Botulinum toxin type A injections: Adverse events reported to the US Food and Drug Administration in therapeutic and cosmetic cases

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Background: Botulinum toxin type A (BTA) (Botox) received Food and Drug Administration (FDA) approval for therapeutic treatment of strabismus and blepharospasm in 1989, cervical dystonia in 2000, and cosmetic treatment of glabellar wrinkles (Botox Cosmetic) in 2002. In 2002 alone there were approximately 1.1 to 1.6 million patients using cosmetic BTA. Our objective was to review adverse event (AE) reporting to the FDA after BTA administration.

Methods: We reviewed all (therapeutic and cosmetic use) serious (per FDA regulations) AEs reported to the FDA for the 13.5 years since licensure of the product (December 1989-May 2003) and nonserious AEs reported from December 2001 to November 2002. AEs are reported to the FDA through the MedWatch system.

Results: We reviewed 1437 AE reports; 406 followed therapeutic use of BTA (217 serious and 189 nonserious) and 1031 followed cosmetic use (36 serious and 995 nonserious). Reported AEs occurred predominantly in female patients, with a median age of 50 years. In the year December 2001 to November 2002, when both serious and nonserious reports were evaluated, the proportion of reports classified as serious was 33-fold higher for therapeutic than for cosmetic cases. The 217 serious AEs reported in therapeutic cases involved a wide spectrum of events and included all 28 reported deaths. Among cosmetic users, no deaths were reported and, of the 36 serious AEs, 30 were included as possible complications in the FDA-approved label. The remaining 6 serious AEs did not display a pattern suggesting a common causal relationship to BTA. Among the 995 cosmetic cases reported to have nonserious AEs, most commonly noted were lack of effect (623, 63%), injection site reaction (190, 19%), and ptosis (111, 11%).

Conclusions: Serious AEs were more likely to be reported for therapeutic than for cosmetic use, which may be related to higher doses, complicated underlying diseases, or both. Among cosmetic cases, few serious AEs were reported, and these were predominantly events that were previously recognized in clinical trials of BTA for the labeled use. This study is limited primarily by the incomplete nature of AE reporting by clinicians. Numerous departures from FDA-approved recommendations for drug dose, dilution, handling, site of injection, and storage were noted in these AE reports. (J Am Acad Dermatol 2005;53:407-15.)

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Justinus Kerner (1786-1862), poet and German physician, first studied the powerful effects of botulinum toxin during the Napoleonic Wars, after it was noted that there was an increase in food-poisoning deaths in persons who had eaten blood sausages. After a series of animal and self-experiments, he hypothesized that the toxin was produced under anaerobic conditions, acted on the autonomic and motor nervous system, and was lethal in small doses.[1] In the 1960s, Scott et al[2-4] investigated therapeutic uses of the drug in monkeys, and later in human beings with strabismus and blepharospasm. The Food and Drug Administration (FDA) approved botulinum toxin type A (BTA) for these therapeutic indications in

1989. In 2000, the FDA expanded the approved indications to include cervical dystonia. In 2002, FDA approved the use of BTA for cosmetic use (Botox Cosmetic, a BTA preparation identical to Botox) "for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients." FDA-approved labeling (the professional package insert) does not specify an upper dosing limit for therapeutic use,[5] but indicates that the maximum dose per treatment session for glabellar lines is 20 U for all injection sites combined.[6]

In the past 20 years, BTA has been used for a wide spectrum of off-label (ie, not approved by FDA) therapeutic[7] and cosmetic indications. Indications not approved by FDA, but studied and reported in the medical literature, include extracervical spasticities,[8,9] especially for patients with cerebral palsy,[10-16] poststroke spasticity,[17,18] and piriformis syndrome.[19,20] Other reports describe off-label uses for a wide range of neurologic,[21-26] dermatologic,[27-32] gastrointestinal,[33-42] and other clinical[43-51] disorders, often without controlled clinical trials. Off-label use of a licensed drug or biologic product occurs with a wide range of products.[52-54] The only cosmetic use of BTA approved by the FDA is for the temporary improvement in the appearance of moderate to severe glabellar lines,[6] but some practitioners inject other sites, particularly the extraglabellar facial areas such as crow's-feet lateral to the eyes and frown lines of the forehead.[55-57] The FDA does not have authority to control decisions made by qualified health care practitioners to prescribe products for conditions other than those described in FDA-approved professional labeling, or to otherwise regulate medical or surgical practice.

