their medication regimens. In a recent survey of migraine patients, 2 out of 3 (67%) sufferers reported they had delayed or avoided taking a prescription medication at some time during the past because of concerns about adverse effects.<sup>8</sup> The subsequent impact of delaying or avoiding the use of prescription medication was more intense pain in 60% of respondents.

There is clearly a pronounced need to improve the options available for preventive treatment of headache, which requires effective, safe agents that have minimal side effects, are well-tolerated for long-term use, and that eliminate or reduce the need to use other headache medications. Intramuscular injections of botulinum toxin type A (BTX-A) have been increasingly used throughout the US as a novel approach to preventive headache treatment that may provide effective, safe, and well-tolerated long-term relief of intractable headache symptoms in patients who have failed conventional approaches to treatment.

### Background

#### **Botulinum neurotoxins**

There are seven botulinum neurotoxin serotypes (A, B, C, D, E, F, and G), produced by *Clostridium botulinum*, all of which inhibit acetylcholine release, though their intracellular target proteins, the characteristics of their actions, and their potencies vary substantially.<sup>9</sup> At the neuromuscular junction, the inhibition of acetylcholine release by BTX-A blocks or reduces contraction of muscles, an effect which has been used therapeutically in disorders characterized by overactive muscle activity such as cervical dystonia (CD), blepharospasm,<sup>10,11</sup> and spasticity.<sup>12</sup>

#### **Botulinum toxin type A**

Botulinum toxin type A (BOTOX®; Allergan, Inc.; Irvine, CA) is currently approved for the treatment of blepharospasm, strabismus, and CD.<sup>13</sup> Binder and colleagues, treating patients for facial lines, noted improvement of migraine symptoms after BTX-A injections.<sup>14</sup> This discovery led to further investigation in clinical trials of BTX-A preventive treatment of migraine and other headache types.

## **What is the evidence that BTX-A affects headache?**

### ***Migraine***

Evers and colleagues, in their evidence-based medicine review of BTX-A treatment of headache established classification standards to enable assessment of the existing evidence.<sup>15</sup> On the basis of the Evers classification, level 1-B evidence was defined by the following: the study was randomized and controlled; had a patient population of greater than 20 with an exact diagnosis being investigated; and had defined and standardized BTX-A doses and injection sites. On the basis of the Evers classification, there is accumulating evidence of BTX-A efficacy in migraine prevention in 5 of 6 clinical trials (Table 1).

### ***Tension-type headache***

The results of randomized, double-blind, placebo-controlled clinical trials of BTX-A treatment of tension-type headache (TTH) have been mixed. Smuts and colleagues conducted a 4-month trial of BTX-A (100 U) in 37 patients with chronic TTH resulting in statistically significant improvements compared to placebo in headache intensity ( $P=0.002$ ) and headache-free days ( $P=0.001$ ) by month 3.<sup>16</sup> Kokoska and colleagues found that BTX-A (50 U) significantly reduced the intensity of chronic TTH compared to placebo ( $P<0.0001$ ).<sup>17</sup> However, Schmitt and colleagues, in a 60-day trial of BTX-A treatment (20 U) of chronic TTH involving 60 patients, found that pain intensity, the number of pain-free days, and consumption of analgesics were not statistically different between the treatment groups.<sup>18</sup> The different outcomes in these trials may be related to injection protocols, dosing, and length of treatment, and perhaps highlight how much we have to learn about the optimal use of BTX-A as a preventive headache treatment and how to study its effects in a research setting.

### ***Secondary headache***

The revised International Headache Society (IHS) headache classification describes headache attributed to craniocervical dystonia (11.2.3). Brin and colleagues, in a randomized, double-blind, placebo-controlled trial of BTX-A treatment (mean dose, 236 U) for craniocervical dystonia involving 170 patients, assessed pain frequency and intensity at 2, 4, 6, 8, and 10 weeks after injection using a 0 (never or none) to 4 (constant or intolerable) scale.<sup>19</sup> At baseline, 92% (80/87) of the BTX-A patients and 93% (76/82) of the placebo patients reported some degree of pain. This study did not specify whether the pain was of neck or head origin, but a distinct pain-relieving effect was evident in these patients. The reduction in pain frequency was significantly greater in BTX-A patients (-0.31) compared to placebo patients (-0.01) at the primary end point (week 6;  $P=0.018$ ). The decrease at week 6 in pain intensity was also greater in BTX-A patients (-0.36) compared to placebo patients (+0.06;  $P<0.001$ ). Follow-up open-label studies have demonstrated how headache symptoms specifically are improved by BTX-A treatment.<sup>20,21</sup>

### ***Evidence from open-label trials involving multiple headache types***

Clinic-based experience, while uncontrolled, provides useful insight into the potential effects of BTX-A treatment. Blumenfeld in a retrospective chart review, recently reported the results of a large, open-label trial using repeat BTX-A treatment cycles and patient-tailored injection protocols.<sup>22</sup> BTX-A (mean dose, 63.2 U) was administered to 271 patients diagnosed with migraine, episodic TTH, mixed headache, and CDH (many of CDH patients were transformed migraine patients) on 2 or more visits for an average of 8.6 months. BTX-A treatment significantly reduced the number of headache days per month from 18.9 to 8.3 ( $P<0.001$ )—a 56% reduction—and headache intensity was significantly decreased by 25% ( $P<0.001$ ). Improvement in headache frequency and intensity was reported by 85.6% of patients.

Similarly, Troost assessed the effects of multiple BTX-A treatments (mean dose, 127 U) in 436 patients with CDH, migraine, and TTH who had previously failed 3 or more pharmacologic therapies over a 3-year period.<sup>23</sup> A total of 397/436 patients (91%) reported some improvement in their headache symptoms after BTX-A treatment.

#### *Evidence of antinociceptive activity*

The evidence of BTX-A efficacy in reducing the symptoms of headache has naturally led to much discussion and research into the potential antinociceptive influence of BTX-A on the sensory pathways. Cui and colleagues demonstrated that local peripheral injection of BTX-A significantly reduced formalin-induced nociceptive behaviors in rats in a dose-related manner with the absence of local muscle weakness.<sup>24</sup> Results of in vitro and in vivo research have confirmed that BTX-A blocks the release of nociceptive mediators such as substance P (SP), glutamate, and calcitonin gene-related peptide (CGRP).<sup>25</sup> BTX-A suppression of SP has been demonstrated in the iris muscles of rabbits<sup>26</sup> and in embryonic rat dorsal root ganglia neurons.<sup>27</sup> BTX-A has also been shown to suppress the release of glutamate in the periphery and dorsal horn<sup>24</sup> and the release of CGRP from autonomic vascular nerve terminals.<sup>28</sup> BTX-A may exert its antinociceptive effects through modification of perception-of-pain signals by directly inhibiting peripheral sensitization of nociceptive fibers and, in turn, by indirectly reducing central sensitization (Aoki, 2003).<sup>25</sup>

## **PART II: ADMINISTERING BTX-A FOR PREVENTIVE HEADACHE TREATMENT**

### **Patient Selection for Preventive BTX-A Treatment**

BTX-A therapy is appropriate for patients with disabling primary headaches for whom other preventive medications are poorly tolerated or contraindicated, for those refractory to other treatments, for those in special patient populations, as well as for those who simply prefer this

treatment (Table 2).<sup>29</sup> Patients with headache and craniocervical dystonia should also be considered candidates for treatment with BTX-A. Contraindications to the use of BTX-A include sensitivity to toxin or neuromuscular disorders such as myasthenia gravis or Eaton-Lambert syndrome.

### **Pretreatment Procedures**

#### **Informed consent**

Once an appropriate patient is selected for BTX-A treatment, the physician should set reasonable treatment goals. Patients should first be told that the use of BTX-A as preventive headache treatment is off-label use; that while there is clinical evidence to support its use as a preventive agent, investigation is ongoing. Patients should also be told that the optimal effects of BTX-A treatment may not be experienced for at least 1 week and will begin to wear off after approximately 3 months, and that multiple treatment cycles may be needed to achieve an optimal therapeutic effect.<sup>22,23</sup> The known side effects of BTX-A treatment should also be made clear; these include possible injection-site pain, headache, rash, bruising, or ptosis. Informed consent should be obtained.

#### **Identifying injection sites**

Once treatment is ready to commence, patients should indicate the anatomical locations of the head most frequently affected by pain. The physician should identify the anatomical areas of tenderness and sites that produce pain on palpation (including the frontalis, temporalis, and posterolateral neck and shoulder regions) and examine the face and neck to assess muscle tone, asymmetry, and brow position.<sup>29</sup>

### **Preparation of BTX for Injection**

One neurotoxin type A (BOTOX<sup>®</sup>) and one type B (MYOBLOC<sup>®</sup>; Elan Pharmaceuticals) are available in the United States. The majority of the evidence has been based on using the type A toxin. Lyophilized BTX-A, available in vials containing 100 U, should be diluted with 2 or 4 mL of preservative-free 0.9% saline, which yields a preparation of 5.0 or 2.5 U per 0.1 mL, respectively.

### **BTX Injection Sites**

The injection sites commonly used for BTX-A treatment of headache are the glabellar and frontal regions, the temporalis muscle, the occipitalis muscle, and the cervical paraspinal region.<sup>29</sup> Patients should be placed in a sitting or supine position for injection of the frontal and temporal regions, and a sitting position for injection of the posterior neck region and trapezius. It appears most of the adverse events associated with BTX-A injections are related to the technique and skill of the injector. Correct injection technique helps minimize adverse events and optimize treatment outcomes.

The precise anatomical location, optimal choice of injection site within a particular muscle, dosages, and volumes used should all be considered carefully. An overview of pertinent guidelines for injection and specific anatomical considerations should be reviewed in Blumenfeld et al.<sup>29</sup> Figure 1 shows the typical injections sites.

### **BTX Injection Protocols for Headache Treatment**

The total BTX-A dose used in a treatment session depends on an individual patient's presentation including the type of headache, the severity of symptoms, and the patient's body size. In my clinical experience and that of others, a total BTX-A dose of 50 U to 100 U per

session has proved effective.<sup>22,23</sup> There are 3 basic BTX injection protocols available: a "fixed-site" approach, a "follow-the-pain" approach, and a "combination" approach (Table 3). The objective of each protocol is to inject at multiple sites within a specific target region based on the particular type of headache being treated.

The fixed-site protocol should be adopted to treat migraine or migrainous headache (Table 4). BTX-A is injected at fixed symmetrical injection sites that include the trigeminal pathway using a range of predetermined doses. Bilateral injections are advisable in the case of unilateral headache as unilateral injection can lead to the development of headache on the other side of the head.

The follow-the-pain protocol should be adopted to treat TTH (Table 5). The injection sites and BTX-A doses are adjusted according to the where the patient feels pain and where the examiner can elicit pain and tenderness on palpation of the muscle.

For patients with features of both migraine and TTH, a combination of the fixed-site and follow-the-pain approaches should be adopted, with generally higher BTX-A doses. Additional injections should be given in areas that are tender or consistently symptomatic (or a combination of both). If it is found upon examination that the patient is experiencing pain around the ear or jaw, in addition to headache, symptoms of temporomandibular disorder may be present and one of the basic protocols should be supplemented with a "follow-the-muscles-of-mastication" protocol.

For some patients with severe headaches, an underlying cause may be CD, which is typically characterized by abnormal muscle contractions in the head and neck area leading to sideways or lateral rotation of the head and twisting of the neck. Almost all the dystonic movements share a

sustained directional quality that may be prolonged or occur in an instant. The symptoms of CD often worsen while walking or during periods of stress and improve with rest or sleep. Muscle hypertrophy is present in almost all CD patients. For an expanded review of the diagnostic criteria for CD, the WE MOVE web site should be reviewed (<http://www.wemove.org>). For these patients, BTX-A must be injected into overactive muscles, since weakening contralateral muscle groups with botulinum toxin injections could worsen the pain. A "follow-the-dystonia" protocol should be adopted with BTX-A injections to the sternocleidomastoid, splenius capitis, levator scapulae, or trapezius muscles.<sup>29</sup> BTX-A injection protocols for patients with CD can be reviewed elsewhere.<sup>30</sup>

### **Safety and Tolerability of BTX-A**

BTX-A has an excellent safety and tolerability profile. There are generally no systemic effects from treatment. The reported effects, which are usually minimal and transient, include blepharoptosis and muscle weakness at injection sites.<sup>16,22,31</sup> Proper injection techniques can minimize adverse effects such as ptosis.<sup>29</sup>

### **Postinjection Procedures**

#### **Instructions to patients**

Patients should be informed that wheals or blebs at the injection sites will disappear within approximately 2 hours. Patients should also keep a headache diary documenting the frequency, location, and severity of headache, and the amount of acute medication taken over a full 4-month period from the start of therapy. BTX-A-induced relief of headache symptoms may take several weeks to reach its maximal benefit and the response to injection may change over time. Patients should be informed that they may achieve a greater therapeutic effect with repeated treatments.<sup>22,23</sup>

### **Treatment evaluation**

Patients should be evaluated 4 to 6 weeks after the first injection. The headache diary will form the basis of the evaluation of BTX-A treatment efficacy and future course of headache treatment. The effects of BTX-A injections wear off typically by 3 to 4 months and repeat injections will be necessary.

### **Approaching insurers**

BTX-A use as a preventive headache treatment is off-label. Discussion should take place with insurers regarding reimbursement. An example of the types of patients typically deemed appropriate for BTX-A preventive headache treatment by insurers is given in Table 6. To build a case that a specific patient is suitable for BTX-A preventive treatment, a letter explaining the need of specific patient to receive BTX-A together with published clinical data will need to be sent to the insurer.

### **Conclusion**

BTX-A may work at multiple points in the pathophysiologic cascade of headache. Although the precise mechanisms by which BTX-A relieves head pain are not fully understood, there is emerging evidence from clinical trials and clinical experience throughout the US of BTX-A treatment reducing the frequency and severity of headache symptoms, improving patient quality of life, and reducing the use of acute headache medications. It is increasingly clear that patient selection, BTX-A dosing, injection protocols, and injection techniques are crucial elements of an optimal treatment outcome. Further study of BTX-A in large, randomized, double-blind, placebo-controlled trials in headache patients should help clarify these critical issues.

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**Table 1. BTX-A in the Preventive Treatment of Migraine**

Reference	Population	Dose Range and Technique	Primary Outcome Measure	Secondary Outcome Measure
Silberstein et al, <i>Headache</i> , 2000	Migraine n = 123	Placebo, 25 U, 75 U Fixed-site	(+) Frequency (25 U)	(+) Intensity (25 U)
Relja et al, <i>Neurology</i> , 2003	Migraine n = 32	Placebo vs 100 U Fixed-site	(+) MIDAS	(+) Med use, (+) cost, (-) HA-free days
Barrientos et al, <i>Headache Pain</i> , 2003	Migraine n = 30	Placebo vs 50 U Fixed-site	(+) Frequency Monthly	(+) Duration, (+) acute meds
Schwaag et al, <i>Cephalalgia</i> , 2003	Migraine n = 60	Placebo, 16 U + saline, 100 U Fixed-site	(-) Frequency	(-) Response rate, (-) migraine days, (-) severe migraine days, (-) # of acute meds
Cady, <i>Cephalalgia</i> , 2004	Migraine n = 57	Placebo vs 139 U Fixed-site	(+) HIT-6 (-) MIDAS	(+) Intensity, (+) patient satisfaction
Ondo et al, <i>Cephalalgia</i> , 2004	CDH n = 60	Placebo vs 200 U Combination	(+) HA-free days	(+) Global impressions, (+) abortive meds, (-) tenderness

HA=headache.

HIT-6=Headache Impact Test 6.

MIDAS=Migraine Disability Assessment Scale.

**Table 2. Patient Selection for BTX-A Preventive Headache Treatment**

- Disabling primary headaches according to IHS criteria
- Refractory to conventional treatments
- Patients experiencing unacceptable side effects (from existing treatment)
- Contraindicated to standard preventive treatments
- Special populations or situations (the elderly, those at risk of unacceptable side effects from trial drugs or traditional treatments, airplane pilots, students studying and preparing for examinations)
- Where there is a risk of misuse or abuse of medications
- ✗ Patients with coexistent jaw, head, or neck muscle spasm
- Patient preference

Adapted from Blumenfeld et al, 2003

**Table 3. BTX-A Injection Protocols**

<b>Protocol</b>	<b>Clinical Application</b>
Fixed-site	Migraine or migrainous headache
Follow-the-pain	TTH
Follow-the-muscles-of-mastication	Temporomandibular disease
Follow-the-dystonia	CD

**Table 4. Fixed-Site BTX-A Injection Protocol**

<b>Muscle</b>	<b>BTX-A Units Injected/ Number of Sites Injected</b>
Procerus	5 1 site
Medial corrugator	2.5-4 2 sites (1 per side)
Lateral corrugator	2.5 2 sites (1 per side)
Frontalis	2.5 per site 4-6 sites per side
Temporalis	2.5-5 4 sites
Suboccipital area	5 (optional) 1-2 sites
Trapezius	15-25 3 sites
Total injection sites	20
BTX-A concentration	100 U/4 mL

**Table 5. Follow-the-Pain BTX-A Injection Protocol**

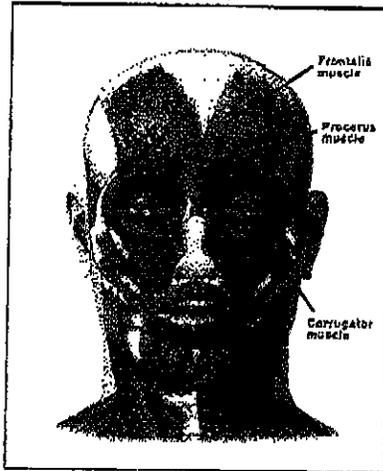
<b>Muscle</b>	<b>Number of Sites Injected</b>
Splenius capitis	1 site
Semispinalis capitis	1 site
Occipitalis	1-2 sites
Sternocleidomastoid	2 sites
Temporalis	4 sites
Frontalis	4-5 sites
BTX-A concentration	100 U/4 mL
Dose at each site	5-10 U per site
Total dose	65-100 U

**Table 6. Patients Typically Deemed Appropriate by Insurers for BTX-A Preventive Treatment of Headache**

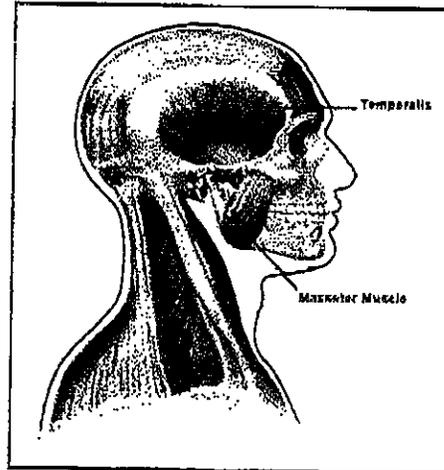
- Intractable migraine headaches at least twice a month
- Chronic daily headaches of 15 headache days per month
- Headache causing disability lasting three or more days
- 3 or more failed trials of at least 3 preventive pharmacologic migraine therapies with or without concomitant behavioral and physical therapies
- Abortive medications are required more than twice a week.
- Abortive medications are contraindicated due to coexisting medical conditions
- Failed trials of abortives after titration to maximal tolerated doses

**Fig 1. Injection sites for BTX-A treatment. Copyright © 2003. Nucleus Medical Art, All Rights Reserved. [www.nucleusinc.com](http://www.nucleusinc.com)**

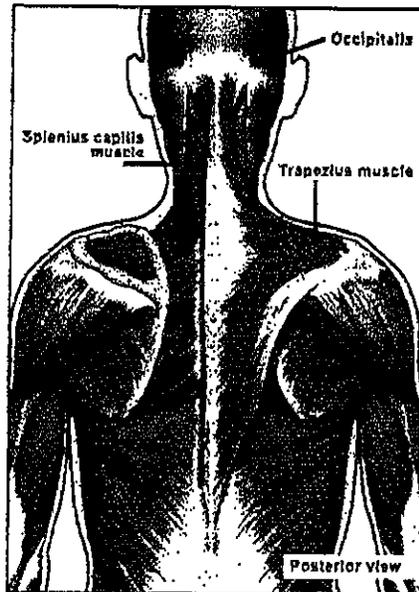
**Injection Sites: Glabellar and Frontal Regions**



**Injection Sites: Temporalis and Masseter Muscles**



**Injection Sites: Occipital, Splenius Capitis, and Trapezius Muscles**



## Views and Perspectives

### Procedures for Administering Botulinum Toxin Type A for Migraine and Tension-type Headache

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Andrew Blitzer, MD

**Key words:** botulinum toxin type A, migraine, tension-type headache

**Abbreviations:** BoNT-A botulinum toxin type A, TTH tension-type headache  
(*Headache* 2003;43:884-891)

Headache can be debilitating, causing lost productivity at work or school, impaired quality of life, and disruptions in family and social life.<sup>1,2</sup> The limited clinical efficacy of current preventive therapies for headache, coupled with the substantial side effects of these treatments, indicate that headache prevention is an area of unmet medical need. Botulinum toxin type A (BoNT-A) is used to treat a variety of overactive muscle and pain disorders.<sup>3-5</sup> Intramuscular injections of BoNT-A may provide an effective, long-lasting, and well-tolerated new approach to headache prevention and management for selected patients.

Investigators have used injection techniques with differing anatomical injection sites, doses, and concentrations of BoNT-A. The method of administering BoNT-A for headache therapy will determine, in part, the overall clinical outcome. Optimizing the protocol for clinical use of BoNT-A is, therefore, likely to improve the outcomes of therapy. This article provides a review of current practical procedures for adminis-

tering BoNT-A therapy to patients with migraine and tension-type headache (TTH).

#### BACKGROUND

Botulinum toxin type A is approved for the treatment of a variety of conditions and pain disorders caused by muscle overactivity.<sup>3-6</sup> Initial serendipitous findings of a therapeutic effect of BoNT-A on migraine when it was used to treat patients for facial wrinkles were followed by a number of clinical studies in patients with headache.<sup>4</sup> These studies have suggested that BoNT-A is effective at reducing both migraine and TTH.<sup>5-11</sup> Exactly why BoNT-A is effective in relieving headache is not clear, but mechanisms of action include direct effects at the neuromuscular junction and direct antinociceptive effects on nerves in the face, head, and neck.<sup>12</sup> The designs of published trials range from small case studies to larger, double-blind, placebo-controlled trials, spanning the level of evidence from A to C, according to evidence-based medical standards. These studies have recently been critically evaluated according to evidence-based criteria.<sup>12,13</sup> While all of these studies have shown BoNT-A therapy to be safe and well-tolerated, the efficacy outcomes within the studies have not been consistent, and the conclusions drawn from the evidence-based reviews have also differed.<sup>12,13</sup>

There is no established or standardized methodology for the injection of BoNT-A for migraine and TTH. Inconsistencies in the way BoNT-A was administered across studies may contribute to variations in the

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clinical study outcomes. Several studies used a fixed-site approach,<sup>8,14,15</sup> while others reported methodologies that were dependent on the anatomical location and distribution of the pain,<sup>16-18</sup> or a combination of the 2 approaches.<sup>19</sup> Other factors such as volume per injection site, number of injection sites per area, the dilution of BoNT-A, and the injection technique vary across studies and have not been consistently reported. In their critical review of the use of BoNT-A therapy for headache, Mathew and Kaup suggest that factors such as injection procedures, selection of appropriate injection sites, and BoNT-A doses play a role in the clinical efficacy outcomes.<sup>12</sup> This finding is supported by the clinical experience of the authors of this article.

As more clinicians involved in the care of patients with disabling headache disorders consider BoNT-A as a potential treatment, there is an increasing need for a standardized protocol for drug administration. We present here a review of the administration of BoNT-A for the treatment of headache, based on our own extensive clinical experience and that of other investigators.