This report summarizes postmarket suspected BTA side effect reports to the FDA after therapeutic and/or cosmetic use of the product, including both labeled and unlabeled indications. It supports recommendations to monitor both labeled and unlabeled indications from a previous FDA review.[58]

Independent surveys by the American Society for Aesthetic Plastic Surgery and the American Society of Plastic Surgeons suggest that, in 2002, between 1.1 and 1.6 million patients in the United States received cosmetic injections with BTA.[55,57] In April 2003, 1 year after licensure of Botox Cosmetic, we undertook a comprehensive review of postlicensure adverse event (AE) reporting to the FDA. This report summarizes postmarket suspected BTA side effect reports to the FDA after therapeutic and/or cosmetic use of the product.

METHODS

The FDA receives reports through the MedWatch system of AEs that follow the use of licensed drug, biologic, and other products.[59] Although manufacturers are required to report all AEs of which they become aware, reporting by clinicians and others is encouraged but remains voluntary. Given the voluntary nature of the reporting by clinicians or others (except manufacturers), AEs reported to MedWatch represent only a subset of the actual number that occur.[59-61]

Multiple factors, including publicity, may influence reporting. Furthermore, an AE reported to have occurred during or after administration of any pharmaceutic product may represent either a simple temporal (only coincidental) or a true causal association with use of the product. In addition, MedWatch reports often lack complete information. For these reasons, it is usually difficult, or impossible, to assess causality from these reports. However, characteristics of individual reports, or patterns in multiple reports, can suggest possible previously unrecognized risks that may warrant further investigation.

We classified AEs as serious if they met the US Code of Federal Regulations 600.80 regulatory definition: "... death, a life-threatening adverse drug experience, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect ... or ... intervention to prevent one of [these outcomes] ...." We refer to all other AEs as nonserious, although some events not meeting the regulatory criteria for serious could still be of significant concern to patients and their physicians (eg, persistent headaches, facial paralysis, or ptosis).

We reviewed serious AEs in the FDA's AE reporting system, since BTA's licensure in December 1989 through May 2003, in which the reporter identified BTA as the primary suspect medication. Because of the large number of nonserious AEs reported with BTA as the primary suspect, we limited review of these reports to the 1-year period from December 2001 through November 2002. Based on the reported indication, we classified BTA recipients as patients of therapeutic or cosmetic use. We classified reported indications as on-label (ie, included in the FDA-approved labeling current at the time of this review), off-label (ie, not included in the current FDA-approved labeling), or possibly on-label (ie, when the reported indication was not well specified). We considered all AEs mentioned in FDA-approved labeling as possible risks to be "known." We reviewed all submitted reports and information;

when a reporter (eg, physician, pharmacist, or manufacturer) communicated an AE related to a drug, that report was accepted at face value and tabulated without reinterpretation.

RESULTS

We reviewed 1437 AE reports, 406 among therapeutic cases and 1031 in cosmetic cases. Annual reports of serious AEs increased from 2 in 1991 to 41 in 2002 (Fig 1), as annual sales increased from 38,000 to 1,505,200 vials in the corresponding years (M. Brin, MD, Allergan, written communication of annual sales data, used with permission, May 2004).

Table I shows the characteristics of the 1437 AE reports. Patients of therapeutic and cosmetic use were predominantly female (68% and 82%) with median ages near 50 years. Indication for use was clearly off-label for a large proportion (45% and 33%) of reported AEs. In the 1-year period from December 1, 2001, to November 30, 2002, during which both serious and nonserious AEs were reviewed, the proportion of reports classified as serious was 33-fold higher for therapeutic than for cosmetic cases (19.5% vs 0.6%, respectively). Median BTA dose was 4-fold higher in reports for therapeutic cases than cosmetic cases (100 vs 25 U).