## METHODS

**Considerations for Preventive Headache Therapy.**—Selection of appropriate candidates for preventive therapy begins with accurate diagnosis and classification. This is based on a comprehensive headache history to rule out secondary headaches resulting from other causes such as tumor, infection, metabolic disorders, or other systemic illness. A medical history, including information on medications used and any prior plastic surgery, must be obtained before treatment. The overall goal of headache prevention is to help the patient to achieve the goals set forth by the US Headache Consortium; namely, to reduce headache frequency, severity, and disability, and improve the quality of life by reducing headache-related distress and symptoms.<sup>20</sup> Specifically, physicians can assess the success of preventive therapy based on the decreased frequency and intensity of headache, improved functioning and decreased disability, reduced use of other headache medications, as well as the increased efficacy of acute headache medications. Nonpharmacologic approaches for managing headache disorders, including exercise and dietary

adjustment, continue to play an important role in headache management.<sup>21</sup>

Patients who are most likely to benefit from preventive therapy include those with recurring migraines that, in the patient's opinion, significantly interfere with their daily routine despite acute treatment; with frequent headaches; concerned about the high cost of acute therapies; with extant uncommon migraine conditions including hemiplegic migraine, basilar migraine, migraine with prolonged aura, or migrainous infarction; and who overuse, cannot tolerate, or poorly comply with acute treatment.

Specifically, BoNT-A therapy may be appropriate for patients with disabling primary headaches for whom other preventive medications are poorly tolerated or contraindicated, for those with compliance problems, for those refractory to other treatments, for special patient populations, as well as for those who simply prefer this treatment (Table 1). In addition, patients with headache and jaw, neck, or head muscle spasms should be considered candidates for treatment with BoNT-A.<sup>22</sup>

Contraindications to the use of BoNT-A include sensitivity to toxin or neuromuscular disorders such as myasthenia gravis or Eaton-Lambert syndrome.

**Pretreatment Considerations.**—Physicians should review the known side effects of BoNT-A treatment, including possible headache, rash, bruising, or

Table 1.—Candidates for Botulinum Toxin Type A Therapy for Headache

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| <ul style="list-style-type: none"> <li>• Patients with disabling primary headaches</li> <li>• Patients who have failed to respond adequately to conventional treatments</li> <li>• Patients with unacceptable side effects (from existing treatment)</li> <li>• Patients in whom standard preventive treatments are contraindicated</li> <li>• Patients in special populations or situations (the elderly, those at risk of unacceptable side effects from trial drugs or traditional treatments, airplane pilots, students studying and preparing for examinations)</li> <li>• Patients misusing or abusing or overusing medications</li> <li>• Patients with coexistent jaw, head, or neck muscle spasm</li> <li>• Patients who prefer this treatment</li> <li>• Patients with disabling primary headaches</li> <li>• Patients who have failed to respond adequately to conventional treatments</li> </ul> |
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eyebrow and eyelid ptosis, with the patient and obtain informed consent. Patients should also be told that multiple treatment cycles may be needed to achieve an optimal therapeutic effect.<sup>19</sup> Have patients indicate the principal sites of their head pain, pointing to the anatomical locations most frequently affected. Examine the face and neck to assess muscle tone, asymmetry, and brow position. Palpate the frontalis, temporalis, and posterolateral neck and shoulder regions to identify areas of tenderness and anatomical sites that produce pain on palpation. Patients can be placed either in a sitting or supine position for injection of the frontal and temporal regions and in a sitting position for injection of the posterior neck region and trapezius.

The total dose of BoNT-A to be administered should be individualized by taking into account the specific features of each patient, including type of headache, severity of symptoms, and body size. One study demonstrated clinical efficacy with a total dose of 25 units (U);<sup>8</sup> however, studies that are more recent suggest that higher doses are needed to secure more consistent efficacy.<sup>13</sup>

**Dilution and Reconstitution Procedures.**—Two BoNT-A complexes (Botox and Dysport) and one type B complex (Myobloc) are approved for clinical use. These 3 products have different dosing, safety, and efficacy characteristics. There are no established methodologies to calculate equivalent doses.<sup>3</sup>

Only one type A toxin is available in the United States. Lyophilized BoNT-A (Botox, Allergan, Inc, Irvine, CA) is available in vials containing 100 U of BoNT-A. One vial is diluted with 2 or 4 mL of preservative-free 0.9% saline, which yields a preparation of 5.0 or 2.5 U per 0.1 mL, respectively.

**Injection Technique.**—Sterile injection technique should be observed for the entire procedure. Injections should be intramuscular; avoid injecting the periosteum and injecting intradermally in order to minimize discomfort and the risk of intra-arterial injection. Inject symmetrically in the frontalis region to avoid facial asymmetry. Visualization and avoidance of the superficial blood vessels helps to minimize risk of bruising. If pain is not present in the inferolateral frontalis regions (lateral suprabrow areas), avoid injection there to reduce the risk of brow ptosis.

**Injection Sites and Procedures.**—The entire anatomical area affected by pain should be injected with sufficient amounts of toxin in adequate volume to maximize clinical effect (unpublished observations). The injection sites commonly used for BoNT-A treatment of headache are the glabellar and frontal regions, the temporalis muscle, the occipitalis muscle, and the cervical paraspinal region.<sup>4,5,7-10,16,17,23</sup>

**Protocols for Injection.**—There are 3 injection protocols commonly used. The overall objective is to inject toxin at multiple sites to ensure complete dispersal of toxin through the target regions. These protocols can be described as a “fixed-site” approach, a “follow-the-pain” approach, and a “combination” approach.

The fixed-site method is often used for patients with migraine or migrainous headache. This approach is based on clinical experience and uses fixed symmetrical injection sites and a range of predetermined doses. Patients treated for unilateral headaches with a unilateral injection may develop headaches on the opposite, untreated side. In 2 studies that utilized a fixed-site approach, one in patients with chronic TTH and the other in patients with migraine, headache symptoms improved significantly more in patients receiving injections of BoNT-A than in patients receiving placebo.<sup>6,23</sup> Using a modification of the fixed-site approach (Table 2), we recently obtained a marked reduction in the use of additional oral headache medications in 37 of 50 patients with migraine.<sup>24</sup>

The follow-the-pain approach is most often used to treat TTH. The sites and doses are adjusted depending on the patient's symptom profile and the location of pain and tenderness. Assess head and neck position, muscle bulk, tender spots, and temporomandibular joint function. The muscles selected for injection in the posterior neck are similar to those injected in patients experiencing pain associated with cervical dystonia. The injection sites are determined by where the patient feels pain and where the examiner can elicit pain and tenderness on palpation of the muscle. A follow-the-pain approach is suitable where torticollis is not present. Subtle torticollis can be a cause of head and neck pain, particularly anterocollis with posterior neck pain (often caused by overactive sternocleidomastoid muscles) or lateral collis (often caused by overactive splenius capitis, sternocleidomastoid, levator scapulae,

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Table 2.—Variations of the Fixed-Site Approach to Botulinum Toxin Type A Injection\*

Muscle	Source, No. of Botulinum Toxin Type A Units Injected, No. of Sites Injected		
	Blumenfeld, 2002 <sup>14</sup>	Silberstein et al, 2000 <sup>8</sup>	Smuts et al, 1999 <sup>23</sup>
Procerus	5	3 or 9, 1 site	—
Medial corrugator	2.5-4	1.5 or 4.5, 4 sites of medial and lateral muscles	—
Lateral corrugator	2.5	1.5 or 4.5, 4 sites of medial and lateral muscles	—
Frontalis	2.5 per site, 4-6 sites per side	2.5 or 7.5 per site, 4 sites	—
Temporalis	2.5-5, 4 sites	3 or 9, 2 sites	9, 2 sites
Suboccipital area	5 (optional)	—	7, 2 sites
Trapezius	15-25, 3 sites	—	9, 2 sites
Botulinum toxin type A concentration	100 U/4 mL	Not reported	100 U/2 mL
Total injection sites	25	11	12

\*All injections were performed bilaterally, with the exception of those in the procerus muscle. —Indicates site was not injected.

or trapezius muscles with pain on the contralateral side). For patients with torticollis, injections must be into overactive muscles, since weakening contralateral muscle groups with botulinum toxin injections could worsen the pain. Botulinum toxin type A injection protocols for patients with torticollis have been reviewed elsewhere.<sup>25</sup>

Bilateral symmetrical frontalis injections help to maintain visible facial symmetry. Elsewhere, injec-

tions, when bilateral, need not be symmetrical. The total dose of BoNT-A ranges from 100 to 150 U. Muscles typically injected for TTH include the frontalis, temporalis, occipitalis, splenius capitis, trapezius, and cervical paraspinal muscles, although the use of a range of muscle sites and doses has been reported in the literature.<sup>7,14,16-18</sup> Table 3 summarizes reported variations in this technique. The patient's clinical response to treatment is used to adjust subsequent doses.

Table 3.—Variations of the Follow-the-Pain Approach to Botulinum Toxin Type A Injection in Patients With Tension-type Headache\*

Muscle	Blumenfeld, 2002 <sup>14</sup>	Relja, 1997 <sup>16</sup>	Wheeler, 1998 <sup>18</sup>	Relja and Korsic, 1999 <sup>17</sup>	Freund and Schwartz, 2000 <sup>7</sup>
Trapezius	2-3 sites	—	X	—	X
Splenius capitis	1 site	—	X	—	X
Semispinalis capitis	1 site	—	—	—	X
Occipitalis	1-2 sites	—	—	—	—
Sternocleidomastoid	2 sites	X	—	X	—
Temporalis	4 sites	X	X	X	—
Frontalis	4-5 sites	X	X	X	—
Corrugators	—	—	X	—	—
Rectus capitis	—	—	—	—	X
Botulinum toxin type A concentration	100 U/4 mL	NR	NR	NR	100 U/1 mL
Dose at each site or	5-10 per site	NR	NR	NR	NR
Total dose, U	65-100	15-35	197	35-80	100

\*—Indicates site not injected; X, muscle injected but number of sites not provided; NR, not reported.

Patients often have coexisting migraine and TTH. In these cases, a combination of the fixed-site and follow-the-pain approaches is used. These patients generally receive higher doses of BoNT-A. The fixed-site approach is supplemented with additional injections of BoNT-A in areas that are tender or consistently symptomatic (or a combination of both).

**Anatomical Considerations—GLABELLAR AREA.**—This area consists of the procerus (a midline muscle) and the corrugator muscles. In the glabellar area, smaller fluid volumes (ie, 0.1 mL) per injection will minimize spread to adjacent muscles. In addition, precise placement of small volumes with slow injection of the toxin is important to prevent dispersion of the toxin. Approximately 12.5 to 20 U are given in the glabellar area at 5 injection sites, 1 in the procerus and 2 in each corrugator (Figure 1).

**PROCERUS MUSCLE.**—The procerus is a triangular muscle between the frontalis muscles. Its apex extends to the bridge of the nose, while its base

sits above the brows. Injections of approximately 2.5 to 5 U should be made in the base of this muscle (Figure 1).

**CORRUGATOR MUSCLE.**—To identify injection sites for the corrugator muscles, have the patient frown. The medial aspect of the corrugator muscle corresponds to where the supratrochlear nerve exits from its foramen. The mid-to-lateral aspect of the corrugator muscle injection site corresponds to the supraorbital nerve course. Direct pressure at the border of the supraorbital ridge can reduce the potential for extravasation of BoNT-A downward into the eyelid and avoid inadvertent weakening of the levator muscle of the upper eyelid and ptosis. By grasping the mid-to-lateral portion of the corrugator muscle between 2 fingers, the deposition of BoNT-A into this area can be more precisely delivered. Eyelid ptosis rarely occurs when proper injection technique is used. Sites and doses are shown in Figure 1 and Table 2.

**FRONTALIS MUSCLE.**—In sites such as the forehead and temporal regions, greater dispersion of the toxin with larger volumes is preferred. In the area of the forehead, the dosage and number of injections may range from 20 to 30 U dispersed among 8 to 12 injection sites. Assess the location of the frontalis muscle by having the patient elevate his or her eyebrows prior to injection. This helps to identify areas where needle placement will occur. Injection of the lower third of the frontalis muscle with BoNT-A will inhibit the patient's ability to raise the brows. To avoid brow ptosis, avoid injecting the area of the forehead over the lateral aspect of the brow. This is the area between the brow and an oblique line drawn from the medial eyebrow to a point approximately 1 cm above the lateral portion of the eyebrow (Figure 1). If this area does require injection, brow ptosis can be reduced by injecting the lateral aspect of the infrabrow or eyelid area to reduce the downward pull of the lateral orbicularis oculi muscle.

The area directly lateral to the brow is the anterior temporal region or "temple" (Figure 2). If the patient has pain in this area, it can be injected with an additional 2.5 U. If pain is present over the lateral supraorbital region and injection is required, patients should be informed that brow ptosis might occur. Most patients are able to adapt well to a lowering effect of the

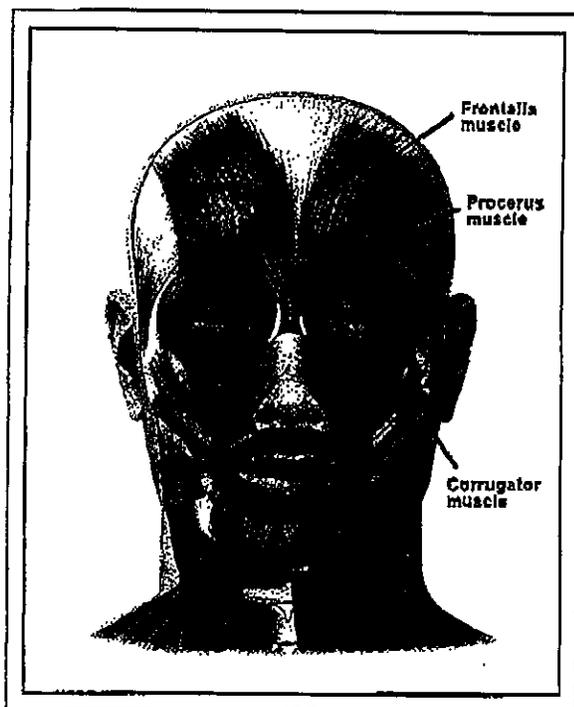


Fig 1.—Injection sites for botulinum toxin type A in the treatment of headache: glabellar and frontal regions. Copyright (c) 2003 Nucleus Medical Art, All rights reserved. [www.nucleusinc.com](http://www.nucleusinc.com)

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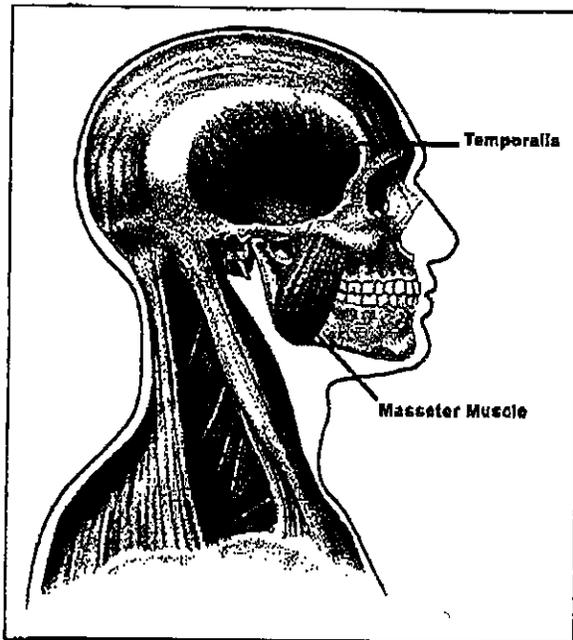


Fig 2.—Injection sites for botulinum toxin type A in the treatment of headache: temporalis, masseter, and suboccipital regions. Copyright (c) 2003 Nucleus Medical Art, All rights reserved. [www.nucleusinc.com](http://www.nucleusinc.com)

lateral part of the brow without significant problems if this area requires injection.

**TEMPORALIS MUSCLE.**—The temporal area, like the frontal area of the forehead, should be injected bilaterally. Having the patients clench their teeth can identify the anterior aspect of the temporalis muscle. This produces an identifiable impulse that can be visualized or palpated. The posterior, superior, and inferior aspects of the temporalis muscle can also be injected (Figure 2). We usually inject approximately 0.2 mL per site (5 U) in 4 sites, providing an average dose of 20 U per temporalis muscle. Because of the large size of this muscle, if needed, a larger volume per site can easily be injected without affecting adjacent muscles.

**OTHER MUSCLES.**—If the patient has posterior neck pain, then the occipital or cervical paraspinal areas should be evaluated (Figure 3). Pain may be present in the occipital area but more typically is located in the cervical paraspinal area, below the nuchal ridge, where the trapezius, splenius capitis, and semispinalis capitis converge. It is not necessary to differentiate the specific muscles injected. Rather, the

areas associated with pain and tenderness on palpation, typically in the region of the splenius capitis, should be injected. Inject 1 or 2 sites on each side with the total dose varying between 5 to 15 U per side (Figure 3). If there is involvement of the trapezius, this area should also be injected (1 to 3 sites per side; dose varying between 5 to 15 additional U). Masseter muscles should be injected in patients with features of temporomandibular disorder. These patients typically respond to 5 to 15 U per side for masseters, combined with injections to temporalis muscles as described above. In patients with torticollis, the overactive muscles should be injected (eg, sternocleidomastoid muscles in patients with anterocollis).

**Side Effects.**—The side effects of BoNT-A injections are minimal and have been described in detail elsewhere.<sup>26,27-29</sup> No systemic reactions have been noted in studies of BoNT-A therapy for headache.

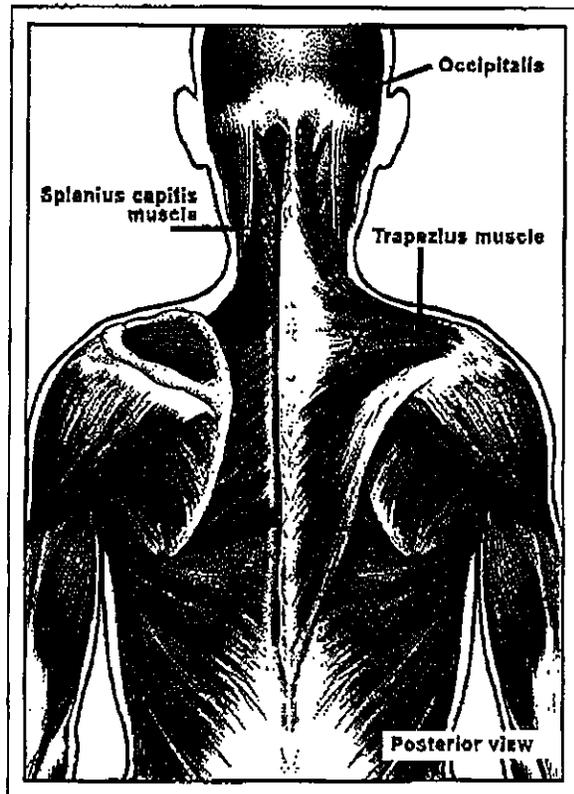


Fig 3.—Injection site for botulinum toxin type A in the treatment of headache: occipitalis muscle. Copyright (c) 2003 Nucleus Medical Art, All rights reserved. [www.nucleusinc.com](http://www.nucleusinc.com)

Silberstein et al reported that treatment-related adverse events were transient and included blepharoptosis, diplopia, and muscle weakness at the injection sites.<sup>8</sup> Furthermore, as described above, minor side effects can be minimized through injection technique.

**Postinjection Patient Management.**—Patients should be reassured that any wheals or blebs at the injection site, particularly on the forehead, will disappear within approximately 2 hours. Patients should also be prepared for the reduction in hyperfunctional lines of the face. The effect on the dynamic, hyperfunctional lines of facial expression may take several days. The headache relief produced by BoNT-A may take several weeks to reach its maximal benefit. The response to injection may change over time; with repeated injections, some patients report a greater therapeutic effect.<sup>12</sup>

Patients should be evaluated 4 to 6 weeks after the first injection. Patients still need acute medications for breakthrough headaches. They should be instructed to maintain a headache diary in order to document the frequency, location, and severity of headache, and the amount of medication taken over a full 4-month period from the start of therapy. The headache diaries provide an extremely important objective measure for determining the effectiveness of treatment and directing future treatment. The need for repeat treatments varies among patients, but typically will be at 3 to 4 months.

## CONCLUSION

The mechanisms by which BoNT-A relieves head pain are not fully understood. However, despite the ambiguity regarding specific mechanisms of action of BoNT-A in headache, empiric evidence and results of clinical investigations suggest that BoNT-A is a promising treatment option for selected patients with headache. Based on the collective experience of investigators, a successful paradigm for the use of botulinum toxin therapy in the treatment of headache is emerging. Preliminary clinical evidence and the aggregate experience with the application of BoNT-A therapy to a variety of disorders in the fields of neurology, facial plastic and reconstructive surgery, and otolaryngology support the idea that selected patients with migraine and TTH can achieve a sustained, well-tolerated, and effective response to BoNT-A therapy. Further clinical

experience and controlled investigations will help to refine the technique for administering BoNT-A therapy for specific patient types and clinical disorders.

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## \* BOTOX<sup>®</sup> Anecdote

**Martin K. Childers, DO**

Many clinician first beginning to use BOTOX<sup>®</sup> in the treatment of pain syndromes find that the use of this emerging treatment in their practice attracts new, unexpected patients to the clinic. For example, many individuals develop painful spasticity (spasms of muscle) in the upper limb following a stroke. The typical scenario is the patient who presents to the pain management specialist with a "fisted hand" syndrome, which often remains problematic for even the most skilled clinician. In this painful condition, flexor muscles of the fingers and wrist contract involuntarily, causing skin problems of the palm, and eventually contribute to contractures.

In my practice, I have successfully treated the painful fisted hand with BOTOX<sup>®</sup> injections, a long-acting neuromuscular blocking agent.

The difficulty for new BOTOX<sup>®</sup> injectors is in locating the correct muscles to treat, and in finding the optimal site to inject. In my

opinion, audio EMG or motor point localization should be used for this purpose. However, not every clinician is skilled or comfortable using such equipment.

When I was lecturing in Sweden, a physiotherapist demonstrated a alternative method to find motor points in surface muscles (like the finger flexors) easily and quickly:

A TENS unit can be used to localize the surface motor point over a muscle quite easily: attach one surface electrode onto the patient's skin, and the other electrode on the back of your own hand. Use a little electrode gel or water and gently run your index finger over the surface of the skin overlying the muscle of interest. Adjust the intensity of the TENS unit until you can actually feel the current beneath your finger, then, decrease the stimulus intensity until you no longer can feel any current except for one point on the skin. This point will correspond to the motor point found using the more traditional technique. If you like, you can verify this by increasing the TENS intensity high enough to elicit a muscle contraction over the tip of your finger!

**SPPM Note:** For more in depth information, please refer to the recent publication written by Dr. Childers, Use of Botulinum Toxin Type A in Pain Management A synopsis is on the book page of this web site. A review will be forthcoming.

## • **Botox Injections for TMJ**

Temporomandibular joint disorder, TMJ, affects approximately 10% of the population in the United States. This painful disease causes pain around the ears, headaches, and often neck pain. Orthotic mouthpieces to prevent grinding of the jaw and teeth, medication, such as antidepressants, and physical therapy are the standard treatment. A nerve block of the temporomandibular joint is often efficacious in relieving this painful condition.

In a recent study with 46 patients, Dr. Brian Freund and Dr. Marvin Schwartz have confirmed that injection of purified Botulinum toxin (Botox) is effective in treating TMJ cases that are resistant to other forms of treatment. "The Botox injections produced a statistically significant improvement in all five measured outcomes-pain, function, mouth opening, tenderness to palpation and bite force," states Dr. Freund. *Institute for Head and Neck Therapy, Pickering, Ont., Oct. 19, 1998.*

Special Note: Lectures on the medical use of Botulinum Toxin are given at the SPPM meetings. For more information visit the meeting page

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Continuing Dental Education Transcript

182262 Previous AGD/ADA # 163900246 Member Since: 5/1/1989  
 Mark J. Escoto, DDS Status: Pre-Fellow  
 2471 Professional Ct Passed Exam:  
 Ste 101 MAGD Accrual Date: 07/22/1997  
 Las Vegas, NV 89128-0830 PostGrad Work:

Current Maintenance Period: 06/01/2004 - 05/31/2007  
 Maintenance Credits Required: 75  
 Current Maintenance Credits: 148  
 Maintenance Credits Needed: 0  
 Current Grace Period:  
 Grace Period Credits Required:  
 Grace Period Credits:  
 Grace Period Credits Needed:

Date of Activity	Program ID#	Provider Organization Name	Subject / Discipline Code Description	Delivery Mode	Verify Code	Approved Hours	Maint. Hrs.
03/29/2006	210303	Straumann USA, LLC	690 Implants	Lecture		2.00	2.00
01/07/2006	218831	Meridian Center of Keller Laboratories,	180 Myofascial Pain Dysfunction/Occlusion	Lecture		7.00	7.00
01/23/2005	208518	Straight Wire Orthodontic Studies	370 Orthodontics	Participation		3.00	3.00
07/2005	208518	Straight Wire Orthodontic Studies	370 Orthodontics	Lecture		22.00	22.00
07/09/2005	301313	EODO	370 Orthodontics	Participation		5.00	5.00
01/09/2005	208518	Straight Wire Orthodontic Studies	370 Orthodontics	Lecture		28.00	28.00
12/05/2004	208518	Straight Wire Orthodontic Studies	370 Orthodontics	Participation		3.00	3.00
12/05/2004	208518	Straight Wire Orthodontic Studies	370 Orthodontics	Lecture		22.00	22.00
10/23/2004	208518	Straight Wire Orthodontic Studies	373 Interceptive Orthodontics	Participation		2.00	2.00
10/23/2004	208518	Straight Wire Orthodontic Studies	370 Orthodontics	Lecture		12.25	12.25
10/16/2004	219258	NV Dental Association	180 Myofascial Pain Dysfunction/Occlusion	Participation		12.50	12.50
09/12/2004	301313	EODO	376 Functional Orthodontics	Participation		2.00	2.00
09/12/2004	208239	Discus Dental Impressions	376 Functional Orthodontics	Lecture		19.50	19.50
08/12/2004	218534	Academy of Laser Dentistry	135 Laser Therapy / Electrosurgery	Lecture		6.00	6.00
06/12/2004	218534	Academy of Laser Dentistry	135 Laser Therapy / Electrosurgery	Participation		2.00	2.00
05/01/2004	301313	EODO	138 Dental Photography	Participation		2.00	2.00
05/01/2004	218534	Academy of Laser Dentistry	138 Dental Photography	Lecture		18.00	18.00
02/08/2004	216102	Army-Fitzsimons Dentac	014 Biochemistry	Lecture		0.00 * P	4.00

- Exclusion Codes**
- G Non-approved post-graduate program
  - P Program Provider not approved
  - V Duplicate - credit given elsewhere
  - X CPE issue expired

5/12/2006

Mark J. Escoto, DDS

182262

(ADA #) 163900246

Date of Activity	Program ID#	Program Provider Organization Name	Subject / Discipline Code Description	Delivery Mode	Verify Code	Approved Hours	Maint. Hrs.
06/22/2003	218833	Dr O' - Expert Resources, Inc	731 Radiology	Participation		4.00	4.00
06/22/2003	218833	Dr O' - Expert Resources, Inc	731 Radiology	Lecture		4.00	4.00
05/24/2003	218833	Dr O' - Expert Resources, Inc	376 Functional Orthodontics	Participation		4.00	4.00
05/24/2003	218833	Dr O' - Expert Resources, Inc	376 Functional Orthodontics	Lecture		4.00	4.00
04/26/2003	218833	Dr O' - Expert Resources, Inc	185 Appliance Therapy	Participation		4.00	4.00
04/26/2003	218833	Dr O' - Expert Resources, Inc	185 Appliance Therapy	Lecture		4.00	4.00
02/23/2002	208239	Discus Dental Impressions	780 Esthetics	Lecture		4.50	4.50
02/23/2002	208239	Discus Dental Impressions	550 Practice Management	Lecture		3.50	3.50
02/18/2002	218833	Dr O' - Expert Resources, Inc	376 Functional Orthodontics	Participation		4.00	4.00
02/18/2002	218833	Dr O' - Expert Resources, Inc	376 Functional Orthodontics	Lecture		4.00	4.00
11/19/2001	218833	Dr O' - Expert Resources, Inc	183 Occlusal Management	Lecture		2.00	2.00
11/19/2001	218833	Dr O' - Expert Resources, Inc	183 Occlusal Management	Participation		2.00	2.00
11/19/2001	218833	Dr O' - Expert Resources, Inc	370 Orthodontics	Participation		2.00	2.00
11/19/2001	218833	Dr O' - Expert Resources, Inc	370 Orthodontics	Lecture		2.00	2.00
01/19/2001	218642	BIOLASE TECHNOLOGY, INC	135 Laser Therapy / Electrosurgery	Lecture		6.00	6.00
02/05/2000	208518	Straight Wire Orthodontic Studies	182 TM Disorders	Lecture		6.00	6.00
08/1999	218833	Dr O' - Expert Resources, Inc	182 TM Disorders	Participation		8.00	8.00
12/18/1999	218833	Dr O' - Expert Resources, Inc	149 Multi-Disciplinary Topics	Lecture		8.00	8.00
10/09/1999	218833	Dr O' - Expert Resources, Inc	182 TM Disorders	Lecture		16.00	16.00
06/26/1999	218833	Dr O' - Expert Resources, Inc	182 TM Disorders	Lecture		8.00	8.00
06/26/1999	218833	Dr O' - Expert Resources, Inc	555 Dental Jurisprudence	Lecture		8.00	8.00
05/08/1999	218833	Dr O' - Expert Resources, Inc	555 Dental Jurisprudence	Lecture		16.00	16.00
05/01/1999	208518	Straight Wire Orthodontic Studies	370 Orthodontics	Participation		84.00	84.00
02/13/1999	214683	American Association of Orthodontics	373 Interceptive Orthodontics	Lecture		5.00	5.00
02/13/1999	214683	American Association of Orthodontics	182 TM Disorders	Lecture		5.00	5.00
02/13/1999	214683	American Association of Orthodontics	370 Orthodontics	Lecture		5.00	5.00
01/30/1999	214683	American Association of Orthodontics	370 Orthodontics	Lecture		5.00	5.00
01/30/1999	214683	American Association of Orthodontics	182 TM Disorders	Lecture		5.00	5.00
01/30/1999	214683	American Association of Orthodontics	373 Interceptive Orthodontics	Lecture		5.00	5.00
12/31/1998	218833	Dr O' - Expert Resources, Inc	370 Orthodontics	Lecture		8.00	8.00
12/19/1998	211859	DR ORDEN, ADAM	182 TM Disorders	Participation		0.00 * P	6.00
12/19/1998	218833	Dr O' - Expert Resources, Inc	182 TM Disorders	Lecture		16.00	16.00

Exclusion Codes

- G Non-approved post-graduate program
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- X CLEPART issue expired

5/12/2006

Date of Activity	Program Provider ID#	Organization Name	Subject / Discipline Code	Description	Delivery Mode	Verify Code	Approved Hours	Maint. Hrs.
12/18/1998	211859	DR ORDEN, ADAM	012	Anatomy	Participation		0.00 * P	6.00
12/18/1998	211859	DR ORDEN, ADAM	149	Multi-Disciplinary Topics	Participation		0.00 * P	6.00
11/16/1998	218833	Dr O' - Expert Resources, Inc	182	TM Disorders	Participation		16.00	16.00
11/10/1998	218833	Dr O' - Expert Resources, Inc	731	Radiology	Participation		8.00	8.00
10/17/1998	214683	American Association of Orthodontics	370	Orthodontics	Lecture		5.00	5.00
10/17/1998	214683	American Association of Orthodontics	182	TM Disorders	Lecture		5.00	5.00
10/17/1998	214683	American Association of Orthodontics	373	Interceptive Orthodontics	Lecture		5.00	5.00
10/11/1998	218833	Dr O' - Expert Resources, Inc	376	Functional Orthodontics	Lecture		12.00	12.00
10/11/1998	218833	Dr O' - Expert Resources, Inc	182	TM Disorders	Lecture		12.00	12.00
08/29/1998	214683	American Association of Orthodontics	182	TM Disorders	Lecture		5.00	5.00
08/29/1998	214683	American Association of Orthodontics	373	Interceptive Orthodontics	Lecture		5.00	5.00
08/29/1998	214683	American Association of Orthodontics	370	Orthodontics	Lecture		5.00	5.00
08/23/1998	208518	Straight Wire Orthodontic Studies	730	Oral Medicine, Oral Diagnosis	Participation		14.00	14.00
06/27/1998	218833	Dr O' - Expert Resources, Inc	180	Myofascial Pain Dysfunction/Occlusion	Lecture		8.00	8.00
06/27/1998	218833	Dr O' - Expert Resources, Inc	550	Practice Management	Lecture		8.00	8.00
06/07/1998	210235	Myotronics-Noromed, Inc	690	Implants	Lecture		14.00	14.00
05/1998	210235	Myotronics-Noromed, Inc	670	Prosthodontics-Removable	Lecture		14.00	14.00
11/05/1997	217153	Pride Institute	149	Multi-Disciplinary Topics	Lecture		7.00	7.00
10/19/1997	210235	Myotronics-Noromed, Inc	730	Oral Medicine, Oral Diagnosis	Lecture		18.00	18.00
07/24/1997	217153	Pride Institute	550	Practice Management	Lecture		14.00	14.00
07/22/1997	217153	Pride Institute	149	Multi-Disciplinary Topics	Lecture		21.00	21.00

**CEs counting toward MAGD**

06/22/1997	210235	Myotronics-Noromed, Inc	180	Myofascial Pain Dysfunction/Occlusion	Participation		14.00	14.00
04/24/1997	217153	Pride Institute	550	Practice Management	Lecture		14.00	14.00
04/22/1997	210235	Myotronics-Noromed, Inc	730	Oral Medicine, Oral Diagnosis	Lecture		14.00	14.00
03/28/1997	209717	CNA Healthpro	555	Dental Jurisprudence	Lecture		4.00	4.00
03/22/1997	210235	Myotronics-Noromed, Inc	182	TM Disorders	Lecture		14.00	14.00
03/02/1997	210235	Myotronics-Noromed, Inc	180	Myofascial Pain Dysfunction/Occlusion	Participation		14.00	14.00
02/28/1997	210235	Myotronics-Noromed, Inc	180	Myofascial Pain Dysfunction/Occlusion	Lecture		7.00	7.00

**Exclusion Codes**

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Mark J. Escoto, DDS

182262

(ADA #) 163900246

<u>Date of Activity</u>	<u>Program ID#</u>	<u>Provider Organization Name</u>	<u>Subject / Discipline Code Description</u>	<u>Delivery Mode</u>	<u>Verify Code</u>	<u>Approved Hours</u>	<u>Maint. Hrs.</u>
02/26/1997	217153	Pride Institute	650 Practice Management	Lecture		14.00	14.00
12/16/1996	217153	Pride Institute	550 Practice Management	Lecture		14.00	14.00
08/16/1996	217153	Pride Institute	130 Electives	Lecture		11.00	11.00
05/30/1996	210804	STERI-OSS, INC	692 Reconstructive Phase Therapy	Lecture		2.00	2.00
10/10/1995	214287	American Dental Association	557 Patient Education/Motivation	Lecture		5.00	5.00
05/15/1994	208673	Zimmer Dental	690 Implants	Participation		20.00	20.00
07/30/1993	216555	Midwest Implant Institute	690 Implants	Lecture		16.00	16.00
05/13/1993	214204	Loma Linda University Denal School	610 Prosthodontics - Fixed	Participation		5.00	5.00
04/15/1993	214204	Loma Linda University Denal School	610 Prosthodontics - Fixed	Participation		5.00	5.00
03/11/1993	214204	Loma Linda University Denal School	610 Prosthodontics - Fixed	Participation		5.00	5.00
02/11/1993	214204	Loma Linda University Denal School	610 Prosthodontics - Fixed	Participation		5.00	5.00
01/14/1993	214204	Loma Linda University Denal School	610 Prosthodontics - Fixed	Participation		5.00	5.00
12/09/1992	214204	Loma Linda University Denal School	610 Prosthodontics - Fixed	Participation		5.00	5.00
11/12/1992	214204	Loma Linda University Denal School	610 Prosthodontics - Fixed	Participation		5.00	5.00
10/21/1992	214204	Loma Linda University Denal School	610 Prosthodontics - Fixed	Participation		5.00	5.00
02/1992	209977	SCRIPPS IMPL DENT ED/RES CTR	492 Soft Tissue Surgery	Lecture		84.00	84.00
02/16/1992	219290	AGD, CA	610 Prosthodontics - Fixed	Lecture		8.00	8.00
02/16/1992	219290	AGD, CA	550 Practice Management	Lecture		2.00	2.00
02/16/1992	219290	AGD, CA	490 Periodontics	Lecture		10.00	10.00
02/16/1992	219290	AGD, CA	310 Oral and Maxillofacial Surgery	Lecture		41.00	41.00
02/16/1992	219290	AGD, CA	180 Myofascial Pain Dysfunction/Occlusion	Lecture		6.00	6.00
02/16/1992	219290	AGD, CA	130 Electives	Lecture		6.00	6.00
02/16/1992	219290	AGD, CA	070 Endodontics	Lecture		2.00	2.00
02/16/1992	219290	AGD, CA	010 Basic Science	Lecture		40.00	40.00
02/16/1992	219290	AGD, CA	730 Oral Medicine, Oral Diagnosis	Lecture		36.00	36.00
02/16/1992	219290	AGD, CA	670 Prosthodontics-Removable	Lecture		9.00	9.00
10/23/1991	212136	San Diego County Dent Society	780 Esthetics	Lecture		6.00	6.00
08/29/1991	212136	San Diego County Dent Society	250 Operative Dentistry	Lecture		6.00	6.00
06/28/1991	212136	San Diego County Dent Society	690 Implants	Lecture		6.00	6.00
03/27/1991	212136	San Diego County Dent Society	690 Implants	Lecture		6.00	6.00

## Exclusion Codes

- G Non-approved post-graduate program
- P Program Provider not approved
- Placeholder - credit given elsewhere
- X DART issue expired

5/12/2006

Mark J. Escoto, DDS

182262

(ADA #) 163900246

<u>Date of Activity</u>	<u>Program ID#</u>	<u>Provider Organization Name</u>	<u>Subject / Discipline Code</u>	<u>Description</u>	<u>Delivery Made</u>	<u>Verify Code</u>	<u>Approved Hours</u>	<u>Maint. Hrs.</u>
03/06/1991	220322	WESTERN GNATH ST CL	690	Implants	Lecture		0.00 * P	3.00
02/13/1991	212136	San Diego County Dent Society	016	Pharmacotherapeutics	Lecture		6.00	6.00
02/12/1991	213686	PAUL REVERE ST CL-CA	253	Tooth-Colored Restorations	Lecture		2.00	2.00
02/03/1991	218203	INTERPORE INTL	690	Implants	Lecture		0.00 * P	14.00
05/16/1990	216209	Navy	250	Operative Dentistry	Lecture		2.00	2.00

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5/12/2006

Mark J. Escoto, DDS

182262

(ADA #) 163900246

**FAGD SUMMARY OF TRANSCRIPT**

<u>DELIVERY</u>	<u>HOURS EARNED</u>	<u>MAX ALLOWED</u>	<u>USABLE HOURS</u>
EXAM STUDY GUIDE	0.00	25	0.00*
LECTURE	414.00	—	414.00*
MILITARY ROTATION	0.00	200	0.00*
PARTICIPATION	88.00	—	88.00*
POSTGRAD	0.00	250	0.00*
SELF INSTRUCTION	0.00	150	0.00*
TEACHING_PUBLICATION	0.00	150	0.00
	<u>502.00</u>		<u>502.00</u>

\* Total earned in these Delivery Modes: 502.00

Minimum combined hours required for these Delivery Modes: 350.00

<u>DISCIPLINE / DESCRIPTION</u>	<u>TOTAL HOURS</u>	<u>TOTAL ALLOWED</u>	<u>TOTAL USABLE</u>
010 BASIC SCIENCE	46.00	150.00	46.00
070 ENDOODONTICS	2.00	150.00	2.00
130 ELECTIVES	38.00	150.00	38.00
180 MYOFASCIAL PAIN DYSFUNCTION/OCCCLUSION	55.00	150.00	55.00
250 OPERATIVE DENTISTRY	10.00	150.00	10.00
310 ORAL AND MAXILLOFACIAL SURGERY	41.00	150.00	41.00
370 ORTHODONTICS	0.00	150.00	0.00
430 PEDIATRIC DENTISTRY	0.00	150.00	0.00
490 PERIODONTICS	94.00	150.00	94.00
550 PRACTICE MANAGEMENT	53.00	150.00	53.00
610 PROSTHODONTICS - FIXED	48.00	150.00	48.00
670 PROSTHODONTICS-REMOVABLE	9.00	150.00	9.00
690 IMPLANTS	50.00	150.00	50.00
730 ORAL MEDICINE, ORAL DIAGNOSIS	50.00	150.00	50.00
750 SPECIAL PATIENT CARE	0.00	150.00	0.00
770 SELF-IMPROVEMENT	0.00	10.00	0.00
780 ESTHETICS	6.00	150.00	6.00
820 POST GRAD EDUCATION	0.00	250.00	0.00
830 TEACHING FULL-TIME	0.00	150.00	0.00
855 FAGD EXAM STUDY GUIDE	0.00	25.00	0.00
860 FAGD EXAM PRE-1984	0.00	150.00	0.00
	<u>502.00</u>		<u>502.00</u>

**Exclusion Codes**

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- X PART issue expired

Mark J. Escoto, DDS

182262

(ADA #) 163900246

**SUMMARY**

Hours Required for FAGD Award:	500.00
Hours Earned towards FAGD Award	502.00
Hours Remaining to achieve FAGD Award:	0.00

\*Congratulations! You may have met the 500-hour requirement for Fellowship. For information on Fellowship, to request a Fellowship application or to schedule the Fellowship Exam call 888-AGD-DENT or contact us online at [www.agd.org](http://www.agd.org).

**Exclusion Codes**

- G Non-approved post-graduate program
- P Program Provider not approved
- V  holder - credit given elsewhere
- X  RT issue expired

5/12/2008

Mark J. Escoto, DDS

182262

(ADA #) 163900246

**MAGD SUMMARY OF TRANSCRIPT**

<u>Delivery</u>	<u>Earned Hours</u>	<u>Maximum Allowed</u>	<u>Total Usable Hours</u>
LECTURE	423.75	--	423.75
PARTICIPATION	181.50	--	181.50
EXAM STUDY GUIDE	0.00	25	0.00
MILITARY ROTATION	0.00	200	0.00
POSTGRAD	0.00	300	0.00
SELF INSTRUCTION	0.00	150	0.00
TEACHING_PUBLICATION	0.00	150	0.00
Total All Delivery Modes	<u>605.25</u>		<u>605.25</u>

**DISCIPLINE SUMMARY**

<u>Discipline/Description</u>	<u>TOTAL PARTICIPATION</u>			<u>TOTAL OVERALL</u>		
	<u>Minimum Hours Required</u>	<u>Total Hours Earned</u>	<u>Hours To Go</u>	<u>Minimum Hours Required</u>	<u>Total Hours Earned</u>	<u>Hours To Go</u>
010 BASIC SCIENCE	12.00	0.00	12.00	12.00	0.00	12.00
070 ENDODONTICS	30.00	0.00	30.00	46.00	0.00	46.00
130 ELECTIVES	30.00	4.00	26.00	46.00	49.00	0.00
180 MYOFASCIAL PAIN DYSFUNCTION/OCCCLUSION	30.00	42.50	0.00	46.00	141.50	0.00
250 OPERATIVE DENTISTRY	30.00	0.00	30.00	46.00	0.00	46.00
370 ORAL AND MAXILLOFACIAL SURGERY	30.00	0.00	30.00	46.00	0.00	46.00
430 PEDIATRIC DENTISTRY	12.00	109.00	0.00	12.00	282.75	0.00
490 PERIODONTICS	12.00	0.00	12.00	12.00	0.00	12.00
550 PRACTICE MANAGEMENT	30.00	0.00	30.00	46.00	0.00	46.00
610 PROSTHODONTICS - FIXED	0.00	0.00	0.00	24.00	49.50	0.00
670 PROSTHODONTICS-REMOVABLE	30.00	0.00	30.00	46.00	0.00	46.00
690 IMPLANTS	30.00	0.00	30.00	46.00	14.00	32.00
730 ORAL MEDICINE, ORAL DIAGNOSIS	30.00	0.00	30.00	46.00	16.00	30.00
750 SPECIAL PATIENT CARE	12.00	26.00	0.00	12.00	48.00	0.00
780 ESTHETICS	12.00	0.00	12.00	12.00	0.00	12.00
	30.00	<u>0.00</u>	<u>30.00</u>	46.00	<u>4.50</u>	<u>41.50</u>
		181.50	302.00	605.30	369.50	

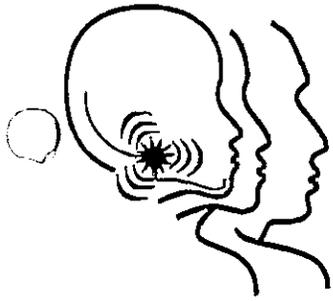
Total Participation Hours Required: 400.00  
 Minimum Participation Hours Still Required: 302.00

Total Overall Hours Required: 600.000  
 Minimum Overall Hours Still Required: 369.50

Once you receive Academy Fellowship you may apply for Mastership. This chart shows how many of your credits will apply toward Mastership, based on the date you completed the hours for Fellowship. You will know you have completed the requirements for Mastership when this chart shows the following: 1) both 'To Go' columns are all zeros, and 2) both 'Total Hours Earned' columns reach the required numbers for Participation and Overall. Contact us at 888-AGD-DENT or www.agd.org for an application for Mastership.

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- X RT issue expired



# Nevada TMJ Institute

Diagnosis and Treatment of Head, Neck,  
Facial Pain and Craniomandibular Disorders

## *CURRICULUM*

## *VITAE*



**MARK J. ESCOTO, D.D.S.  
F.I.C.C.M.O., Dpl. A.A.P.M., Dpl. C.F.O.**

**A Beautiful Smile  
2471 Professional Ct.  
Las Vegas, NV 89128  
702.256-5353  
702.243-7581 fax**

**Nevada TMJ Institute  
2471 Professional Ct.  
Las Vegas, NV 89128  
702.259.4TMJ  
702.243.7581 fax**

**Curriculum Vitae**

**BIOGRAPHICAL:**

Resident of Las Vegas, Nevada for more than thirty years.

Received all elementary and secondary education in Las Vegas, Nevada.

Graduated from Pre-Dental Program, University of Nevada at Reno with a Bachelor of Science in 1986.

Received a D.D.S. Degree from the University of the Pacific in 1989.

Maintained a private practice in Dentistry in San Diego, California from 1989 to 1991.

Has maintained a private practice in Dentistry in Las Vegas, Nevada from 1991 to present.

**Mark J. Escoto, D.D.S.  
F.I.C.C.M.O., Dpl. A.A.P.M., Dpl. C.F.O.**

Page 2

**MEMBER:**

County Dental Society

Nevada Dental Association

American Dental Association

Academy of General Dentistry

International Association of Orthodontics

American Association for Functional Orthodontics

Functional Freedom Corporation

American Academy of Pain Management

The College of Forensic Orthopedics

International College of Cranio-Mandibular Orthopedics

North American Neuromuscular Study Club

**FELLOW:**

International College of Cranio-Mandibular Orthopedics  
(F.I.C.C.M.O.)

**DIPLOMATE:**

American Academy of Pain Management (Dpl. A.A.P.M.)  
Founder with Diplomate status in the College of Forensic  
Orthopedics (Dpl. C.F.O.)

**Mark J. Escoto, D.D.S.**  
**F.I.C.C.M.O., Dpl. A.A.P.M., Dpl. C.F.O.**  
Page 3

**CONTINUING EDUCATION:**

Advanced Surgical Techniques in Implantology

Branmark Prosthetic Course

Loma Linda Advanced Implant Study Club

Scripps Implant Dentistry Education and Research Center: Certification  
Received in 1992

Interpore IMZ Osteointegrated Implant System Seminar

Neuromuscular Orthopedic and Orthodontics

Midwest Implant Institute: Sinus Elevation

In the past five years, Dr. Escoto has concentrated his Continuing Education Studies in Clinical Orthodontics and TMD with a focus on:

Forensic Radiology (Analysis & Interpretation)

Tomographic Radiology

Temporomandibular Dysfunction (TMD)

Bio-instrumentation in TMD Diagnosis

Clinical Orthodontics : Diagnosis & Treatment

Orthodontic/TMD: Diagnosis & Treatment

Clinical Examination of Trauma Victims

TMD & Physical Therapy Treatment Specifically for Whiplash Victims

Neuromuscular Orthotic Treatment for Trauma Victims

**Mark J. Escoto, D.D.S.**  
**F.I.C.C.M.O., Dpl. A.A.P.M., Dpl. C.F.O.**

Page 4

**PUBLICATIONS:**

Las Vegas Review Journal- May 14, 1999  
Article: Are You Suffering From Pain?