AEs after therapeutic use

Of the 406 reports related to therapeutic use, 217 met the FDA's definition of serious. As shown in Table II, these AE reports covered a wide spectrum of events, including 28 deaths and 17 seizures.

Among the 28 deaths, 6 were attributed to respiratory arrest, 5 to myocardial infarction, 3 to cerebrovascular accident, 2 to pulmonary embolism, 2 to pneumonia (1 known to be aspiration pneumonia), 5 to other known causes, and 5 to unknown causes of death. Death occurred a median of 3 days after BTA injection (range: <1 hour-120 days). The median age of BTA recipients who died was 44 years (range: 3-91 years). Of 28 patients who died, 26 had underlying systemic diseases with elevated risk of mortality, in addition to the symptoms for which they received BTA. The possibility of a causal role for underlying diseases made it difficult to evaluate the role of BTA in the fatalities.

Apart from reported deaths, a wide spectrum of serious AEs was reported among therapeutic cases (Table II). Most of the serious AEs (91%, 198/217) corresponded to potential risks described in the FDA-approved labeling (eg, dysphagia [n = 26], muscle weakness [n = 13], allergic reactions [n = 11], flu-like syndromes [n = 10], injection site trauma [n = 9], arrhythmia [n = 9], myocardial infarction [n = 6]). There were no more than 3 reports of any single serious unlabelled AE among therapeutic cases. Most of the 189 nonserious AEs reported for therapeutic cases were likewise included in the approved labeling.

After excluding cases that occurred more than 16 days posttreatment, 17 patients with therapeutic use were classified as having experienced seizures, which is not listed in the approved labeling. A history of seizure was noted for 3 patients; another 12 had a pre-existing condition that may have elevated their risk for seizure (eg, history of cerebral infarction). Among the two without a seizure history or predisposing condition, it was unclear from the report whether seizure or syncope occurred. Time from BTA administration to reported seizure ranged from a few minutes to 16 days (median: 2 hours).

AEs after cosmetic use

No deaths were reported for cosmetic cases. Among the 36 patients who experienced serious AEs, 30 were labeled AEs and were similar to those that occurred among therapeutic cases, including headaches, focal facial paralysis, muscle weakness, dysphagia, flu-like syndromes, and allergic reactions. Among 6 unlabelled serious reports, there was no more than one of any particular type of serious AE. About a third (13 of 36) of the patients with cosmetic use and serious AEs had an underlying disease that may have been related to the reported AE (eg, a BTA user with asthma was reported with respiratory compromise after BTA injection; a BTA user with a history of heart murmur was reported with arrhythmia post-BTA injection).

Among 995 cosmetic cases with a nonserious AE, lack of intended cosmetic effect was most commonly noted (623, 63%). Injection site reaction (190, 19%), ptosis (111, 11%), muscle weakness (51, 5%), and headache (46, 5%) were also frequently reported; all are recognized possible sequelae of BTA use. For 124 of the 995 reports, more than one AE was reported. Specific AEs that were not mentioned in the approved labeling each constituted less than 1% of the 995 reports received.

DISCUSSION

Clinical characteristics of AE reports submitted to the FDA for therapeutic cases differed from those of cosmetic BTA cases. For therapeutic cases, doses were higher, a larger proportion of AEs reported were classified as serious, deaths were reported, and patients tended to have serious underlying diseases. For cosmetic cases, no deaths were reported; patients typically had no underlying disease reported, and patients were injected with much smaller doses of BTA, albeit most still in excess