Las Vegas Review Journal – June 2, 1999  
Article: Why More Women Are Chronic Pain Victims

Las Vegas Review Journal – August 4, 1999  
Article: Splint/Orthotic Therapy for TMJ/TMD Patients

Picture This Journal – Winter/Spring 2000-1  
Article: Making the Best Smiles for Over a Decade

The Functional Orthodontist – Winter 2000  
Volume 17 \* No. 1 (Pages 32 to 34)  
Article: Removal of second molars to alleviate crowding and to  
Facilitate orthodontic treatment

**PROFESSIONAL LECTURES:**

14<sup>th</sup> Annual BioResearch Workshop Conference  
Presentation: Waterlase use in Dentistry

Las Vegas, Nevada Women's Fair, February 2003  
Presentation: Why More Women Are Chronic Pain Victims

## **A More Predictable Approach To Temporomandibular Dysfunction (TMD)**

**Howard Katz BDS**

Temporomandibular disorders often impair the quality of life of affected individuals. TMD's cause patient suffering and may "devastate its victim" 1 In advanced stages, the condition might be accompanied by tooth sensitivity, abrasion, fractures, mobility, or loss, 2 dental caries; alveolar bone loss; headaches; earaches and hearing loss 3,4 adverse, cumulative, irreversible effects on dental implants .5 6 and aesthetic restorations; diminished facial height which may in turn change one's appearance and cause mandibular over closure 7 ; hypertrophy of the masseter muscle, which in turn can adversely affect one's appearance. 8

As we enter the Twenty-first Century, dental experts are still searching for a non-aggressive preventative treatment for TMD and bruxism. TMD is not an acceptable diagnosis. It refers to a group of diseases with overlapping and similar signs and symptomatology. It is a generic disease like back problem or digestive disorder. It is not specific enough and limits one to treatment that is palliative and non definitive, such as analgesics, relaxation therapy and hot and cold packs. Virtually any other treatment relates to a more specific diagnosis.

The following is a list of etiologies of TMD's involving pain: trauma, capsulitis, neuralgia, neuritis, myalgia, myositis, myofascial pain syndrome, tension headache, cervicalgia, osteoarthritis, rheumatoid arthritis, hysterical conversion, hypochondriasis and hyperalgesia. A list of TMD's involving dysfunction includes: trauma, ankylosis, fibromyalgia, synovitis, disc-condyle adhesions, discitis, odontalgia, disc displacement with reduction, disc displacement without reduction, muscle trismus, neoplasia, infectious disease, osteoarthritis and rheumatoid arthritis. These disorders and dysfunctions do not have a common cause or common treatment. Each one has unique characteristics which must be addressed for optimal results. If dentists were to think of themselves as "physicians with a special interest in the diagnosis and treatment of orofacial pain," they are faced with making a differential diagnosis based on consideration of between 125-135 different possibilities, of which 18-23 would generally be considered within the focus of TMD experts. Epidemiology and double-blind controlled studies on TMD are being challenged. Normal has never been definitely defined and there are not two well-delineated states such as diseased and disease-free relative to TMD's. TMD is not one disease entity but a grouping of many different conditions. In virtually all epidemiologic research, TMD's have been studied as a group, so the results are meaningless. Pain as a gold-standard is unscientific. It is irrefutable having no testable observable or measurable phenomenology. Psychometric testing based on the patient's self-report of pain has never been proven to be more appropriate than objective physiologic measurement for the study of TMD phenomenology. No double-blind study based on pain can possibly be considered hard scientific evidence. (Allen Moses DDS)

Dr. Gordon Christensen states in an interview published in 'Dentistry Today' that "occlusion remains the major untreated disease in dentistry." We probably treat caries too much; we treat periodontal disease a little bit; *and we don't even talk about occlusion.* Occlusal disease affects at least one-third of the population. It is time that the profession becomes more involved in this area of dentistry. As long as untreated continues, the situation keeps getting worse. Thus, "by 40 or 50 years of age, most . . . have worn their teeth to the degree that extensive tooth restorations must be performed" 12. Despite almost one century of research, and despite well over one thousand publications on the subject, "no entirely satisfactory treatment has been identified" 13, 14. The American Dental Association has attempted to strongly encourage the profession to be more aware of TMD and to find a solution for TMD and bruxism. Dr. Christianson concludes: "Today's practitioners can avail themselves of various management strategies to control bruxism, but may not be able to stop it." 6. This approach will need to be supplemented by other therapies aimed at eliminating what by now is probably an ingrained behavioral pattern.

For almost a century dentists have relied on **splint therapy** for TMD and bruxism . 9 Splints have the ability to align the jaws to each other and to protect the teeth. Much current research on the treatment of TMD has been centered on the use of such dental appliances. In the United States alone, some 3.6 million splints are annually prescribed by dentists in an effort to combat bruxism (1.6 million splints), myofascial pain (0.9 million), and TMJ pain (1.1 million)--a \$1 billion industry. 10 Though covering or separating the teeth may be effective to prevent occlusal wear caused by bruxism, this treatment is often not effective for preventing and eliminating other symptoms of TMD. 11. Most splints are largely ineffective in treating TMD.

**Ice and heat** therapies are used to reduce the jaw pain and muscle tension. Application of moist warm towels directly to the jaw joints (5-15 minutes), followed by cold or ice applications (a few minutes), and then repeating this combination 2-5 times per day is sometimes helpful in the short term. Wrapping the jaw in a hot moist towel and **exercising** it through a range of motion has been recommended. 15. These jaw exercises may complement other approaches, but are not effective on their own. Pain from TMD has been related to depression or other emotional problems. **Drugs** are often prescribed for the stress and the brain malfunction etiological theories of TMD. These include anti-anxiety agents, muscle relaxants, and other drugs. They are of limited value in the treatment of the great majority of chronic TMD patients, and they often have untoward side effects. Commonly used antidepressants including Prozac, Paxil and Zoloft may cause bruxism (tooth grinding) and associated headaches. 16. Sufferers usually awaken in the morning with the headache and frequently have an accompanying sleep disorder. Although the pathophysiology of tension headaches are not well understood, it is probable that the headaches arise from afferent fibers in the pericranial musculature, and that sustained contractions of the pericranial muscle may cause tension headaches. 17 Dr James Boyd who developed the NTI-tss and the protocol for its use claims that prolonged nocturnal clenching contributes to migraines. 18

There are some schools of thought that TMD is a response to incorrect mandibular posture. In order for the masticatory system to function ideally the mandible has to be in a correct spatial (3 dimensional) relationship with the skull.<sup>19</sup> They suggest that treatment for bruxism and TMD may include major occlusal adjustments through full mouth rehabilitation sometimes in addition to orthodontics. This technique is irreversible, for it involves the grinding down most of the teeth (and artificially restoring others). The view of the majority of practitioners agreed that "occlusal equilibration is costly and relatively ineffective"<sup>20</sup>

Newer, more robust ceramic materials and better dental bonding with a gnathologically correct occlusion have shown promise in the treatment of TMD and bruxing. These procedures are very technique sensitive and costly. Not all dentists are competent in performing this treatment and a very small percentage of the TMD population can afford it. Moreover, even if malocclusion triggered the bruxing habit, there are no guarantees that its removal will eliminate or reduce bruxing, for the habit may have become an ingrained, self sustaining behavioral pattern. The majority of practitioners agree that "occlusal equilibration is costly and relatively ineffective" despite some spectacular claims in the older and more recent bruxism literature.<sup>21</sup>

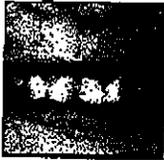
The most promising and exciting new addition to the dentists' arsenal against TMD is having **Botulinum Toxin A** injected into the painful muscles. A group of 46 patients with TMD were measured for subjective and objective responses to treatment with botulinum toxin A (BTX-A). BTX-A injections produced significant improvements in pain, function, mouth opening, and tenderness to palpation.<sup>22</sup> Many other studies have demonstrated similar benefits to TMD patients.<sup>23</sup> Botulinum toxin paralyzes or weakens the injected muscle but leaves the other muscles unaffected. The injections "block extra contraction [of the muscle] but leave enough strength for normal use," says Barbara Karp, M.D., deputy clinical director of the National Institutes of Health's National Institute of Neurological Disorders and Stroke. "Intra muscular injections of botulinum toxin re-establish the balance between masticatory closing and opening muscles. This relieves muscle pain, reverses masseteric hypertrophy with improvement of the face outline and restores normal kinetics of temporo-mandibular joints. Moreover, botulinum toxin injections eliminates habits of tooth grinding and clenching, and the consequences hereof. One single session of injections is curative for 2/3 of the patients. Injections of botulinum toxin in masseter and temporalis muscles are an efficient treatment of bruxism and TMJ dysfunction, cheap with no lasting side effect."<sup>24</sup> Local site-of-injection side effects from botulinum toxin injections are rare, assuming proper technique is used.

The novice should begin with injection of muscles he or she can inject with low risk of incorrect placement. The hard-to-find muscles should be avoided when starting out. It is recommended that the novice clinician attend an educational program covering injection technique, sites and doses. Improved injection technique can also be achieved by injecting and dissecting a few cadavers. The general latency for botulinum toxin type A is 1 week, its duration is 2 to 3 months, and it is recommended that injection be done no more than once every 12 weeks to avoid development of antibodies against the toxin. Depending on the target muscle, injection dose is 10 to 50 U of Botox type A per site

with a total dose of 200 U in the masticatory system. More than this can be used (400 U maximum) if other sites in the head and neck are included in the injection protocol. Most of the orofacial muscles are easily palpable muscles or have definitive bony landmarks to help with the localization process.<sup>25</sup>

Botulinum toxin has "an amazing safety record," says Bill Habig, Ph.D., the recently retired deputy director of FDA's division of bacterial products in the Center for Biologics Evaluation and Research. "Considering it's one of the most toxic materials known and there was a lot of concern about it, it's turned out to be very safe," he says.<sup>26</sup> In 2003, less than two years after it was approved by the FDA for wrinkles, the US consumer spent more than \$875MM dollars on Botox injections. This is to treat a condition that does not effect ones comfort or health. Many dental patients who are already being treated with Botox for wrinkles could be cured of their dentally related diseases with a slight modification in injection protocol.

Botulinum toxin's time to enter the field of dentistry has arrived. Despite the expense many patients will pay for Botox especially when it will make them feel better and look better. It will have its detractors like those who opposed cosmetic dentistry. Let us not forget that the elimination of pain is one of the noblest causes that dentists have!



Before

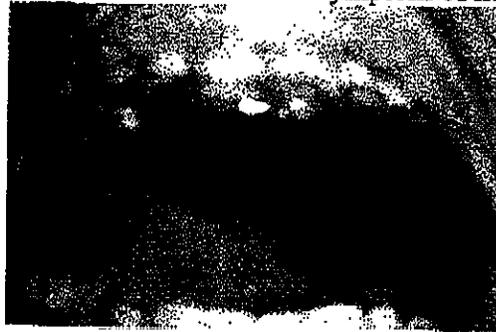
#### **A Case History:**

I'll always remember the first day I met Matti. The only thing sadder than her was the contents of her pink, blue and two green containers. They will filled with opaque, cracked, stained and ugly splints - the kind your patients are embarrassed to show you. Deep creases burrowed multiple parallel lines across her concerned forehead. Her eyes angled downwards at the corners, matching the shape of her lips and unhappiness. Swollen masseter muscles made her jaws seem wider than her upper face, almost like she had a mild case of mumps.

Her main reason for visiting my office was that she had heard that I had helped someone at a singles bar she frequented with a "jaw headache" problem. She had had episodic pain for many years in her temple, masseter and forehead. Other times it felt like it wrapped around her entire skull. Lately she carried large Costco containers of Advil and Tylenol in her purse. She took a cocktail of the two when the pain became so bad that she could not concentrate. Over the decades in dentistry I have seen many patients like Matti. Periodontally she had a couple of four's, and one five in the upper and lower molar region. Otherwise her gums looked good. No bleeding on probing. Her x-rays revealed that she had lost all her first molars and her upper left second molar - she said they were lost due to failed root canals. Her upper upper left molars were replaced fifteen years ago with a blade implant which failed after four and a half years. The other three quadrants had three unit bridges. Every tooth in her mouth, besides her lower cuspids and incisors were crowned with black margined PFM's, the kind most of us did before the Metal-free Age. Matti could have had a second career as a mobile porcelain shade guide. Every

tooth in her mouth was a different color. Some porcelain had sheared and chipped off the surfaces of 5, 12 and 13.

Matti awoke most mornings with a ringing in her ears and a severe pain on both sides of her head. Her jaws clicked and popped as she struggled to open her mouth. At best she could open wide enough to fit two fingers vertically between her teeth. Over the years her psycho-therapist had prescribed Zoloft and Prozac for her depression. The pills often seemed to make her headaches worse. Her physician had informed her that he could find nothing wrong with her and her headaches were a symptom of her depression.



Her previous dentist had made her three or four splints, both in hard acrylic and thermoplastic material. She had either chewed through them after her dentist had made them too thin after equilibrating them, or did not fit after new crowns were seated. The discoloration and smell of the stale saliva-old acrylic combo discouraged her from wearing them. She had tried thermoplastic splints but the taste made her nauseas. After dental visits she was more inclined to wear them with professional motivation from her hygienist or dentist; but if she did not see him for some time she wore them less and less. Her previous dentist had asked her to wear them as much as possible both during the night and day.

The best to she could was to attempt to wear them part of the time to satisfy him but was not comfortable while eating or speaking with them in her mouth. She ultimately wore them part of the time to satisfy her conscience and her dentist. However she would often awaken with the splint in her mouth and still have severe pain on the sides of her head and jaw. It was obvious that duplicating the same splint again would duplicate the existing outcome- supervised, perpetuated masticatory muscle spasm!

My treatment plan for Matti went as follows: my first goal was to relax the masticatory muscles. The fastest relief I could give her was to place a NTI-tss into her mouth. This would bring some immediate relief to her tired muscles by inhibiting her clenching reflex, and confirm my diagnosis. I was reluctant to perform any minor adjustments on her old crowns because I wanted her jaw muscles out of spasm and thereafter I anticipated the jaw would re-align itself differently. Her clenching habit to care of the occlusal equilibration by shearing off most interfering cusps. Once the jaw muscles relaxed I intended following with a functional orthotic which would allow her chew, bite and relax in a more comfortable posture. On mentioning this to her, she immediately

shook her head from side to side. She also objected to wearing anything in her mouth during the day, including a smaller, daytime NTI-tss. Her job involved speaking all day. This prevented her from wearing the device while at work. I explained that the goal of ideal treatment was to restore all the teeth in such a way that they looked natural and that when the opposing teeth met, the mandible would be re-positioned in a more comfortable position. Otherwise the treatment would perpetuate her pain. The teeth would eventually break again.

After a week Matti returned to my office. She had experienced a huge improvement on awakening and the jaw ache was not as severe as before. But by late afternoon the TMJ and the muscles around it were painful.

When I recommended augmenting the effects of the NTI-tss with Botulinum neurotoxin, she was apprehensive. Her first concern was having poison injected into her. I assured her that it was a safe, natural protein with minimal side-effects. But this wasn't her main concern. Despite her extensive history of dental treatment she was petrified of needles. Her muscles were also tender. She was scared that injecting them would be painful and she would possibly faint. It was decided that we would place her in a recumbent position in the dental chair and would use nitrous oxide to relax her while we gave the Botox. On the day of treatment Matti was given a disclosure form to sign after the pro's and con's of Botox treatment was covered. Correct nitrous oxide protocol was followed. I decided to inject the masseters, temporalis and frontalis muscles. The tender spots and hypertrophied areas were easy to locate with finger pressure. After five minutes she was adequately less anxious to begin injecting. We used a .031 gauge ultra-fine needle that was almost unnoticeable to her during the injections. BTX-A was injected into two areas of both masseter muscles (5 U at each site) and 3 equidistant spots on both temporalis muscles (5 U at each site). Eight areas were injected with 2.5U at each site across the upper forehead avoiding the outside of the pupils. Immediately after the injections there was some skin tenderness at the injection sites. The one side of her forehead had a tiny bruise visible at another injection site not covered by hair.

I followed up with Matti every two weeks for the following 4 months. After 8 days Matti was pain free, she could almost fit four fingers vertically into her mouth, and the muscles were no longer tender to touch. The deep forehead furrows had disappeared off most of her forehead. The sad individual tormented by pain had been replaced by a happy, smiling person. She remained pain free for about 14 weeks. When the tenderness returned it had a lot less of a vengeance than before. However we decided to follow the same dose protocol as we had done 4 months previously. Matti's pain relief lasted 6 months before she requested more BTX A injections. We timed this to coincide with her hygiene visits. We also reduced the dose to each site by fifty percent. Each temporalis site was injected with 2.5 U. Each masseter site was injected with 2.5 U. The entire procedure did not take longer than five minutes.

Matti considers my office trendy because we offer state of the art treatments like cosmetic dentistry and Botox. She is seriously considering having a full mouth rehabilitation.

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Many of these references were found using an article from Moti Nissani Ph.D, a geneticist at Wayne University.

## **CAN BOTULINUM TOXIN A (BOTOX) SAVE YOUR TEETH AND ENHANCE YOUR SMILE?**

**Howard Katz DDS**

**Andy Blumenfeld MD**

Modern dentistry has trained the general public to demand and accept innovative treatments from their neighborhood dentist. There was a time when you had a toothache you would go to a dentist to pull your tooth out - that is all they were trained to do. Dentists have not always performed the specialized, sophisticated treatments that they do today like restore and replace teeth with implants, root canal treatments, crowns and cosmetic dentistry, straightening teeth with invisible braces. As successful treatments became more predictable and acceptable more and more general dentists performed them.

Dental disease is caused by two predominate causes. Treatments have been designed to combat the effects of these:

A) micro-organisms that destroy dental hard tissue and provoke the immune system to destroy gums and bone

B) excessive muscle forces that predispose to wear and breakdown of the teeth, gums, bone and the tissues of the TMJ.<sup>1</sup> In this article the methods of using Botulinum Neurotoxin A as an adjunctive treatment used to control muscle function that cause and contribute to disease are discussed.

The damage caused by excessive biting forces and dental trauma is being treated with intra-oral appliances, occlusal adjustments, sophisticated dental restorations and/or surgery. These are all excellent treatment options but they are not for every patient. While occlusion used to be regarded as the main cause of disease affecting the masticatory system, muscular and psychological factors are as important. Precise differentiation of the individual causal etiological factors is generally not possible. The term Temporomandibular Dysfunction is used to cover every disease effecting the normal masticatory function. Unfortunately there is no common treatment for every cause of TMD because it encompasses too many different disease entities. These separate diseases have to be isolated and then treated.

The dental profession has always prided itself in that the focus of oral healthcare has been based on prevention. The focus of treatment should be in the prevention and reduction of these destructive habits. Extra-capsular TMD is often transient and the least invasive treatment options are usually best used to begin treatment. Orthognathic surgery, orthodontics and a neuromuscular rehabilitation of the occlusion are invasive, irreversible and expensive for the majority of patients. There is no guarantee to the patient that these major treatments will be effective. Sophisticated restorations are not only very technique sensitive, they involve the removal of additional healthy tooth material. The most esthetic, conservative restorations may not withstand the forces applied to them. There is also a reluctance to have perfectly healthy teeth prepared for ceramic or gold restorations when the teeth are esthetically pleasing and asymptomatic.

Intra-oral splints can be very effective in preventing excessive wear and enabling the jaw to function in the most relaxed posture. Yet there is a very low compliance with intra-oral splints and other protective removable appliances worn over the teeth even when they are effective. Patients do not like to have appliances in their mouths impeding normal function like eating and speaking. Less than one in five patients will wear a prescribed appliance as prescribed by their treating dentist.

Many dentists have bleach trays and comfortable intra-oral devices for their own mouths that they do not use as often as they should. Why should our patients be any different.

The continued use of analgesics, narcotics, steroids and anti-inflammatories for associated dento-facial symptoms is not ideal, nor conducive to health. There are many unwarranted side-effects. Certain patients like airline pilots, air-traffic control personnel, surgeons, military personnel and anyone else operating heavy machine equipment should not be taking narcotics. Yet patients will opt for this despite the inherent risks and danger because of their ease of use.

An extremely effective way to prevent damage and to enhance treatment to dental hard tissue and restorations would be to de-program the muscles responsible for excessive destructive forces and other gnathologically related diseases.

#### THE NEW PARADIGM:

There is clearly a pronounced need to improve the options available for preventive treatment of muscle generated dental disease, which requires effective, safe agents that have minimal side effects, are well-tolerated for long-term use, and that eliminate or reduce the need to use other irreversible treatments or medications. Intramuscular injections of Botulinum toxin type A (BTX-A) have been increasingly used throughout the US as a novel approach to preventive treatment that may provide effective, safe, and well-tolerated long-term relief of intractable symptoms in patients who have failed conventional approaches to treatment. The public does not yet associate Botulinum neurotoxin A with their dentist but they very soon and enthusiastically will. Dentists are skilled in the anatomy of the lower facial anatomy and chewing apparatus. They are also prolific injectors. Dentists have the advanced training in recognizing and treating force related dental problems. This reduces the risk of side-effects associated with unskilled injectors and injection technique.

#### Background Botulinum neurotoxins

There are seven botulinum neurotoxin serotypes (A, B, C, D, E, F, and G), produced by *Clostridium botulinum*, all of which inhibit acetylcholine release, though their

intracellular target proteins, the characteristics of their actions, and their potencies vary substantially.<sup>2</sup> At the neuromuscular junction, the inhibition of acetylcholine release by BTX-A blocks or reduces contraction of muscles, an effect which has been used therapeutically in disorders characterized by overactive muscle activity such as cervical dystonia (CD), blepharospasm,<sup>3,4</sup> and spasticity.<sup>5</sup>

Botulinum toxin A (Botox) is the muscle relaxant that has been popularized in the elimination of facial lines.<sup>6</sup>

Botulinum toxin type A (BOTOX<sup>®</sup>; Allergan, Inc.; Irvine, CA) is currently approved for the treatment of blepharospasm, strabismus, and CD.<sup>7</sup> Binder and colleagues, treating patients for facial lines, noted improvement of migraine symptoms after BTX-A injections.<sup>8</sup> This discovery led to further investigation in clinical trials of BTX-A preventive treatment of migraine and other dento-facial diseases including TMD.

Btx A has been proven to successfully eliminate or reduce excessive clenching by desensitizing spindle cells within tense muscles, the main cause of force related dental disease, when injected into the chewing muscles. Parafunctional clenching to the extent that it effects oral function causes damage to oral tissues is usually transient. For this reason aggressive irreversible treatments should be avoided. Particularly where compliance is a problem, Botulinum toxin A (Botox) offers this option.

Preventative control of biting parafunctions and excessive forces on the chewing apparatus will be the most significant paradigm in dental treatment since local anesthetic and the dental drill. Dentists will have the ability to reduce the need for major aggressive treatments that involve surgery or drilling many teeth. "Surgical procedures that alter anatomic relationships without addressing factors contributing to pathogenesis may be more prone to failure and recurrence of [TMD] symptoms. It is clear that excessive loading on articular tissues is one of the causative factors that must be identified and addressed by all clinicians treating patients with TMJ pathology" <sup>2</sup>

The public does not yet associate Botulinum neurotoxin A with their dentist but they very soon and enthusiastically will. Dentists are skilled in the anatomy of the lower facial anatomy and chewing apparatus. They are also prolific injectors. Dentists have the advanced training in recognizing and treating force related dental problems. They are also very familiar with facial anatomy. It will be possible to teach dentists fairly easily how to treat their patients with BTX A and how to avoid the major side-effects. These are caused predominately by incorrect injection technique. This reduces the risk of side-effects associated with unskilled injectors.

## **ADMINISTERING BTX-A FOR PREVENTIVE DENTALLY RELATED CONDITIONS**

**Patient selection:** BTX-A therapy is appropriate for patients for whom other preventive treatments and medications are poorly tolerated or contraindicated, for those refractory to other treatments, for those in special patient populations, as well as for those who simply prefer this treatment. Contraindications to the use of BTX-A include sensitivity to toxin or neuromuscular disorders such as myasthenia gravis or Eaton-Lambert syndrome.

## **Pretreatment Procedures**

### **Informed consent**

Once an appropriate patient is selected for BTX-A treatment, the dentist should set reasonable treatment goals. Patients should first be told that the use of BTX-A as preventive treatment is off-label use; that while there is clinical evidence to support its use as a preventive agent, investigation is ongoing. Patients should also be told that the optimal effects of BTX-A treatment may not be experienced for at least 1 week and will begin to wear off after approximately 3 months, and that multiple treatment cycles may be needed to achieve an optimal therapeutic effect.<sup>22,23</sup> Galvez-Jimenez N, Lampuri C, Patino-Piccinillo R, Hargreave M. Dystonia and headaches: the response to botulinum toxin therapy. [Abstract] Cephalalgia. 2003;23:760.

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The known side effects of BTX-A treatment should also be made clear; these include possible injection-site pain, headache, rash, bruising, or ptosis. Informed consent should be obtained.

**Identifying injection sites:** Once treatment is ready to commence, patients should indicate the anatomical locations of the head most frequently affected by pain or muscles tender to touch. The treating dentist should be able to identify the anatomical areas of tenderness and sites that produce pain on palpation (including the frontalis, temporalis, masseter, pterygoids, posterolateral neck and shoulder regions) and examine the face and neck to assess symmetry.

#### **Preparation of BTX for Injection**

One neurotoxin type A (BOTOX<sup>®</sup>) and one type B (MYOBLOC<sup>®</sup>; Elan Pharmaceuticals) are available in the United States. The majority of the evidence has been based on using the type A toxin. Lyophilized BTX-A, available in vials containing 100 U, should be diluted with 2 or 4 mL of preservative-free 0.9% saline, which yields a preparation of 5.0 or 2.5 U per 0.1 mL, respectively. **BTX Injection Sites**

The injection sites commonly used for BTX-A treatment of dental related conditions are the glabellar and frontal regions, the temporalis muscle, the masseter, the depressor anguli oris, the pterygoid muscles, and the cervical paraspinal region. Blumenfeld AM, Binder W, Silberstein SD, Blitzer A. Procedures for administering botulinum toxin type A for migraine and tension-type headache. *Headache*. 2003;43:824-831 Patients should be placed in a sitting or supine position for injection of the frontal and temporal regions, and a sitting position for injection of the posterior neck region and trapezius. It appears most of the adverse events associated with BTX-A injections are related to the technique and skill of the injector. Correct injection technique helps minimize adverse events and optimize treatment outcomes. The precise anatomical location, optimal choice of injection site within a particular muscle, dosages, and volumes used should all be considered carefully. Bilateral injections are advisable in the case of unilateral headache or TMD pain as unilateral injection can lead to the development of symptoms on the other side of the face.

#### **Safety and Tolerability of BTX-A**

BTX-A has an excellent safety and tolerability profile. There are generally no systemic effects from treatment. The reported effects, which are usually minimal and transient, include blepharoptosis (droopy upper eyelid) and muscle weakness at

***BOTOX***

Language being considered and discussed by NSBME regarding BOTOX:

Amend NRS 630.020 by adding paragraphs to define the use of lasers and the injection of botox as the practice of medicine.

Move the current paragraph 4 to become paragraph 6. Insert new paragraphs 4 and 5.

***“4. The revision, destruction, incision or other structural alteration of human tissue is the practice of medicine. Since laser and intense pulsed light therapy involve the revision, destruction, incision and removal of human tissue, both fall within the definition of the practice of medicine.***

***(a) A licensed physician with appropriate and specific training in acceptable laser surgery and intense pulsed light therapy may delegate certain procedures to certified or licensed non-physicians in compliance with appropriate statutes and regulations. The physician must directly supervise the non-physician to protect the best interests and welfare of each patient. Laser treatment involving the globe of the eye must be performed by licensed ophthalmologists.***

***5. The injection of botox, cosmetic and chemotherapeutic substances is considered the practice of medicine and may not be delegated to medical assistants or any other staff with comparable or lesser training.”***

Rationale: The protection of the public requires greater restriction and control of the use of lasers and intense pulsed light therapy, and the injection of botox and other cosmetic or anesthetic substances. These procedures should be performed by, or under the direction of, a licensed physician.

For KK'S  
Book  
8/25/2006

U.S. Food and Drug Administration

**FDA Talk Paper**

631

FDA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available.

T02-20  
April 15, 2002

Media Inquiries: 301-827-6242  
Consumer Inquiries: 888-INFO-FDA

## FDA APPROVES BOTOX TO TREAT FROWN LINES

FDA today announced the approval of Botulinum Toxin Type A (Botox Cosmetic) to temporarily improve the appearance of moderate to severe frown lines between the eyebrows (glabellar lines), a medical condition that is not serious. The product's manufacturer, Allergan, Inc., Irvine, California, is now allowed to market Botulinum Toxin Type A for this new indication.

Botulinum Toxin Type A is a protein produced by the bacterium *Clostridium botulinum*. When used in medical settings as an injectable form of sterile, purified botulinum toxin, small doses of the toxin are injected into the affected muscles and block the release of the chemical acetylcholine that would otherwise signal the muscle to contract. The toxin thus paralyzes or weakens the injected muscle.

Botox was first approved in December 1989, to treat two eye muscle disorders (blepharospasm and strabismus) and in December 2000 to treat cervical dystonia, a neurological movement disorder causing severe neck and shoulder contractions.

In placebo-controlled, multicenter, randomized clinical trials involving a total of 405 patients with moderate to severe glabellar lines who were injected with Botox Cosmetic, data from both the investigators' and the patients' ratings of the improvement of the frown lines were evaluated. After 30 days, the great majority of investigators and patients rated frown lines as improved or nonexistent. Very few patients in the placebo group saw similar improvement.

In these studies, the severity of the glabellar lines was reduced somewhat for up to 120 days for those patients who received Botox Cosmetic. Most of the patients in the study were female, and the majority was under 50 years old. It is recommended that Botox Cosmetic be injected no more frequently than once every three months, and the lowest effective dose should be used.

The most common adverse events following injection were headache, respiratory infection, flu syndrome, blepharoptosis (droopy eyelids) and nausea. Less frequent adverse reactions (less than 3% of patients) included pain in the face, redness at the injection site and muscle weakness. These reactions were generally temporary, but could last several months.

Because Botox Cosmetic is a prescription drug, it must be used carefully under medical supervision.

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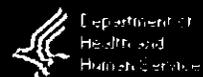
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# U.S. Food and Drug Administration



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## Product Approval Information - Licensing Action

### DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
1401 Rockville Pike  
Rockville, MD 20852-1448

December 21, 2000

Submission Tracking No. (STN) 103000/1004  
(Replaces Reference Number: 91-0184)

Mr. Peter A. Kresel  
Allergan, Inc.  
2525 Dupont Drive  
P.O. Box 195  
Irvine, CA 92713-9534

Dr. Mr. Kresel:

The Supplement to your License Application for Botulinum Toxin Type A (BOTOX), to include the indication of treatment of cervical dystonia, submitted under Section 351 of the Public Health Service Act, has been approved.

Under this approval, BOTOX is indicated for the treatment of cervical dystonia in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia.

We acknowledge your commitments dated December 13, 2000, and December 15, 2000, for the following postmarketing clinical study:

1. You have agreed to initiate a postmarketing study to evaluate the safety and immunogenicity of BOTOX in patients with cervical dystonia. You have made the following commitments for timeframes of conducting the study and submission to related materials to the Center for Biologics Evaluation and Research (CBER):
  - a. The study protocol will be finalized and submitted to CBBER for review and comment by the end of January 2001.

- b. The study will be initiated by the end of March, 2001.
- c. A sufficient number of study subjects will be enrolled such that a minimum of 250 subjects will complete the two years of follow-up monitoring.
- d. Enrollment of study subjects will be completed in approximately 3.5 years, with the last subject to be entered by the end of December 2004.
- e. All study subjects will be followed until the 2-year clinical observation period for the last enrolled patient is completed in December 2006.
- f. Database closure and initiation of data analysis will occur in December 2006.
- g. The clinical study final report will be completed and submitted to CBER by April 2007.
- h. In addition, you have agreed to include interim data analyses in the annual reports on the status of this study.

Be advised that as of April 12, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). A waiver for pediatric studies for this application is granted under 21 CFR 601.27.

This information will be placed in your biologics license application file for this product.

Changes in the manufacturing process, manufacturing facility, product testing, packaging or labeling for Botulinum Toxin Type A (BOTOX) may require the submission of a supplement to your biologics license application for review and approval prior to implementation.

It is required that adverse experience reports be submitted in accordance with the adverse events reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-120, Food and Drug Administration, 1401 Rockville Pike, MD 20852-1448.

It is required that reports of errors and accidents in manufacture be submitted in accordance with the error and accident reporting requirements for licensed biological products (21 CFR 600.14). All error and accident reports should be identified promptly according to 21 CFR 600.14 and submitted to the Director, Office of Compliance, Center for Biological Evaluation and Research, HFM-600, 1401 Rockville Pike, MD 20852-1448.

Please submit final printed labeling at the time of use and include implementation information on FDA Form 2567. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with an FDA form 2567 or Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a

FDA Form 2567 or Form 2253.

All promotional claims must be consistent with and no contrary to approved labeling. No comparative promotional claim or claim of superiority over other similar products should be made unless data to support such claims are submitted to and approved by the Center for Biological Evaluation and Research.

Please acknowledge receipt of this letter to the Director, Division of Vaccines and Related Products Applications, HFM-475, Center for Biological Evaluation and Research.

Sincerely yours,  
--- signature ---

Karen L. Goldenthal, M.D.  
Director  
Division of Vaccines and Related Products Applications  
Office of Vaccines Research and Review  
Center for Biologics Evaluation and Research

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*Last Updated: 1/25/2001*

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Date created: September 25, 2003

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FDA/Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
1401 Rockville Pike  
Rockville MD 20852-1448

**APR 12 2002**

Submission Tracking No. (STN): BL 103000/5000

Mr. Peter A. Kresel  
Allergan, Inc.  
2525 Dupont Drive  
P.O. Box 195  
Irvine, CA 92713-9534

Dear Mr. Kresel:

The Supplement to your License Application, for Botulinum Toxin Type A to include the indication of treatment of glabellar lines, has been approved.

Under this approval, Botulinum Toxin type A will be marketed and labeled for this indication as BOTOX COSMETIC.

Botulinum Toxin Type A (BOTOX) is currently licensed for the treatment of cervical dystonia in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia and the treatment of strabismus and blepharospasm associated with dystonia. Under this approval, Botulinum Toxin Type A (BOTOX COSMETIC) may be used for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients  $\leq$  65 years of age.

Under this approval, BOTOX COSMETIC shall be supplied, in vials, as a lyophilized formulation at a dose of 100 U per vial and the expiration dating period shall be 24 months when stored at  $-5^{\circ}\text{C}$  to  $-20^{\circ}\text{C}$ .

We acknowledge your March 11, 2002, submission of the final report for reproductive toxicity testing studies to BB IND ——. This submission is currently under review and we reserve the right to comment further on the contents of

that submission and request further revisions to the labeling for BOTOX COSMETIC as warranted.

We acknowledge your commitment of March 26, 2002, to review the post-marketing adverse event surveillance data after one year of commercial distribution and propose revised labeling as warranted.

We have reviewed your request for a waiver from the requirement to assess the safety and effectiveness of the product in pediatric populations. Please be advised that a waiver for this application is granted under 21 CFR 601.27.

This information will be placed in your License Application File for this product.

Changes in the manufacturing process, manufacturing facility, product testing, packaging or labeling for Botulinum Toxin Type A (BOTOX and BOTOX COSMETIC) may require the submission of a supplement to your biologics license application for review and approval prior to implementation.

It is required that adverse experience reports be submitted in accordance with the adverse events reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, MD 28052-1448.

It is required that reports of errors and accidents in manufacture be submitted in accordance with the error and accident reporting requirements for licensed biological products (21 CFR 600.14). All error and accident reports should be identified promptly according to 21 CFR 600.14 and submitted to the Director, Office of Compliance, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit final printed labeling at the time of use and include implementation information on FDA Form 2567. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies

of the proposed introductory advertising and promotional labeling with an FDA Form 2567 or Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2567 or Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other similar products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,

*Karen L. Goldenthal, M.D.*

Karen L. Goldenthal, M.D.  
Director  
Division of Vaccines and  
Related Products Applications  
Office of Vaccines  
Research and Review  
Center for Biologics  
Evaluation and Research

**BOTOX<sup>®</sup> COSMETIC** (Botulinum  
Toxin Type A)  
Purified Neurotoxin Complex

Manufactured by:  
Allergan Pharmaceuticals (Ireland) Ltd.  
A subsidiary of: **Allergan, Inc.**  
2525 Dupont Dr.  
Irvine, California 92612

**Description:** BOTOX<sup>®</sup> COSMETIC (Botulinum Toxin Type A) Purified Neurotoxin Complex is a sterile, vacuum-dried purified botulinum toxin type A, produced from fermentation of Hall strain *Clostridium botulinum* type A grown in a medium containing casein hydrolysate, glucose and yeast extract. It is purified from the culture solution by dialysis and a series of acid precipitations to a complex consisting of the neurotoxin, and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing albumin human and is sterile filtered (0.2 microns) prior to filling and vacuum-drying.

One unit (U) of BOTOX<sup>®</sup> COSMETIC corresponds to the calculated median intraperitoneal lethal dose (LD<sub>50</sub>) in mice. The method utilized for performing the assay is specific to Allergan's product, BOTOX<sup>®</sup> COSMETIC. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for the various mouse LD<sub>50</sub> assays, Units of biological activity of BOTOX<sup>®</sup> COSMETIC cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. Therefore, differences in species sensitivities to different botulinum neurotoxin serotypes precludes extrapolation of animal-dose activity relationships to human dose estimates. The specific activity of BOTOX<sup>®</sup> COSMETIC is approximately 20 units/nanogram of neurotoxin protein complex.

Each vial of BOTOX<sup>®</sup> COSMETIC contains 100 units (U) of *Clostridium botulinum* type A neurotoxin complex, 0.5 milligrams of albumin (human), and 0.9 milligrams of sodium chloride in a sterile, vacuum-dried form without a preservative.

**Clinical Pharmacology:** BOTOX<sup>®</sup> COSMETIC blocks neuromuscular transmission by binding to acceptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, BOTOX<sup>®</sup> COSMETIC produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by BOTOX<sup>®</sup> COSMETIC.

**Pharmacokinetics**

Botulinum Toxin Type A is not expected to be present in the peripheral blood at measurable levels following IM injection at the recommended doses. The recommended quantities of neurotoxin administered at each treatment session are not expected to result in systemic, overt distant clinical effects, i.e. muscle weakness, in patients without other neuromuscular dysfunction. However, sub-clinical systemic effects have been shown by single-fiber electromyography after IM doses of botulinum toxins appropriate to produce clinically observable local muscle weakness. These side effects may be due to local spread of toxin from the injection site and/or misplaced injections.

Clinical studies have reported changes in clinical electromyographic parameters (i.e., jitter) in muscles distant to the site of BOTOX<sup>®</sup> injection. This may indicate spread of the toxin via circulation, retro- or ortho-grade axonal transport, or some action of the toxin at a third, central, or unidentified site.

**Clinical Studies:**

*Glabellar Lines:*

Two phase 3 randomized, multi-center, double blind, placebo-controlled, parallel-group studies of identical design were conducted to evaluate **BOTOX® COSMETIC** for use in the temporary improvement of the appearance of moderate to severe glabellar facial lines. The studies enrolled healthy adult patients (ages 18 to 75) with glabellar lines of at least moderate severity at maximum frown. Patients were excluded if they had an infection or skin problem at the injection site, history of facial nerve palsy, marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin, inability to substantially lessen glabellar lines even by physically spreading them apart or had a known history of neuromuscular disorder or other disorder that could interfere with neuromuscular function. Subjects received a single treatment of intramuscular injection with either **BOTOX® COSMETIC** (N=405, combined studies) or placebo (N=132, combined studies). Injection volume was 0.1 ml/injection site, for a dose/injection site in the active treatment groups of 4U. Patients were to be injected intramuscularly in five sites, 1 in the procerus muscle and 2 in each corrugator supercillii muscle, for a total dose in the active treatment groups of 20 U.

The co-primary efficacy measurements were the investigator's rating of glabellar line severity at maximum frown at Day 30 post-injection and the subject's global assessment of change in appearance of glabellar lines at Day 30 post-injection. For the investigator rating, a photoguide was provided to each study center to assist in grading the severity of glabellar lines using a 4-point grading scale (0=none 1=mild 2= moderate 3=severe). A responder was defined as having a severity grade of 0 or 1.

For the global assessment of change in appearance of glabellar lines, the subject responded to the question, "How would you rate the change in the appearance of your glabellar lines compared with immediately before your most recent injection?" The ratings of responses by subjects were from +4 (complete improvement, about 100%) to -4 (very marked worsening, about 100% worse or greater). A responder was defined as having a grade of at least +2 (moderate improvement, about 50%).

A secondary efficacy endpoint was the investigator's rating of glabellar line severity at rest at Day 30 post-injection in those subjects who at baseline demonstrated a glabellar line severity score *at rest* of moderate or severe.

For the investigators' rating, the criteria for effectiveness was a 30 percentage point difference between **BOTOX® COSMETIC** and placebo treatment groups in the incidence of subjects with an investigator's rating of glabellar line severity of none or mild at maximum frown. For the subjects' rating, the criteria for effectiveness was a 25 percentage point difference between **BOTOX® COSMETIC** and placebo treatment groups in the incidence of subjects with a score of at least +2 (moderate improvement) in subject's global assessment of change in the appearance of glabellar lines.

The combined results of these two efficacy trials with the same design are presented here. There were 210 subjects (161 subjects in the **BOTOX® COSMETIC** treated group and 49 subjects in the placebo treated group) who had glabellar line severity scores at rest of moderate or severe.

The mean age was 46.0 years, with a range of 22 to 78 years. Of these, 68.2% (366/537) were ≤ 50 years of age and 31.8% (171/537) were ≥ 51 years of age and 6.0% were ≥ 65 years of age.

Most of the subjects were female, 81.9% (440/537) and Caucasian, 83.8% (450/537).

In these studies, the severity of glabellar lines was reduced for up to 120 days in the **BOTOX® COSMETIC** group compared to the placebo group as measured both by investigator rating of glabellar line severity at maximum frown and at rest, and by subject's global assessment of change in appearance of glabellar lines. By Day 7, 74% (299/405) of subjects had achieved a severity score of none or mild at maximum frown by the investigator's assessment. This increased to 80% (325/405) by the primary efficacy endpoint day of Day 30, compared to 3% of placebo-treated patients (Table 1). By Day 7, 83% (334/405) of subjects assessed moderate or better improvement in their own appearance (+2 or better). This increased to 89% (362/405) by the primary efficacy endpoint day of Day 30, compared to 7% of placebo-treated patients (Table 2). Based on resting appearance as judged by the investigator, 68% (110/161) of subjects achieved a severity score of none or mild at Day 7, and 74% (119/161) by the efficacy endpoint day of Day 30 (Table 3).

**TABLE 1.**  
**Investigator's Assessment—Responder Rates Assessed at Maximum Frown (% and Number of Subjects with Severity of None or Mild)**

DAY	BOTOX® COSMETIC	PLACEBO	DIFFERENCE <sup>a</sup>	P-VALUE
7	73.8% 299/405	6.1% 8/132	67.8% (61.9, 73.7)	<0.001
30*	80.2% 325/405	3.0% 4/132	77.2% (72.4, 82.1)	<0.001
60	70.2% 283/403	1.5% 2/130	68.7% (63.7, 73.6)	<0.001
90	47.6% 192/403	2.3% 3/128	45.3% (39.8, 50.8)	<0.001
120	25.3% 102/403	1.6% 2/128	23.8% (19.0, 28.5)	<0.001

<sup>a</sup> 95% confidence intervals are shown in parentheses

\* Day 30: Co-Primary Efficacy Timepoint

**TABLE 2.**  
**Subject's Assessment—Responder Rates of Appearance (% and Number of Subjects with at Least Moderate Improvement)**

DAY	BOTOX® COSMETIC	PLACEBO	DIFFERENCE <sup>a</sup>	P-VALUE
7	82.5% 334/405	9.1% 12/132	73.4% (67.2, 79.5)	<0.001
30*	89.4% 362/405	6.8% 9/132	82.6% (77.3, 87.8)	<0.001
60	81.9% 330/403	3.8% 5/130	78.0% (73.0, 83.1)	<0.001
90	63.0% 254/403	3.1% 4/128	59.9% (54.3, 65.5)	<0.001
120	39.0% 157/403	0.8% 1/128	38.2% (33.2, 43.2)	<0.001

<sup>a</sup> 95% confidence intervals are shown in parentheses

\* Day 30: Co-Primary Efficacy Timepoint

**TABLE 3.**

**Investigator's Assessment—Responder Rates Assessed at Rest in Subjects with Moderate or Severe Severity Score at Baseline (% and Number of Subjects with Severity of None or Mild)**

DAY	BOTOX® COSMETIC	PLACEBO	DIFFERENCE <sup>a</sup>	P-VALUE
7	68.3% 110/161	24.5% 12/49	43.8% (29.8, 57.9)	<0.001
30*	73.9% 119/161	20.4% 10/49	53.5% (40.3, 66.7)	<0.001
60	72.7% 117/161	24.5% 12/49	48.2% (34.3, 62.1)	<0.001
90	70.8% 114/161	34.7% 17/49	36.1% (21.1, 51.2)	<0.001
120	59.0% 95/161	34.7% 17/49	24.3% (9.0, 39.7)	0.007

<sup>a</sup> 95% confidence intervals are shown in parentheses

\* Day 30: Secondary Endpoint

The responder rates for both co-primary efficacy variables were higher for subjects ≤ 50 years of age than for those ≥ 51 years to ≤ 65 years of age (Tables 4 and 5). Efficacy was higher for both groups compared to those subjects ≥ 65 years of age (Tables 6 and 7). In the cervical dystonia trial, there was also a consistently observed treatment-associated effect between subjects greater than and less than 65 years of age. (See Precautions: Geriatrics) There were no statistically significant between-group differences for the investigator's assessment at maximum frown for this age group. There was a statistically significant difference in favor of **BOTOX® COSMETIC** for the subject's global assessment at all time points except Day 120 (p ≤ 0.036).

**TABLE 4.**

**Investigator's Assessment--Responder Rates of Glabellar Line Severity by Age Distribution**

Investigator's Assessment at Maximum Frown % rated 0 or 1 ≤ 50 years			Investigator's Assessment at Maximum Frown % rated 0 or 1 > 50 years		Investigator's Assessment at Maximum Frown % rated 0 or 1 > 65 years	
DAY	BOTOX® COSMETIC	Placebo	BOTOX® COSMETIC	Placebo	BOTOX® COSMETIC	Placebo
7	80.7% 226/280	5.8% 5/86	58.4% 73/125	6.5% 3/46	34.8% 8/23	11.1% 1/9
30*	84.6% 237/280	2.3% 2/86	70.4% 88/125	4.3% 2/46	39.1% 9/23	22.2% 2/9
60	73.6% 206/280	1.2% 1/85	62.6% 77/123	2.2% 1/45	30.4% 7/23	12.5% 1/8
90	50.4% 141/280	1.2% 1/83	41.5% 51/123	4.4% 2/45	30.4% 7/23	12.5% 1/8
120	28.6% 80/280	0% 0/83	17.9% 22/123	4.4% 2/45	4.3% 1/23	12.5% 1/8

\* Day 30: Co-Primary Efficacy Timepoint

**TABLE 5.**  
**Subject's Assessment--Responder Rates of Glabellar Line Severity by Age Distribution**

DAY	Subject's Assessment % +2 or better ≤ 50 years		Subject's Assessment % +2 or better > 50 years		Subject's Assessment % +2 or better > 65 years	
	BOTOX <sup>®</sup> COSMETIC	Placebo	BOTOX <sup>®</sup> COSMETIC	Placebo	BOTOX <sup>®</sup> COSMETIC	Placebo
7	86.8% 243/280	7.0% 6/86	72.8% 91/125	13.0% 6/46	52.2% 12/23	11.1% 1/9
30 *	91.8% 257/280	3.5% 3/86	84.0% 105/125	13.0% 6/46	69.6% 16/23	11.1% 1/9
60	84.6% 237/280	3.5% 3/85	75.6% 93/123	4.4% 2/45	65.2% 15/23	0% 0/8
90	63.2% 177/280	2.4% 2/83	62.6% 77/123	4.4% 2/45	65.2% 15/23	0% 0/8
120	41.1% 115/280	1.2% 1/83	34.1% 42/123	0% 0/45	17.4% 4/23	0% 0/8

\* Day 30: Co-Primary Efficacy Timepoint

**TABLE 6.**  
**Investigators Assessment--Responder Rates at Maximum Frown (% and Number of Subjects with Severity of None or Mild) for Subjects >65 Years of Age**

DAY	BOTOX <sup>®</sup> COSMETIC N=23	PLACEBO N=9	DIFFERENCE	RELATIVE RISK	P-VALUE
7	34.8% 8/23	11.1% 1/9	23.67 (-4.62, 51.96)	3.13 (0.45, 21.58)	0.188
30 *	39.1% 9/23	22.2% 2/9	16.91 (-16.8, 50.61)	1.76 (0.47, 6.62)	0.373
60	30.4% 7/23	12.5% 1/8	17.93 (-11.7, 47.58)	2.43 (0.35, 16.85)	0.326
90	30.4% 7/23	12.5% 1/8	17.93 (-11.7, 47.58)	2.43 (0.35, 16.85)	0.326
120	4.3% 1/23	12.5% 1/8	-8.15% (-32.5, 16.23)	0.35 (0.02, 4.94)	0.426

\* Day 30: Co-Primary Efficacy Timepoint

**TABLE 7.**  
**Subject's Assessment-- Responder Rates at Maximum Frown (% and Number of Subjects with Severity of None or Mild) for Subjects >65 Years of Age**

DAY	BOTOX® COSMETIC N=23	PLACEBO N=9	DIFFERENCE	RELATIVE RISK	P- VALUE
7	52.2% 12/23	11.1% 1/9	41.06 (12.11, 70.02)	4.70 (0.71, 31.05)	0.036
30 *	69.6% 16/23	11.1% 1/9	58.45 (30.61, 86.30)	6.26 (0.97, 40.52)	0.003
60	65.2% 15/23	0% 0/8	65.22 (45.75, 84.68)	11.63 (0.77, 174.7)	0.002
90	65.2% 15/23	0% 0/8	65.22 (45.75, 84.68)	11.63 (0.77, 174.7)	0.002
120	17.4% 4/23	0% 0/8	17.39 (1.90, 32.88)	3.38 (0.20, 56.59)	0.214

\* Day 30: Co-Primary Efficacy Timepoint

Exploratory analyses of subsets by patient gender suggest that both genders receive benefit, although female patients may receive somewhat greater amounts than male patients. The responder rates for both co-primary efficacy variables were higher for female subjects than for males (Tables 8 and 9).

**TABLE 8.**  
**Investigator's Assessment--Responder Rates of Glabellar Line Severity by Gender**

Investigator's Assessment At Maximum Frown % rated 0 or 1 FEMALE		Investigator's Assessment At Maximum Frown % rated 0 or 1 MALE	
DAY	BOTOX® COSMETIC	BOTOX® COSMETIC	
30 *	84.7% 283/334	59.2% 42/71	
120	27.7% 92/332	14.1% 10/71	

\* Day 30: Co-Primary Efficacy Timepoint

**TABLE 9.**  
**Subject's Assessment--Responder Rates of Glabellar Line Severity by Gender**

Subject's Assessment % +2 or better FEMALE		Subject's Assessment % +2 or better MALE	
DAY	BOTOX® COSMETIC	BOTOX® COSMETIC	
30 *	93.1% 311/334	71.8% 51/71	
120	42.8% 142/332	21.1% 15/71	

\* Day 30: Co-Primary Efficacy Timepoint

There were too few non-Caucasian patients enrolled to draw any conclusions regarding relative efficacy in racial subsets. The responder rates for both co-primary efficacy variables were slightly higher for Caucasian than for non-Caucasian subjects (Tables 10 and 11).

**TABLE 10.**  
**Investigator's Assessment--Responder Rates of Glabellar Line Severity by Race**

Investigator's Assessment At Maximum Frown % rated 0 or 1 CAUCASIAN		Investigator's Assessment At Maximum Frown % rated 0 or 1 NON-CAUCASIAN	
DAY	BOTOX <sup>®</sup> COSMETIC	BOTOX <sup>®</sup> COSMETIC	
30 *	81.2% 277/341	75.0% 48/64	
120	25.7% 87/339	23.4% 15/64	

\* Day 30: Co-Primary Efficacy Timepoint

**TABLE 11.**  
**Subject's Assessment--Responder Rates of Glabellar Line Severity by Race**

Subject's Assessment % +2 or better CAUCASIAN		Subject's Assessment % +2 or better NON-CAUCASIAN	
DAY	BOTOX <sup>®</sup> COSMETIC	BOTOX <sup>®</sup> COSMETIC	
30 *	89.7% 306/341	87.5% 56/64	
120	40.1% 136/339	32.8% 21/64	

\* Day 30: Co-Primary Efficacy Timepoint

Responder rates for both co-primary efficacy variables tended to be lower for subjects with a severe baseline score at maximum frown compared to subjects with a moderate baseline score (Tables 12 and 13). The proportion who had their score rated as none to mild at rest after treatment was higher in the **BOTOX<sup>®</sup> COSMETIC** treated group as compared to the placebo treated group ( $p \leq 0.022$ ) for every time-point beginning at Day 7 through Day 120 in study 010 and through Day 90 in study 023.

**TABLE 12.**  
**Investigator's Assessment--Responder Rates of Glabellar Line Severity by Baseline Glabellar Line Severity at Maximum Frown**

Investigator's Assessment At Maximum Frown % rated 0 or 1 MODERATE			Investigator's Assessment At Maximum Frown % rated 0 or 1 SEVERE	
DAY	BOTOX <sup>®</sup> COSMETIC	Placebo	BOTOX <sup>®</sup> COSMETIC	Placebo
30 *	95.8% 159/166	1.8% 1/56	69.5% 166/239	1.4% 1/74
120	39.6% 65/164	1.8% 1/55	15.5% 37/238	1.4% 1/73

\* Day 30: Co-Primary Efficacy Timepoint

**TABLE 13.**  
**Subject's Assessment--Responder Rates of Glabellar Line Severity by Baseline Glabellar Line Severity**

Subject's Assessment % +2 or better MODERATE			Subject's Assessment % +2 or better SEVERE	
DAY	BOTOX <sup>®</sup> COSMETIC	Placebo	BOTOX <sup>®</sup> COSMETIC	Placebo
30 *	94.0% 156/166	7.1% 4/56	86.2% 206/239	4.1% 3/74
120	50.6% 83/164	0% 0/55	31.0% 74/239	1.4% 1/73

\* Day 30: Co-Primary Efficacy Timepoint

On completion of the efficacy trial, participants were invited to participate in a multicenter, open-label, non-comparative study to evaluate the safety of repeated treatments with **BOTOX<sup>®</sup> COSMETIC** using the same dose and procedure from the previous studies. Only patients who had a glabellar line severity rating of mild or greater at maximum frown at the time of enrollment were admitted to the open-label safety evaluation study. A total of 373 subjects (72.6%) were enrolled in this open-label study and 318 subjects completed the study. There were a total of 258 subjects who received **BOTOX<sup>®</sup> COSMETIC** in the previous trials and both injections of **BOTOX<sup>®</sup> COSMETIC** during this trial (for a total treatment time of 12 months). Of these, 239 subjects completed the 120 days of follow-up after the final injection. The open-label study was designed specifically to evaluate the safety of repeated treatments. In the open-label, repeat injection study, blepharoptosis was reported for 2.1% (8/373) of subjects in the first treatment cycle and 1.2% (4/343) of subjects in the second treatment cycle. Adverse events of any type were reported for 49.1% (183/373) of subjects.

**Cosmetic Indications and Usage:**

**BOTOX<sup>®</sup> COSMETIC** is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients ≤ 65 years of age.

**Contraindications:** **BOTOX<sup>®</sup> COSMETIC** is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any ingredient in the formulation.

**Warnings:**

Do not exceed the recommended dosage and frequency of administration of **BOTOX<sup>®</sup> COSMETIC**. Risks resulting from administration at higher dosages are not known.

Caution should be exercised when administering **BOTOX<sup>®</sup> COSMETIC** to individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis, or motor neuropathy) or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome). Patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of **BOTOX<sup>®</sup> COSMETIC**. Published medical literature has reported rare cases of administration of a botulinum toxin to patients with known or unrecognized neuromuscular disorders where the patients have shown extreme sensitivity to the systemic effects of typical clinical doses. In some of these cases, dysphagia has lasted several months and required placement of a gastric feeding tube.

Dysphagia is a commonly reported adverse event following treatment of cervical dystonia patients with all botulinum toxins. In these patients, there are reports of rare cases of dysphagia severe enough to warrant the insertion of a gastric feeding tube. There is also a case report where a patient developed aspiration pneumonia and died subsequent to the finding of dysphagia.

There have also been rare reports following administration of **BOTOX** for other indications of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease.

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

**Precautions:**

*General:* Epinephrine should be available or other precautionary methods taken as necessary should an anaphylactic reaction occur.

The safe and effective use of **BOTOX<sup>®</sup> COSMETIC** depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. Physicians administering **BOTOX<sup>®</sup> COSMETIC** must understand the relevant neuromuscular and/or orbital anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures. Caution should be used when **BOTOX<sup>®</sup> COSMETIC** treatment is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle(s).

Reduced blinking from **BOTOX<sup>®</sup> COSMETIC** injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders. In the use of **BOTOX** for in the treatment of blepharospasm, one case of corneal perforation in an aphakic eye requiring corneal grafting has occurred because of this effect. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision or past pointing. Covering the affected eye may alleviate these symptoms.

Caution should be used when **BOTOX<sup>®</sup> COSMETIC** treatment is used in patients who have an inflammatory skin problem at the injection site, marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin or the inability to substantially lessen glabellar lines by physically spreading them apart as these patients were excluded from the Phase 3 safety and efficacy trials.

Injection intervals of **BOTOX<sup>®</sup> COSMETIC** should be no more frequent than every three months and should be performed using the lowest effective dose (See Adverse Reactions, Immunogenicity).

*Information for Patients:*

Patients or caregivers should be advised to seek immediate medical attention if swallowing, speech or respiratory disorders arise.

*Drug Interactions:*

Co-administration of **BOTOX<sup>®</sup> COSMETIC** and aminoglycosides<sup>1</sup> or other agents interfering with neuromuscular transmission (e.g., curare-like nondepolarizing blockers, lincosamides, polymyxins, quinidine, magnesium sulfate, anticholinesterases, succinylcholine chloride) should only be performed with caution as the effect of the toxin may be potentiated.

The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

*Pregnancy: Pregnancy Category C*

Administration of **BOTOX<sup>®</sup> COSMETIC** is not recommended during pregnancy. There are no adequate and well-controlled studies of **BOTOX<sup>®</sup> COSMETIC** in pregnant women. When pregnant mice and rats were injected intramuscularly during the period of organogenesis, the developmental NOEL (No Observed Effect Level) of **BOTOX<sup>®</sup> COSMETIC** was 4 U/kg. Higher doses (8 or 16 U/kg) were associated with reductions in fetal body weights and/or delayed ossification.

In a range finding study in rabbits, daily injection of 0.125 U/kg/day (days 6 to 18 of gestation) and 2 U/kg (days 6 and 13 of gestation) produced severe maternal toxicity, abortions and/or fetal malformations. Higher doses resulted in death of the dams. The rabbit appears to be a very sensitive species to **BOTOX<sup>®</sup> COSMETIC**.

If the patient becomes pregnant after the administration of this drug, the patient should be apprised of the potential risks, including abortion or fetal malformations that have been observed in rabbits.

*Carcinogenesis, Mutagenesis, Impairment of fertility:* Long term studies in animals have not been performed to evaluate carcinogenic potential of **BOTOX<sup>®</sup> COSMETIC**.

The reproductive NOEL following intramuscular injection of 0, 4, 8, and 16 U/kg was 4 U/kg in male rats and 8 U/kg in female rats. Higher doses were associated with dose-dependent reductions in fertility in male rats (where limb weakness resulted in the inability to mate), and testicular atrophy or an altered estrous cycle in female rats. There were no adverse effects on the viability of the embryos.

*Nursing mothers:* It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **BOTOX<sup>®</sup> COSMETIC** is administered to a nursing woman.

*Pediatric use:* Use of **BOTOX® COSMETIC** is not recommended in children.

*Geriatric use:* Clinical studies of **BOTOX® COSMETIC** did not include sufficient numbers of subjects aged 65 and over to determine statistically whether they respond differently from younger subjects. However, in the two identical phase 3 randomized 3:1, multi-center, double blind, placebo-controlled, parallel-group efficacy studies, the responder rates for both co-primary efficacy variables were higher for subjects  $\leq 50$  years of age compared to those subjects  $\geq 65$  years of age. Analysis based on a combined data set showed that, for the investigator's assessment endpoint of subjects aged 65 and over at Day 30, 39% (9/23) of subjects were responders compared to 22% (2/9) in the placebo group. This difference is neither statistically different ( $p = 0.228$ ) nor exceeds the pre-specified 30-percentage-point difference required by the definition of clinically significant. There were no statistically significant between-group differences for the investigator's assessment at maximum frown for this age group. There was a statistically significant difference in favor of **BOTOX® COSMETIC** for the subject's global assessment at all time points ( $p = 0.036$ ) except Day 120 ( $p = 0.214$ ). (See Clinical Trials Section)

There were too few patients over the age of 75 to allow any meaningful comparisons. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased cardiac function and of concomitant disease or other drug therapy.

#### **Adverse Reactions:**

##### *General:*

The most serious adverse events reported for other indications studied include rare spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility, after treatment with botulinum toxin. There have also been rare reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease (See Warnings). The exact relationship of these events to the botulinum toxin injection has not been established. Additionally, a report of acute angle closure glaucoma one day after receiving an injection of botulinum toxin for blepharospasm was received, with recovery four months later after laser iridotomy and trabeculectomy. Focal facial paralysis, syncope and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm.

##### Glabellar Lines:

In clinical trials of **BOTOX® COSMETIC** the most frequently reported adverse events following injection of **BOTOX® COSMETIC** were headache, respiratory infection, flu syndrome, blepharoptosis and nausea.

Less frequently occurring (<3%) adverse reactions included pain in the face, erythema at the injection site and muscle weakness. While local weakness of the injected muscle(s) is representative of the expected pharmacological action of botulinum toxin, weakness of adjacent muscles may occur as a result of the spread of toxin. These events are thought to be associated with the injection and occurred within the first week. The events were generally transient but may last several months.

The data described in Table 14 reflect exposure to **BOTOX® COSMETIC** in 405 subjects aged 18 to 75 who were evaluated in the randomized, placebo-controlled clinical studies to assess the use of **BOTOX® COSMETIC** in the improvement of the appearance of glabellar lines (See Clinical Studies). Adverse events of any cause were reported for 43.7% of the **BOTOX® COSMETIC** treated subjects and 41.5% of the placebo treated subjects. The incidence of blepharoptosis was higher in the **BOTOX® COSMETIC** treated arm than in placebo (3.2% vs. 0%,  $p$ -value = 0.045).

In the open-label, repeat injection study, blepharoptosis was reported for 2.1% (8/373) of subjects in the first treatment cycle and 1.2% (4/343) of subjects in the second treatment cycle. Adverse events of any type were reported for 49.1% (183/373) of subjects overall. The most frequently reported of these adverse events in the open-label study included respiratory infection, headache, flu syndrome, blepharoptosis, pain and nausea.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not be predictive of rates observed in practice.

**TABLE 14.**  
**Randomized Double Blind Studies: Rates of Adverse Events Reported by >2 or more Subjects in the BOTOX<sup>®</sup> Cosmetic Group, by Treatment Group.**

<b>Adverse Event (in order of decreasing frequency for BOTOX<sup>®</sup> Cosmetic)</b>	<b>BOTOX<sup>®</sup> Cosmetic (N=405)</b>	<b>Placebo (N= 130)</b>
Overall	177 (43.7%)	54 (41.5%)
Body as a Whole		
Headache	54 (13.3%)	23 (17.7%)
Pain in Face	9 (2.2%)	1 (0.8%)
Flu Syndrome	8 (2.0%)	2 (1.5%)
Pain at Injection Site	7 (1.7%)	1 (0.8%)
Edema at Injection Site	6 (1.5%)	3 (2.3%)
Pain in back	4 (1.0%)	3 (2.3%)
Injury accidental	3 (0.7%)	1 (0.8%)
Respiratory System		
Infection	14 (3.5%)	5 (3.8%)
Bronchitis	6 (1.5%)	1 (0.8%)
Sinusitis	6 (1.5%)	1 (0.8%)
Pharyngitis	5 (1.2%)	2 (1.5%)
Dyspnea	3 (0.7%)	0 (0.0%)
Infection sinus	3 (0.7%)	2 (1.5%)
Laryngitis	3 (0.7%)	0 (0.0%)
Rhinitis	3 (0.7%)	2 (1.5%)
Skin and Appendages		
Erythema	7 (1.7%)	2 (1.5%)
Skin Tightness	4 (1.0%)	0 (0.0%)
Irritation Skin	3 (0.7%)	0 (0.0%)
Digestive System		
Nausea	12 (3.0%)	3 (2.3%)
Dyspepsia	4 (1.0%)	0 (0.0%)
Tooth Disorder	4 (1.0%)	0 (0.0%)
Liver Function Abnormal	3 (0.7%)	2 (1.5%)
Special Senses		
Blepharoptosis	13 (3.2%)	0 (0.0%)
Nervous System		
Dizziness	5 (1.2%)	2 (1.5%)
Paresthesia	4 (1.0%)	1 (0.8%)
Anxiety	3 (0.7%)	0 (0.0%)
Twitch	3 (0.7%)	0 (0.0%)
Musculoskeletal System		
Muscle Weakness	8 (2.0%)	0 (0.0%)
Urogenital System		
Infection Urinary Tract	4 (1.0%)	1 (0.8%)
Hemic and Lymphatic System		
Ecchymosis	7 (1.7%)	3 (2.3%)
Cardiovascular		
Hypertension	4 (1.0%)	0 (0.0%)

In published literature of the use of botulinum toxin type A for facial lines, there has been a single reported incident of diplopia, which resolved completely in three weeks. Transient ptosis, the most frequently reported complication, has been reported in the literature in approximately 5% of patients.

Immunogenicity:

Treatment with **BOTOX<sup>®</sup> COSMETIC** for cosmetic purposes may result in the formation of antibodies that may reduce the effectiveness of subsequent treatments with **BOTOX<sup>®</sup> COSMETIC** for glabellar lines or **BOTOX<sup>®</sup>** for other indications. Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of **BOTOX<sup>®</sup> COSMETIC** treatment of the appearance of glabellar lines and the effectiveness of **BOTOX<sup>®</sup>** in the treatment of other clinical indications such as cervical dystonia, blepharospasm and strabismus by inactivating the biological activity of the toxin. The rate of formation of neutralizing antibodies in patients receiving **BOTOX<sup>®</sup> COSMETIC** has not been well studied.

The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies of the use of **BOTOX<sup>®</sup>** in the treatment of other clinical indications suggest that **BOTOX<sup>®</sup>** injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. The potential for antibody formation may be minimized by injecting the lowest effective dose given at the longest feasible intervals between injections.

**Passive Adverse Event Surveillance**

The following adverse reactions have been identified since the drug has been marketed: skin rash (including erythema multiforme, urticaria and psoriasiform eruption), pruritus, and allergic reaction. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to botulinum toxin.

Between January 1, 1990 and August 31, 2000, there have been 7 spontaneous reports of serious adverse events documented as being related to the reported cosmetic use of **BOTOX<sup>®</sup>**, including anaphylactic reaction, myasthenia gravis, decreased hearing, ear noise and localized numbness, blurred vision and retinal vein occlusion, glaucoma, and vertigo with nystagmus.

**Reporting Adverse Events**

Adverse events following use of **BOTOX<sup>®</sup> COSMETIC** should be reported to the Medical Affairs Division, Allergan Pharmaceuticals (1-800-433-8871). Adverse events may also be reported to the U. S. Department of Health and Human Services (DHHS) Adverse Event Reporting System. Report forms and reporting requirement information can be obtained from Adverse Event Reporting System (AERS) through a toll free number 1-800-822-7967.

**Overdosage:**

Signs and symptoms of overdose are not apparent immediately post injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for up to several weeks for signs or symptoms of systemic weakness or muscle paralysis.

An antitoxin is available in the event of immediate knowledge of an overdose or misinjection. In the event of an overdose or injection into the wrong muscle, immediately contact Allergan for additional information at (800) 433-8871 from 8:00 a.m. to 4:00 p.m. Pacific Time, or at (714) 246-5954 for a recorded message at other times. The antitoxin will not reverse any botulinum toxin induced muscle weakness effects already apparent by the time of antitoxin administration.

**Dosage and Administration:**

**For Intramuscular Injection Only**

**BOTOX<sup>®</sup> COSMETIC** is to be reconstituted with 0.9% sterile, non-preserved saline (100 units in 2.5 mL saline) prior to intramuscular injection. The resulting formulation will be 4.0 U per 0.1 mL and a total treatment dose of 20 U in 0.5 mL. The duration of activity of **BOTOX<sup>®</sup> COSMETIC** for glabellar lines is approximately 3-4 months. The safety and effectiveness of more frequent dosing with **BOTOX<sup>®</sup> COSMETIC** has not been clinically evaluated and is not recommended.

Reconstituted **BOTOX<sup>®</sup> COSMETIC** should be clear, colorless and free of particulate matter.

**BOTOX<sup>®</sup> COSMETIC** is supplied as a single patient use vial. The product and diluent do not contain a preservative. Once opened and reconstituted it should be stored in a refrigerator (2° to 8°C) and used within four hours. Discard any remaining solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not freeze reconstituted **BOTOX<sup>®</sup> COSMETIC**.

The method utilized for performing the potency assay is specific to Allergan's Botulinum Toxin Type A. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for the various potency assays, Units of biological activity of Botulinum Toxin Type A cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. Therefore, differences in species sensitivities to different botulinum neurotoxin serotypes precludes extrapolation of animal dose-activity relationships to human dose relationships.

**Dilution Technique:**

Using a 21-gauge, 2.5"-length needle and an appropriately sized syringe draw up a total of 2.5 mL of 0.9% sterile saline. Insert the needle at a 45° angle and slowly inject into the **BOTOX<sup>®</sup> COSMETIC** vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently rotate the vial and record the date and time of reconstitution on the space on the label.

Draw at least 0.5 mL of the properly reconstituted toxin into the sterile syringe, preferably a tuberculin syringe and expel any air bubbles in the syringe barrel. Remove the needle used to reconstitute the product and attach a 30-gauge needle. Confirm the patency of the needle.

**Injection Technique:**

Glabellar facial lines arise from the activity of the corrugator and orbicularis oculi muscles. These muscles move the brow medially, and the procerus and depressor supercillii pull the brow inferiorly. This creates a frown or "furrowed brow". The location, size, and use of the muscles vary markedly among individuals. Lines induced by facial expression occur perpendicular to the direction of action of contracting facial muscles. An effective dose for facial lines is determined by gross observation of the patient's ability to activate the superficial muscles injected.

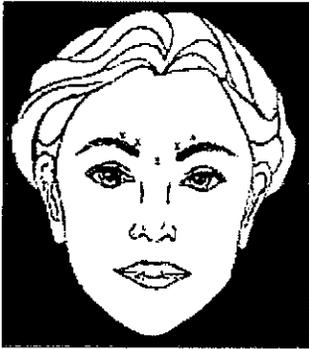
In order to reduce the complication of ptosis the following steps should be taken:

- Avoid injection near the levator palpebrae superioris, particularly in patients with larger brow depressor complexes.
- Medial corrugator injections should be placed at least 1 centimeter above the bony supraorbital ridge.
- Ensure the injected volume/dose is accurate and where feasible kept to a minimum.
- Do not inject toxin closer than 1 cm above the central eyebrow.

Allergan (ELN 1145)  
**BOTOX<sup>®</sup> COSMETIC** (Botulinum Toxin Type A) Purified Neurotoxin Complex  
(Glabellar Lines)

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Using a 30-gauge needle, inject a dose of 0.1 mL into each of 5 sites, 2 in each corrugator muscle and 1 in the procerus muscle for a total dose of 20 U. Typically the initial doses of reconstituted **BOTOX<sup>®</sup> COSMETIC** induce chemical denervation of the injected muscles one to two days after injection, increasing in intensity during the first week.



**How Supplied:** **BOTOX<sup>®</sup> COSMETIC** is supplied in a single patient use vial. Each vial contains 100 U of vacuum-dried *Clostridium botulinum* type A neurotoxin complex. NDC 0023-1145-01.

**Rx Only**

**Single use vial.**

**Storage:**

Store the vacuum-dried product in a freezer at or below -5°C. Administer **BOTOX<sup>®</sup> COSMETIC** within four hours after the vial is removed from the freezer and reconstituted. During this four hours, reconstituted **BOTOX<sup>®</sup> COSMETIC** should be stored in a refrigerator (2° to 8°C). Reconstituted **BOTOX<sup>®</sup> COSMETIC** should be clear, colorless and free of particulate matter.

All vials, including expired vials, or equipment used with the drug should be disposed of carefully as is done with all medical waste.

Revised: March 2002

Manufactured by:  
Allergan Pharmaceuticals (Ireland) Ltd.  
a subsidiary of:  
Allergan, Inc.  
2525 Dupont Dr.  
Irvine, CA 92612

**References:**

1. Wang YC, Burr DH, Korthals GJ, Sugiyama H. Acute toxicity of aminoglycoside antibiotics as an aid in detecting botulism. *Appl Environ Microbiol* 1984; 48:951-955.



Food and Drug Administration  
Center for Biologics Evaluation and Research  
1401 Rockville Pike  
Rockville MD 20852-1448

VIA FACSIMILE AND USPS

September 5, 2002

Mr. Peter A. Kresel  
Allergan, Inc.  
2525 Dupont Drive  
Irvine, CA 92623-9534

Dear Mr. Kresel:

Through routine monitoring and surveillance the Advertising and Promotional Labeling Branch (APLB) of FDA's Center for Biologics Evaluation and Research has identified promotional materials for your product, BOTOX® COSMETIC Botulinum Toxin Type A, that are in violation of the Food, Drug and Cosmetic Act and its implementing regulations. APLB has reviewed several direct-to-consumer (DTC) promotional and broadcast (15 and 30 second air-time) pieces and has concluded that these materials contain misleading statements about BOTOX® Cosmetic. Copies of all referenced materials are enclosed.

**Misleading statements:**

"It seems like everybody is talking about Botox® Cosmetic, the highly effective, non-surgical procedure that can dramatically reduce your toughest wrinkle within 7 days." This statement is prominently presented at the beginning of the Patient Brochure (Tab A) and is misleading because it does not emphasize that this is a temporary procedure. In addition, the term "toughest wrinkle" does not adequately specify the approved indication for use and misleadingly suggests that Botox Cosmetic is for use in all tough wrinkles. Please immediately cease distribution of these, and similarly worded, materials and revise these statements to clearly emphasize the temporary duration of this product and to appropriately identify the approved indication for use, e.g. "those tough lines between your eyebrows."

"Is BOTOX® Cosmetic right for you? If doing all you can to look your best is important to you, Botox® Cosmetic may be for you." These statements in the Patient Brochure (Tab A) are misleading because they fail to state that the product is indicated for patients from 18 to 65 years of age. It is not until several pages later in the brochure that the approved age range is presented to the reader. Please revise this, and all similar presentations, at the time of your next printing to accurately and clearly define the approved population when discussing "Is BOTOX® Cosmetic ...right for you?"

The dilution table on the physician page of your website, [www.botoxcosmetic.net](http://www.botoxcosmetic.net), (Tab B) listing the amount of diluents to be added to the lyophilized vial of BOTOX® Cosmetic and the resulting dose in units per 0.1mL is misleading. The chart promotes four other dilutions and doses that are not approved for the glabellar lines indication for BOTOX® Cosmetic, which could confuse the physician and/or promote off-label use. Please immediately revise this chart to only include the approved dilution scheme. In addition, please revise the statement, "Recommended dose is 4 units at each of the 5 injection sites," to "recommended dose is 4.0 units per 0.1 mL at each of the 5 injection sites for a total treatment dose of 20 units in 0.5mL."

"So you can frown, smile, or look surprised—without the furrows, creases, and wrinkles." This and similar quotes were identified in your Patient Brochure, Quick Reference Guide, and Patient Education Video (Tabs A, C, and D). These statements do not adequately identify the approved indication for use and are misleading to the reader. Please revise this, and similar, statements to appropriately identify the approved indication for use, e.g. "...so you can frown, ..., and wrinkles between your eyebrows."

**Violative Reminder Advertisements:**

The "WOW" DTC television (TV) reminder advertisements (ads), transcripts in Tab E, are in violation of 21 CFR 202.1(e)(2)(i), regarding reminder advertisements. These ads, which 1) focus attention on complexion and image, 2) make repeated references to age, and 3) make the statement, "Ask your dermatologist or plastic surgeon about BOTOX Cosmetic" include the indication for use of the product. These examples strongly suggest that the product is intended to treat the signs of aging or glabellar lines.

Allergan should immediately stop all broadcasts of these ads and all other promotional activities for Botox Cosmetic that contain the same or similar presentations until such time that you have revised these, and all other relevant, pieces to comply with the applicable regulations and have submitted them to FDA.

This is not intended to be an all-inclusive list of deficiencies associated with your promotion of the above product. It is your responsibility to ensure that all materials distributed within the United States are in conformance with each requirement of the Act and applicable regulations.

You should respond in writing within ten days of the date of this letter. Your response should include a statement confirming that the requested items were immediately discontinued, of your intent to comply with each recommendation above, a list of all similarly violative materials, and a description of the method for discontinuation and the discontinuation date.

Your response should be directed by facsimile, to 301-827-3528, or in writing to Mr. Glenn N. Byrd, Chief, APLB, at the address listed on the following page. Should you

Page 3 Mr. Kresel

have any questions or concerns involving this matter, please contact Ms. Maryann Gallagher, Regulatory Review Officer at 301-827-3028.

Center for Biologics Evaluation and Research  
Office of Compliance and Biologics Quality  
Division of Case Management  
Advertising and Promotional Labeling Branch, HFM-602  
1401 Rockville Pike, 200S  
Rockville, MD 20852-1448

Sincerely,

*Kathleen M Lewis*  
for Mary A. Malarkey  
Director, Division of Case Management  
Office of Compliance and Biologics Quality  
Center for Biologics Evaluation  
and Research

Enclosures

cc: Mr. David Garbe



## FDA Talk Paper

T04-26  
July 20, 2004

Media Inquiries: 301-827-6242  
Consumer Inquiries: 888-INFO-FDA

### FDA Approves Botox to Treat Severe Underarm Sweating

FDA has approved Botulinum Toxin Type A (Botox) to treat severe underarm sweating known as "primary axillary hyperhidrosis" that cannot be managed by topical agents such as prescription antiperspirants. Botox has already been approved for several other purposes. Today's approval allows the product's manufacturer, Allergan, Inc., Irvine, Calif., to market Botulinum Toxin Type A for this new indication.

Botulinum Toxin Type A is a protein produced by the bacterium *Clostridium botulinum*. When used to treat primary axillary hyperhidrosis, small doses of an injectable form of the sterile purified botulinum toxin stop release of the chemical messenger acetylcholine, temporarily blocking the nerves in the underarm that stimulate sweating.

Botox was first approved in December 1989 to treat two eye muscle disorders (blepharospasm and strabismus). Since then it has been approved to treat cervical dystonia, a neurological movement disorder causing severe neck and shoulder muscle contractions. Most recently, in 2002, it was approved as Botox Cosmetic to temporarily improve the appearance of moderate to severe frown lines between the eyebrows.

In two placebo-controlled, multicenter, randomized, double-blind clinical trials involving over 600 adults, those who received Botox had significantly reduced underarm sweating as compared to the placebo group. In one study, four weeks after being injected, the percentage of people showing a 50% reduction in sweating was 91% in the group receiving Botox compared to 36% in the placebo group. In another study, the average duration of response following the first treatment was 170 days.

The most common adverse events following treatment (occurring in three to 10% of patients) included injection site pain and hemorrhage, sweating in other parts of the body, flu-like symptoms, headache, fever, itching, and anxiety.

Before being treated for primary axillary hyperhidrosis, patients should be evaluated for other potential causes of the problem, such as hyperthyroidism, to avoid symptomatic treatment of hyperhidrosis with Botox without addressing a potentially serious underlying disease that requires other forms of treatment.

The safety and effectiveness of Botox for hyperhidrosis in body areas other than the axillae (armpits) has not been established.

Because Botox is a prescription drug, it must be used carefully under medical supervision for all the product's approved indications.

#####

FDA Website Management Staff

Act, as amended, 15 U.S.C. 18, and Section 5 of the Federal Trade Commission Act, as amended, 15 U.S.C. 45, by eliminating the next most likely entrant in the market for cosmetic botulinum toxins. The proposed Consent Agreement would remedy the alleged loss of potential competition that would result from the merger in this market.

Botulinum toxin is an increasingly popular, non-surgical treatment for wrinkles caused by repetitive muscle movement, such as the "worry lines" that appear on the forehead when a person frowns. Botulinum toxin is uniquely effective in temporarily eliminating these "dynamic wrinkles" because it is the only product that can paralyze the underlying muscles associated with these wrinkles. Although there are many products and procedures that can be used to treat facial wrinkles, such as dermal fillers, topical creams, lasers, chemical peels, and surgery, botulinum toxin therapy is sufficiently differentiated from these other products and procedures that they are not close economic substitutes.

Allergan is the dominant supplier of cosmetic botulinum toxin in the United States. Allergan's Botox® is the only botulinum toxin type A approved by the U.S. Food and Drug Administration ("FDA") for the treatment of facial wrinkles. In 2002, Ipsen granted Inamed the exclusive rights to develop and distribute a botulinum toxin type A product for facial cosmetic indications in the United States. Tentatively branded Reloxin®, Inamed's cosmetic botulinum toxin product is currently in Phase III clinical trials and is expected to be the first serious challenger to Botox® in the United States. Other firms' cosmetic botulinum toxin development programs lag well behind Inamed's Reloxin® program.

Entry into the market for cosmetic botulinum toxin would not be timely, likely, or sufficient in its magnitude, character, and scope to deter or counteract the anticompetitive effects of the Acquisition. Developing and obtaining FDA approval for manufacture and sale of cosmetic botulinum toxin takes at least two years due to substantial regulatory and technological barriers.

According to the Commission's complaint, the proposed acquisition likely would cause significant anticompetitive harm to consumers in the U.S. market for cosmetic botulinum toxin by eliminating potential competition between Allergan and Inamed. The entry of Reloxin®, which is expected to be the second botulinum toxin product to receive FDA approval

for the treatment of facial wrinkles, would increase competition and likely reduce prices to consumers. Accordingly, allowing Allergan to control both Botox® and Reloxin® would likely force customers to pay higher prices for cosmetic botulinum toxin.

The proposed Consent Agreement contains several provisions designed to ensure the successful and timely entry of Reloxin® by requiring that: (1) Allergan and Inamed divest the Reloxin® development and distribution rights, including the ongoing clinical trials and certain intellectual property, back to Ipsen; (2) Allergan and Inamed take steps to ensure that confidential business information relating to Reloxin® will not be obtained or used by Allergan; and (3) Ipsen and/or its future marketing partner have the opportunity to enter into employment contracts with certain key individuals who have experience relating to Reloxin®.

The Commission has appointed Charles A. Riepenhoff, Jr. of KPMG LLG as Interim Monitor to oversee the transfer of confidential business information back to Ipsen and to ensure compliance with all of the provisions of the proposed consent order. Mr. Riepenhoff has over thirty-four years of experience in the health care industry. To ensure that the Commission remains informed about the status of the proposed assets and transfers of assets, the proposed Consent Agreement requires Allergan and Inamed to file reports with the Commission periodically until the divestitures and transfers are accomplished.

The purpose of this analysis is to facilitate public comment on the Consent Agreement, and it is not intended to constitute an official interpretation of the Consent Agreement or to modify its terms in any way.

By direction of the Commission, with Commissioner Rosch recused.

Donald S. Clark,  
*Secretary.*

[FR Doc. E6-3550 Filed 3-13-06; 8:45 am]

BILLING CODE 6750-01-P

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Centers for Disease Control and Prevention

**Disease, Disability, and Injury Prevention and Control Special Emphasis Panel: Occupational Safety and Health Education, PAR-05-107, and Research Center and Occupational Safety and Health Training Projects Grants, PAR-05-126**

Correction: This notice was published in the Federal Register on March 1, 2006, Volume 71, Number 40, page 10538. The titles for the Special Emphasis Panel meetings have been changed.

*Titles:* Program Announcement for Research (PAR) 05-107, Occupational Safety and Health Education and Research Centers, and Program Announcement for Research (PAR) 05-126, Occupational Safety and Health Training Project Grants.

**FOR MORE INFORMATION CONTACT:** Charles N. Rafferty, PhD, Designated Federal Official, National Institute for Occupational Safety and Health, CDC, 1600 Clifton Road, NE., Mailstop E-74, Atlanta, GA 30333, Telephone Number (404) 498-2582.

The Director, Management Analysis and Services Office, has been delegated the authority to sign Federal Register notices pertaining to announcements of meetings and other committee management activities, for both CDC and the Agency for Toxic Substances and Disease Registry.

Dated: March 8, 2006.

Alvin Hall,

*Director, Management Analysis and Services Office, Centers for Disease Control and Prevention.*

[FR Doc. E6-3564 Filed 3-13-06; 8:45 am]

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. 2002D-0260] (formerly Docket No. 02D-0260)

**Guidance for Industry on Prescription Drug Marketing Act—Donation of Prescription Drug Samples to Free Clinics; Availability**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the

availability of a guidance for industry entitled "Prescription Drug Marketing Act—Donation of Prescription Drug Samples to Free Clinics." The guidance provides information for free clinics that receive donated prescription drug samples from licensed practitioners or other charitable institutions. The guidance discusses concerns that have been expressed by certain individuals regarding regulatory requirements for drug sample donations. The guidance announces that FDA, after reviewing an independent study report analyzing the potential effects of the regulations on free clinics, has decided to propose revisions to those regulations. In the interim, FDA intends to exercise its enforcement discretion and does not intend to object if a free clinic fails to comply with certain regulatory requirements for drug sample donations. **DATES:** General comments on agency guidance documents are welcome at any time.

**ADDRESSES:** Submit written requests for single copies of this guidance to the Division of Drug Information (HFD-240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing your requests. Submit written comments on the guidance to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

**FOR FURTHER INFORMATION CONTACT:** Meredith S. Francis, Office of Regulatory Policy (HFD-7), Center for Drug Evaluation and Research, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

**SUPPLEMENTARY INFORMATION:**

**I. Background**

FDA is announcing the availability of a guidance for industry entitled "Prescription Drug Marketing Act—Donation of Prescription Drug Samples to Free Clinics." Section 203.39 (21 CFR 203.39) of the agency's regulations sets forth requirements for donation of prescription drug samples to charitable institutions. "Charitable institution" or "charitable organization" is defined in § 203.3(f) as "a nonprofit hospital, health care entity, organization, institution, foundation, association, or corporation that has been granted an exemption under section 501(c)(3) of the

Internal Revenue Code of 1954, as amended." Under § 203.39, a charitable institution may receive drug samples donated by a licensed practitioner or another charitable institution for dispensing to its patients, or may donate a drug sample to another charitable institution for dispensing to its patients, provided certain requirements are met. These requirements include, among other things, that a drug sample donated to a charitable institution must be inspected by a licensed practitioner or registered pharmacist, and that drug sample receipt and distribution records be maintained by the institution and retained for a minimum of 3 years.

In the **Federal Register** of June 27, 2002 (67 FR 43330), FDA announced the availability of a draft guidance entitled "Prescription Drug Marketing Act Regulations for Donation of Prescription Drug Samples to Free Clinics." The draft guidance announced that FDA, in the exercise of its enforcement discretion, did not intend to object if a free clinic failed to comply with the requirements in § 203.39. The draft guidance defined the term "free clinic," which is not otherwise defined in the Federal Food, Drug, and Cosmetic Act or regulations, as a charitable institution or organization, under § 203.3(f), that actually provides health care services and relies in whole or part on drug donations and volunteer help to achieve its goals. Thus, charitable institutions that receive donated drug samples but do not provide health care services, or that provide health care services but do not rely at least in part on drug donations and volunteer help to provide those services, would not be considered free clinics. According to the draft guidance, FDA intended to exercise enforcement discretion while the agency studied the potential impact of the regulation on the ability of free clinics to receive and distribute prescription drug samples. Interested persons were given the opportunity to submit comments on the draft guidance by September 25, 2002.

Since issuing the draft guidance, FDA has received a completed study report from Eastern Research Group (ERG) analyzing the burden imposed on free clinics by the requirements in § 203.39 and the potential regulatory alternatives. According to the ERG study report, implementing § 203.39 as written could impose a significant financial burden on free clinics. Based in part on the study report's conclusions, FDA is announcing today that it intends to exercise enforcement discretion while the agency proposes revisions to § 203.39 as applied to free clinics. Specifically, as FDA works to propose

regulatory revisions, the agency does not intend to object if a free clinic fails to comply with certain parts of the regulation. The guidance clarifies that the agency's exercise of enforcement discretion with regard to certain requirements of § 203.39 will not extend to fraud or other illegal conduct involving drug samples, and that the agency could, at its discretion, initiate enforcement action for violations of any and all applicable statutory and regulatory provisions implicated by fraudulent or illegal activity. We note also that neither this notice, nor its corresponding guidance, affects or alters any requirements imposed by the U.S. Drug Enforcement Administration (DEA) on any free clinic, person, or other entity with regard to controlled substances donated to those entities. All DEA requirements relating to controlled substances remain fully in effect.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). It represents the agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

**II. Comments**

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

**III. Electronic Access**

Persons with access to the Internet may obtain the document at either <http://www.fda.gov/cder/guidance/index.htm> or <http://www.fda.gov/ohrms/dockets/default.htm>.

Dated: March 6, 2006.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. E6-3532 Filed 3-13-06; 8:45 am]

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San Francisco Chronicle

## Oral surgeons have their eyes on noses Bill would let them do elective work

John M. Hubbell, Chronicle Sacramento Bureau  
Saturday, May 15, 2004

**(05-15) 04:00 PDT Sacramento --**  
The right to perform a nose job is up  
for grabs in the state Legislature.



In an issue that swirls around Californians' endless efforts to keep up appearances, oral and maxillofacial surgeons are bidding to perform a number of common elective operations now considered the general domain of plastic surgeons. Under proposed legislation, medical professionals more associated with reconstruction of a jaw could tackle everything from eye lifts to wrinkle-erasing Botox injections.

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Oral surgeons -- many of whom are not medical doctors -- contend that the state unfairly bars them from undertaking lucrative elective surgery even as they routinely perform identical tasks when medically necessary. The bill would require them to pay a \$150 fee and gain board certification before performing the procedures at patients' requests.

"It's an equity issue," Liz Snow, public policy director for the California Dental Association, said Friday. "Many oral surgeons are currently doing work on noses. The common types of injuries in ERs are car accidents or bar fights, which frequently involve broken noses."

But some plastic surgeons see the bill, SB1336 by Sen. John Burton, D-San Francisco, as nothing less than brazen encroachment on their field of expertise.

"This goes through, I'll absolutely guarantee them they'll be doing breast surgery," said Dr. Harvey Zarem, president of the California Society of Plastic Surgeons. Oral surgeons "do great jaw work -- period. They tend to think if you have the right instruments, you can do anything. But to do a face-lift on a 55-year-old lady is a totally

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different story."

Burton's bill -- of which Republican Sen. Jim Brulte is a co-author -- cleared the Senate Business and Professions Committee in April and is scheduled to come before the Senate Appropriations Committee on Monday. Burton, who collected \$34,000 in political donations from dentist and oral surgeon groups this election cycle, could not be reached for comment.

Oral surgeons commonly perform some types of facial procedures only when a patient needs them. "Just a few weeks ago, I injected Botox into a jaw muscle, but not for cosmetic issues," said Earl Freymiller, a professor of oral surgery at the UCLA School of Medicine.

In several other states, "if you're allowed to fix a nose that's smunched, you're allowed to fix a nose somebody doesn't like," said Mark Rakich, lobbyist for the California Association of Oral and Maxillofacial Surgeons.

Thomas Hiser, the group's president, said, "Some of the plastic surgery procedures are less traumatic than taking out 25 teeth from somebody."

Hiser said oral surgeons would never aspire to move below the chin. "Breast surgery," he said, "is out of the question."

Nips and tucks are on the rise in America. Last year, doctors performed more than 125,000 face-lifts, 172,000 rhinoplasties and 2.27 million Botox treatments -- the latter increasing by 37 percent over 2002, according to the American Society for Aesthetic Plastic Surgery.

The average nose job costs up to \$7,000, Zarem said, about half of which is a surgeon's fee.

The profession does not track frequency of procedures by state, but California is understood to be the general leader.

"There's certainly an attitude of California to look your best," said Zarem, who has treated household names from his Santa Monica practice. "You can tell the difference between standing at the corner in Los Angeles and standing at the corner in Omaha."

California has about 1,500 plastic surgeons -- "no shortage," the bill's legislative analysis states. But with an estimated 800 oral surgeons practicing in the state, a change in law could widen a prospective patient's options if oral surgeons move en masse into the field.

"Fights between different types of ... practitioners have always been an important part of medicine," said Dr. David Magnus, director of Stanford University's Center for Biomedical Ethics. "One practice tries to take advantage of a niche. You see it between psychology and psychiatry -- you see it (with) nurse practitioners."

"M.D.s are often more expensive than non-M.D.s," he added. Though elective surgery is at issue here, "in an era of managed care, one thing you have to worry about is that health-care plans may push patients into less expensive alternatives."

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Surgeons quarreling over who can lift a chin may have a distinctly California élan, but "all ... specialties have tried to expand the areas in which they can operate," said Craig McDow, a San Francisco oral surgeon whose practice sits close to Union Square.

"I think of it more as an ability for one to exercise their craft and offer patients perhaps another option, and another technique that may truly address a patient's concern," McDow said. If plastic surgeons "felt it was a money grab, then the other side ... would be: 'We're trying to hold on to all the money we make.' "

*E-mail the writer at [jhubbell@sfchronicle.com](mailto:jhubbell@sfchronicle.com).*

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## A-Z TOPICS: SCIENCE IN THE NEWS

## STUDY SUGGESTS BOTOX MAY PROVIDE RELIEF FOR PATIENTS WITH TRIGEMINAL NEURALGIA

- [Overview](#)
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## Overview

Recent articles from [The New York Times](#), [WebMD](#), and [Health Day News](#) report that Botox (botulinum-A neurotoxin) may be effective in treating patients with trigeminal neuralgia, based on the findings of a small, unblinded pilot study in the October 25 issue of *Neurology*.<sup>1</sup>

Trigeminal neuralgia, or tic douloureux, is an intense facial pain caused by irritation of the trigeminal nerve, a cranial nerve with sensory branches that pass through the face and jaw. Current treatment options for trigeminal neuralgia include anticonvulsant medications such as carbamazepine (Tegretol) or phenytoin (Dilantin), which are not always effective and have side effects, and surgical interventions.

In the published study, a Brazilian and American research team investigated the therapeutic use of Botox in 13 patients with trigeminal neuralgia. Ten days post-treatment, the patients reported significant reductions in pain and most were reportedly symptom-free after 20 days. Sixty days after treatment, four patients no longer required preventive medication, and the others had their medication reduced by more than half.

Although the results of this pilot study are promising, large-scale randomized clinical trials on the therapeutic use of Botox for trigeminal neuralgia are needed to confirm the results, determine the duration of the effects, and more carefully assess any adverse events. As noted by the study authors, a placebo-controlled clinical trial is required to confirm their results. This is consistent with the findings of a recent systematic review, which identified no randomized controlled trials in this area and presented no definitive conclusions on administering Botox for the treatment of rare head and neck pain syndromes.<sup>2</sup>

The ADA has not taken a specific position on dentists administering Botox; however, a number of state dental boards have or are in the process of developing policy for its use. All dentists who are considering using Botox for treatment of dental conditions should consult their state dental board to determine if this falls within the scope of practice in their respective state and, if so, what specific requirements are necessary.

## Endnotes

1 Piovesan EJ, Tieve HG, Kowacs PA, Della Coletta MV, Werneck LC, Silberstein SD. An open study of botulinum-A toxin treatment of trigeminal neuralgia. *Neurology* 2005;65:1306-1308.

2 Sycha T, Kranz G, Auff E, Schnider P. Botulinum toxin in the treatment of rare head and neck pain syndromes: a systematic review of the literature. *J Neurol*. 2004 Feb;251 Suppl 1:119-30.

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*The Journal of the American Dental Association*

- ▶ [Treating Severe Bruxism with Botulinum Toxin](#) (February 2000)

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### Additional Resources

- ▶ [ADA Guide to Dental Therapeutics, Third Edition \(Chapter 20, Neurological Drugs\)](#)
- ▶ [ADA State Legislative Report, May 2005 | PDF file/32k](#)   ("Nip/Tuck" section)
- ▶ [ADA Government Affairs Report, August 2005 | PDF file/51k](#)    
("Scope of Dental Practice" section)
- ▶ [Botox: A Good Mix for Dentistry](#)  (Dental Products Report)
- ▶ [National Human Genome Research Institute, Learning about Trigeminal Neuralgia](#) 
- ▶ [National Institute of Neurological Disorders and Stroke](#)   
(Trigeminal Neuralgia Information Page)
- ▶ [Trigeminal Neuralgia](#)  (Medline Plus)

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Science in the News is a service by the American Dental Association (ADA) to present current information about science topics in the news. The ADA is a professional association of dentists committed to the public's oral health, ethics, science and professional advancement; leading a unified profession through initiatives in advocacy, education, research and the development of standards. As a science-based organization, the ADA's evaluation of the scientific evidence may change as more information becomes available. Your thoughts would be greatly appreciated.

Document Posted November 2005

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## CLINICAL PHARMACOLOGY

### JADA Continuing Education

# TREATING SEVERE BRUXISM WITH BOTULINUM TOXIN

ENG-KING TAN, M.D. and JOSEPH JANKOVIC, M.D.

**Background.** Locally administered botulinum toxin, or BTX, is an effective treatment for various movement disorders. Its usefulness in treating bruxism, however, has not been systematically evaluated.

**Subjects and Methods.** The authors studied 18 subjects with severe bruxism and whose mean duration of symptoms was 14.8 ± 10.0 years (range three–40 years). These subjects audibly ground their teeth and experienced tooth wear and difficulty speaking, swallowing or chewing. Medical or dental procedures had failed to alleviate their symptoms. The authors administered a total of 241 injections of BTX type A, or BTX A, in the subjects' masseter muscles during 123 treatment visits. The mean dose of the BTX A was 61.7 ± 11.1 mouse units, or MU (range 25–100 MU), per side for the masseter muscles.

**Results.** The mean total duration of response was 19.1 ± 17.0 weeks (range six–78 weeks), and the mean peak effect on a scale of 0 to 4, in which 4 is equal to total abolishment of grinding, was 3.4 ± 0.9. Only one subject (5.6 percent) reported having experienced dysphagia with BTX A.

**Conclusion.** The results of this study suggest that BTX administered by skilled practitioners is a safe and effective treatment for people with severe bruxism, particularly those with associated movement disorders. It should be considered only for those patients refractory to conventional therapy. Future placebo-controlled studies may be useful in further evaluating the potential of BTX in the treatment of bruxism.

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## CLINICAL PHARMACOLOGY

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# TREATING SEVERE BRUXISM WITH BOTULINUM TOXIN

ENG-KING TAN, M.D. and JOSEPH JANKOVIC, M.D.

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## ▶ ABSTRACT

**Background.** Locally administered botulinum toxin, or BTX, is an effective treatment for various movement disorders. Its usefulness in treating bruxism, however, has not been systematically evaluated.

**Subjects and Methods.** The authors studied 18 subjects with severe bruxism and whose mean duration of symptoms was  $14.8 \pm 10.0$  years (range three–40 years). These subjects audibly ground their teeth and experienced tooth wear and difficulty speaking, swallowing or chewing. Medical or dental procedures had failed to alleviate their symptoms. The authors administered a total of 241 injections of BTX type A, or BTX A, in the subjects' masseter muscles during 123 treatment visits. The mean dose of the BTX A was  $61.7 \pm 11.1$  mouse units, or MU (range 25–100 MU), per side for the masseter muscles.

**Results.** The mean total duration of response was  $19.1 \pm 17.0$  weeks (range six–78 weeks), and the mean peak effect on a scale of 0 to 4, in which 4 is equal to total abolishment of grinding, was  $3.4 \pm 0.9$ . Only one subject (5.6 percent) reported having experienced dysphagia with BTX A.

**Conclusion.** The results of this study suggest that BTX administered by skilled practitioners is a safe and effective treatment for people with severe bruxism, particularly those with associated movement disorders. It should be considered only for those patients refractory to conventional therapy. Future

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placebo-controlled studies may be useful in further evaluating the potential of BTX in the treatment of bruxism.

Bruxism is a diurnal or nocturnal parafunctional activity that includes tooth clenching, bracing, gnashing and grinding.<sup>1</sup> Its prevalence rates range from 5 to 96 percent in the adult population.<sup>2-5</sup> Differences in the methodology and the definitions of bruxism used in different studies contribute to the varied reported prevalence rates.

Bruxism is of great interest to dentists, oral surgeons, psychologists, neurologists, primary care physicians and others who provide treatment. Although many etiologic factors such as stress and occlusal disorders have been proposed,<sup>2,6-7</sup> bruxism's exact pathophysiology still is unknown.

Bruxism has been reported in certain neurological disorders such as Rett syndrome,<sup>8</sup> mental retardation,<sup>9</sup> anoxic encephalopathy<sup>10</sup> and cerebellar hemorrhage.<sup>11</sup> Tooth clenching, grinding or both have been reported to be particularly prevalent in patients with idiopathic, tardive and post-traumatic cranial dystonia, which is a neurological disorder manifested by abnormal spasms and movements involving the orolingualfacial musculature.<sup>12-14</sup> The majority of these patients had diurnal symptoms, though some had both diurnal and nocturnal symptoms.<sup>12</sup> These symptoms appear to be different than those of subjects with nocturnal grinding frequently reported in the dental literature.

Various treatment modalities have been reported to be useful for bruxism,<sup>2,15-20</sup> but there is no general agreement as to what is the best therapeutic option.

Botulinum toxin, or BTX, is the most potent known biological toxin and is a safe and effective for treatment of various forms of neurological disorders.<sup>21,22</sup> Training guidelines have been established for the use of BTX.<sup>23-25</sup> This neurotoxin is produced by the anaerobic bacterium *Clostridium botulinum* and exerts its paralytic effects by inhibiting the release of acetylcholine at the neuromuscular junction. The toxin is a zinc endopeptidase that cleaves one or more proteins in the docking of the acetylcholine with the presynaptic membrane, thus inhibiting the release of the acetylcholine into the neuromuscular junction. This results in local chemodenervation and focal muscle weakness.

Seven antigenically distinct types of BTX have been recognized: A, B, C, D, E, F and G. Type A, which cleaves the plasma protein SNAP-25, is the most common commercially used type of BTX, but clinical experience with types B, C and F is increasing.<sup>26</sup>

BTX is administered by intramuscular injection, and its effects last an average of three to six months. The extent of this transient denervation is dependent on the dose and volume of the toxin.

The unit of measurement for BTX type A, or BTX A, is the mouse unit, or MU. One MU is equivalent to the amount of toxin found to kill 50 percent of a group of 18- to 20-gram female Swiss Webster mice. The usual maximum recommended dose is 300 to 400 MU per session and not more than 400 MU per three-month period. The dose, however, varies depending on the size of the target muscle, the intensity of contraction and other factors such as response to the initial treatment.

To date, no anaphylaxis or deaths attributable to BTX A have been reported. BTX is contraindicated in patients with neuromuscular disease, who are receiving aminoglycosides or who are pregnant or lactating. Long-term effects of BTX are mild and may include alterations in muscle fiber size.<sup>27</sup>

No known reports exist on quantified results; however, there have been a few anecdotal reports demonstrating the effectiveness of BTX in patients with bruxism.<sup>28-30</sup>

In an open-label prospective study, we evaluated the effectiveness and complications of BTX A (BOTOX, Allergan Inc.) treatment in patients with severe bruxism. These patients' bruxism was manifested by diurnal or nocturnal tooth grinding, and a majority of them had associated movement disorders.

## ► SUBJECTS AND METHODS

We included in the study patients who were evaluated at Baylor College of Medicine's Parkinson's Disease Center and Movement Disorders Clinic over an eight-year period, who complained of teeth clenching and grinding as their predominant symptoms, and who satisfied the following diagnostic criteria: tooth-grinding sounds corroborated by family members or caregivers; difficulty in chewing, swallowing or speech; tooth wear; receipt of medical therapies and dental procedures that failed to alleviate bruxism; and pain or hypertrophy of masseter muscles from palpation during a clinical examination. In addition to the diagnosis of bruxism, we required at least one follow-up evaluation after BTX treatment. We excluded patients with histories of severe trauma to the jaw, dental surgeries or both that preceded their bruxism, as we were not sure whether the procedures were performed to treat the bruxism or for other reasons such as to treat trauma.

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A total of 18 subjects, 17 of whom were women, met our criteria to participate in the study. Their mean age was  $50.6 \pm 20.7$  years (range 18–80 years), and the average time they had experienced bruxism was  $14.8 \pm 10.0$  years (range three–40 years). The mean duration of follow-up was  $3.3 \pm 2.8$  years (range 0.4–eight years). All of the subjects had diurnal or nocturnal tooth grinding or both, but the majority had predominant diurnal symptoms. The most common associated movement disorder was dystonia (Table 1<sup>□</sup>).

**View this table:** [TABLE 1 FEATURES IN SUBJECTS WITH BRUXISM.](#)

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Before we administered BTX injections, the subjects were required to sign a written informed consent form that had been approved by Baylor College of Medicine's Institutional Review Boards for Human Research.

We placed each subject in the supine position, localized the muscles by careful palpation and then injected BTX A in the masseter muscles—the active muscles that caused the grinding—at two to three sites. We administered a total of 241 BTX A injections in the subjects' masseter muscles during 23 treatment visits—121 injections in the right masseter muscles and 120 injections in the left masseter muscles. The mean dose of BTX A was  $61.7 \pm 11.1$  MU (range 25–100 MU) per side for the masseter muscles. (The formulation and preparation of BTX A have been described previously.<sup>21</sup>) The mean time interval between BTX A treatments was  $5.0 \pm 1.8$  months (range 3.2–9.7 months).

We also administered BTX A injections in the relevant muscles of 14 subjects who had evidence of associated dystonia—a clinical diagnosis defined as muscle spasm resulting in abnormal posturing—in other anatomical regions (face, neck, and arms and legs) on clinical examination.

We defined latency of response of BTX A's effect as the number of days between the injection and the first sign of improvement after the injection. We defined peak effect as the maximum benefit obtained from the injection; it was rated on a scale of 0 to 4 (0 = no effect, 1 = mild improvement, 2 = moderate improvement but no change in function, 3 = moderate improvement in severity and function, and 4 = marked improvement in severity and function). We determined each subject's peak effect after a careful review of his or her daily diary (a self-assessment of severity of symptoms) and own perception of response, as well as interviewing his or her spouses and friends. We defined the maximum duration of response as the number of weeks during which the subjects experienced peak effect and defined total duration of response as the entire period after the injection was administered during which subjects experienced any improvement.

We collected the following information and entered it into a database:

- demographic data;
- etiology of bruxism;
- duration of bruxism;
- associated dystonia or movement disorders in other body parts;
- family history of bruxism or movement disorders;
- site and number of BTX A injections;
- mean and cumulative muscle dose;
- number of treatment visits;
- number of subjects and treatment visits with complications;
- types, duration and severity of complications;
- response to BTX—measured by peak effect—latency to response and maximum and total duration of response.

## ► RESULTS

The subjects' mean latency to response was  $2.7 \pm 1.7$  days (range 0.5–five days). Their mean maximum and total duration of response were  $11.7 \pm 4.1$  weeks (range 2.5–18 weeks) and  $19.1 \pm 17$  weeks (range six–78 weeks), respectively. The mean peak effect of BTX was

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3.4 ± 0.9 (range 0–4).

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Only one subject (5.6 percent) reported experiencing an adverse effect—dysphagia—with BTX A, and some adverse effects were noted at six of the 123 treatment visits (4.9 percent). The mean duration of complications was 34.7 ± 7.0 days (range 21–40 days).

## ► CASE REPORTS

**Case 1.** A 79-year-old woman with a long history of bipolar disorder came to Baylor College of Medicine's Parkinson's Disease Center and Movement Disorders Clinic because she walked slowly and had abnormal mouth and tongue movements. In addition, she complained of experiencing severe tooth grinding for three years. The audible grinding sounds that occurred day and night regularly disturbed her family members. She experienced severe tooth wear, particularly on her mandibular teeth, and underwent various dental procedures, including insertion of dentures. This treatment temporarily alleviated her grinding, but the relief did not last. Her speech and swallowing were affected by the severe grinding. She had been prescribed various pharmacological therapies by her physicians but had not experienced any relief.

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When we examined her, we noted that she had mild parkinsonian symptoms and a symptomatic shuffling gait, as well as stereotypical movements of her tongue and mouth. Audible tooth-grinding sounds were noted at the time of examination. She also had jaw tenderness and bilateral masseter muscle spasms on clinical palpation. Although she was diagnosed with early Parkinson's disease, her parkinsonism and severe bruxism were likely secondary to neuroleptic usage, as she had a history of exposure to neuroleptics for treatment of her bipolar disorder, and she had tongue and mouth movement suggestive of tardive dyskinesia.

We injected 60 MU of BTX A in each of both masseter muscles, as well as 10 MU of BTX in the submental muscle because of presence of a mild spasm in this muscle.

She reported improvement of her grinding within few days, and it gradually stopped one month after the injection. Her jaw pain also resolved, and she was able to speak and swallow without problems. She did not receive any further BTX A injections. At one and one-half years after she received BTX A treatment, her grinding did not recur, though there were a few episodes of tooth clenching.

**Case 2.** We examined a 19-year-old woman with cerebral palsy and seizures secondary to perinatal anoxia at the clinic. Abnormal muscle spasms in her face, neck, and arm and leg muscles had developed by time she was two years of age. She had experienced tooth wear resulting in broken teeth that had been restored. Her evaluation stemmed from grinding that was mostly intermittent, though there were occasions when she would grind continuously throughout the day. Her parents had noticed audible tooth-grinding sounds predominantly during the day.

When we examined her, we found the presence of eyelid muscles spasms (blepharospasm) and mild neck and limb muscles spasms, and heard grinding sounds. She had jaw tenderness and bilateral masseter muscle spasms on clinical palpation.

We injected 50 MU of BTX in each of both masseter muscles, as well as 30 MUs of BTX in her eyelid and brow muscles.

Her parents reported that her grinding improved by at least 75 percent within a day of the injection. The improvement had lasted for four months.

## ► DISCUSSION

While no central nervous system structures associated with teeth grinding have been identified, it has been speculated that, in some cases, bruxism may be a part of dystonia and share similar pathophysiology.<sup>12</sup> A higher prevalence rate of bruxism has been reported in cranial-cervical dystonia compared with normal controls.<sup>12</sup> Patients with neurological disorders such as Rett syndrome and anoxic encephalopathy or who are in a comatose state might have more severe bruxism.

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It has been postulated that the activation of phasic jaw activity depends on the interaction among the motor, limbic and autonomic systems, resulting in either disinhibition or facilitation of a "central bruxism generator."<sup>31</sup> There is evidence of anatomical connections between the limbic system, pontine reticular formation and the trigeminal motor nucleus.<sup>32</sup>

How a single dose of BTX A injection in the masseter muscles totally abolishes severe bruxing behavior, as illustrated in our first case report, is intriguing. There also has been a reported case of total resolution of bruxism—caused by a brain injury—after a single injection of BTX.<sup>28</sup> We speculate that jaw muscle paralysis induced by BTX A may disrupt the feedback loop from the trigeminal motor nucleus and inhibit the central bruxism generator. Alternatively, it also may deactivate periodontal mechanoreceptors during mastication, which have been thought to have a facilitatory effect on jaw closure motoneurons.<sup>33</sup>

## ► CONCLUSIONS

This study of 18 subjects with severe bruxism provides evidence that BTX A administered appropriately into the masseter muscles is a safe and effective treatment for this condition.

The subjects had experienced their symptoms for a mean of 14.8 years before the initial injection. Before BTX A treatment, the subjects' bruxism had failed to respond to various medical therapies and dental procedures, providing further evidence of its severity (Table 1). Marked relief of grinding and functional improvement in chewing,

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swallowing or speaking was reported in 16 subjects (88.9 percent) after BTX A treatment. The mean latency to response of action of BTX was relatively short (2.7 days) in our subjects, and the total effect of each injection lasted up to a mean of 19.1 weeks (Table 2). On the average, subjects received BTX A injections at a regular interval of five months; each time a mean dose of about 62 MU per side was injected in the masseter muscles. This dose was, on average, higher than the treatment we gave to patients with jaw closing dystonia in a previous study.<sup>21</sup> We did not administer BTX A in the temporalis muscles of our subjects and do not know if this would have further improved the results.

**View this table:** TABLE 2 TREATMENT, RESPONSE AND COMPLICATIONS OF BOTULINUM TOXIN TYPE A.  
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The treatment complication rate was low. Only one subject (5.6 percent) reported experiencing transient dysphagia, which did not require change of diet after we injected the BTX A. This complication constituted only six of the 123 treatment visits (4.9 percent) in the study. The complication rate was comparable to that of patients with dystonia treated with BTX in our previous study.<sup>21</sup>

A chief difficulty in assessing the severity of bruxism and a response to therapy is the lack of consensus on the definition of bruxism; a validated severity scale is not available. Based on various criteria used in the literature,<sup>20</sup> we had defined severe bruxism in those with daily audible teeth grinding as corroborated by family members or caregivers.

All of the subjects in the study were partially disabled by the bruxism because of impaired chewing, swallowing or speaking; tooth wear; and temporomandibular joint tenderness or hypertrophy of the masseter muscles on palpation. While this study has shown that BTX A is effective for treating severe bruxism, it must be pointed out that our subjects appear to be more affected by bruxism than patients with nocturnal symptoms who are frequently encountered in a dental practice. Most of the subjects in this study had associated diurnal movement disorders such as dystonia.

In summary, our study of a select group of subjects (the majority of whom had associated movement disorders) has demonstrated that BTX A injections can be a safe and effective treatment for severe tooth grinding. It is, however, an expensive treatment and should be considered as a therapeutic option only for those who have complicated or disabling bruxism and are refractory to other medical and dental therapy. BTX A should be administered only by clinicians with knowledge of its pharmacology and the relevant anatomy of the sites to be injected. Experience and skill in the techniques of injections will minimize the risk of unnecessary complications. Future placebo-controlled studies may be useful to further evaluate the potential of BTX A treatment in bruxism.

## FOOTNOTES

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# American Board of Oral and Maxillofacial S

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## General Information

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## FAQ

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### What is Oral and Maxillofacial Surgery?

Oral and Maxillofacial Surgery is the specialty of dentistry which includes the diagnosis, surgical and adjunctive treatment of disease, injuries and defects involving both the functional and esthetic aspects of the hard and soft tissues of the oral and maxillofacial region.

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### What does it mean to be Board Certified in Oral and Maxillofacial Surgery?

#### Education

Your Board Certified Oral and Maxillofacial Surgeon has graduated from an accredited dental school and is licensed in the state in which he/she practices. In addition, this individual has completed an oral and maxillofacial surgery residency program approved by the American Dental Association's Commission on Dental Accreditation.

The American Board of Oral and Maxillofacial Surgery is recognized by the American Dental Association as the specialty board for oral and maxillofacial surgery. The Board is responsible for reviewing all applicants for board certification as well as administering the examinations involved in the certification process.

During his/her oral and maxillofacial surgery residency, your board certified Oral and Maxillofacial Surgeon received graduate training in other disciplines such as general surgery, plastic surgery, medicine, anesthesia and pathology. Oral and Maxillofacial Surgeons are trained to treat patients in the hospital, outpatient facilities, surgery centers and in private offices.

#### **Certification**

In order to become board certified, an individual must complete an intensive application and examination process. Applicants for board certification in oral and maxillofacial surgery must provide verified written evidence of their educational and training qualifications. In addition, these individuals must provide evidence of their experience in all aspects of oral and maxillofacial surgery. Letters of recommendation from board certified Oral and Maxillofacial Surgeons attesting to an applicant's acceptable ethical and moral standing in the profession and community are also required as part of the certification procedure. The applications of all candidates for board certification are reviewed by the Board's Credentials Committee.

#### **Continued Competence**

Finally, your board certified Oral and Maxillofacial Surgeon was required to pass both a thorough written qualifying examination and a rigorous oral certifying examination to be certified as a Diplomate of the American Board of Oral and Maxillofacial Surgery. Diplomates are encouraged to maintain current competence by ongoing continuing education.

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Diplomates are recertified in current competency every ten years by a comprehensive written examination.

Continuing professional education is an important tool keeping Oral and Maxillofacial Surgeons current on new developments in the field. This is accomplished through national meetings, seminars, lectures, special courses, panels, symposia, and self study. The Board Certified Oral and Maxillofacial Surgeon has demonstrated a commitment to continued professional development. The American Board of Oral and Maxillofacial Surgery encourages its Diplomates to continue their professional development through various educational experiences.

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#### **What services do Board certified Oral and Maxillofacial Surgeons provide?**

##### **Removal of Diseased and Impacted Teeth, and Anesthesia**

Oral and Maxillofacial Surgeons remove impacted, damaged, and non-restorable teeth. They also provide sophisticated, safe, and effective anesthesia services in their office including intravenous (IV) sedation and general anesthesia.

##### **Dental Implants**

Oral and Maxillofacial Surgeons, in close collaboration with restorative dentists, help plan and then place implants used to replace missing teeth. They can also reconstruct bone in places needing bone for implant placement and modify gingival (gum) tissue surrounding implants when necessary to make teeth placed on implants look even more natural.

##### **Facial Trauma**

Oral and Maxillofacial Surgeons care for facial injuries by repairing routine and complex facial skin lacerations (cuts), setting fractured jaw and facial bones, reconnecting severed nerves and ducts, and treating other injuries. These

procedures include care of oral tissues, the jaws, cheek and nasal bones, the forehead, and eye sockets.

**Pathologic Conditions**

Oral and Maxillofacial Surgeons manage patients with benign and malignant cysts and tumors of the oral and facial regions. Severe infections of the oral cavity, salivary glands, jaws, and neck are also treated.

**Reconstructive and Cosmetic Surgery**

Oral and Maxillofacial Surgeons correct jaw, facial bone and facial soft tissue problems left as the result of previous trauma or removal of pathology. This surgery to restore form and function often includes moving skin, bone, nerves, and other tissues from other parts of the body to reconstruct the jaws and face. These same skills are also used when oral and maxillofacial surgeons perform cosmetic procedures for improvement of problems due to unwanted facial features or aging.

**Facial Pain Including Temporomandibular Joint Disorders**

Oral and Maxillofacial Surgeons possess skills in the diagnosis and treatment of facial pain disorders including those due to temporomandibular joint (TMJ) problems.

**Correction of Dentofacial (Bite) Deformities and Birth Defects**

Oral and Maxillofacial Surgeons, usually in conjunction with an orthodontist, surgically reconstruct and realign the upper and lower jaws into proper dental and facial relationships to provide improved biting function and facial appearance. They also surgically correct birth defects of the face and skull including cleft lip and palate.

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**What does it mean to be a candidate for certification?**

There is no specific status that indicates a surgeon's (candidate's) progress through the certification process. Rather the ABOMS will respond to inquiries by confirming whether an individual is a candidate actively participating in the ABOMS certification process. All references to "board eligibility" for candidates have been discarded. This decision was made for a variety of reasons. There is an issue of use of the term by those who were not actively pursuing certification and thus misleading the public and other communities of interest. In addition, the term has a variety of meanings within the communities of interest and therefore has lost its precise usefulness. Lastly the term has become obsolete for many of the parties seeking a surgeon's certification status.

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**Public Disclosure**

Upon written inquiry, the Board will verify the status of any Diplomate or candidate. The Board will routinely report by mail, fax, or at [www.aboms.org](http://www.aboms.org) whether individuals are certified or not. Additional information regarding an individual's status will be provided to any party only upon receipt of a written request and a signed release of information from the individual in question.

Patients: may contact the ABOMS directly at 312.642.0070 to verify board

certification status of their oral and maxillofacial surgeon.

Interested Parties: may access this information utilizing the "Verification of Certification" menu selection on this website.

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