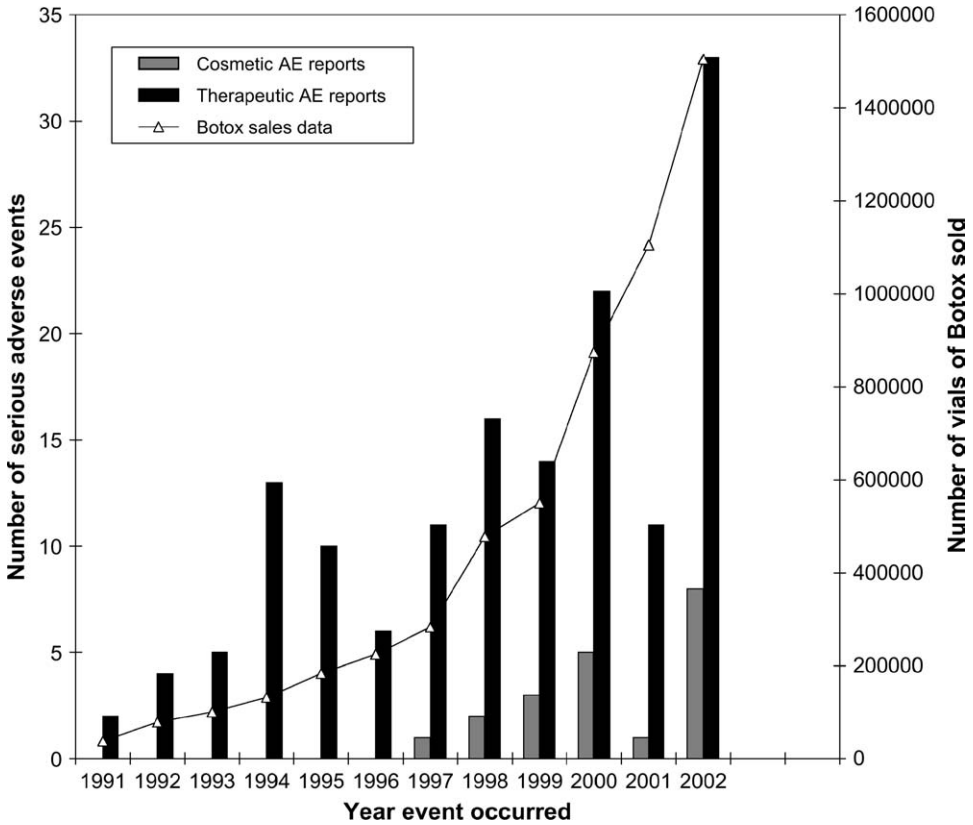

Fig 1. Serious adverse events and botulinum toxin type A sales figures (used with permission from M. Brin, MD, Allergan), January 1989 to December 2002.

of the recommended maximum dose of 20 U (Table I). For both therapeutic and cosmetic BTA cases, the serious AEs reported were generally already included in the approved labeling.

Biases in reporting and undercounting may have influenced our results. Although regulation requires manufacturers to send the FDA all AE reports that they receive, the initial reporting by clinicians or others is voluntary. Therefore, our data likely include only a small proportion of all AEs that occur after BTA injection.[59-61] Further, AEs may be only temporally but not necessarily causally associated with exposure to BTA. Other possible causes of the reported events may include underlying disease (eg, cerebral palsy may promote aspiration pneumonia) or a concomitant medication (eg, muscle weakness with a muscle relaxant). Despite these limitations, AE reports to the FDA have resulted in early identification of multiple major drug safety issues.[61]

Many of the AEs reported after use of BTA were biologically plausible; for example dysphagia and ptosis occurred after injections near the throat and eyes, respectively. BTA blocks neuromuscular transmission by binding to receptor sites on motor nerve terminals and inhibiting the release of acetylcholine.[6] Consistent with this mechanism, BTA recipients experienced dysphagia, ptosis, and other facial muscle weaknesses. Some of these AEs were likely caused by BTA, and they are mentioned in the approved labeling. These pharmacologically predictable AEs linked to tissue diffusion of BTA constituted a large share of reports to the FDA for BTA.

It is unclear whether BTA causes seizures. Some of the reported seizures appear to follow a syncopal (possibly vasovagal) episode; this phenomenon has also been reported with vaccine injection.[62] The majority of seizures were reported for patients with either a history of seizures or predisposing conditions for seizure (eg, cerebral palsy or traumatic brain injury). Arguing against a single pathophysiologic mechanism, reported elapsed time from BTA administration to seizure varied widely.

Careful attention to drug dose, dilution, handling, storage, and site of injection are required for optimal treatment outcome. In our review of AE reports, we found numerous examples of lack of adherence to these precepts. Dosing modifications primarily involved the administration of amounts outside recommended guidelines: the maximum labeled cosmetic dose is 20 U but we found a wide range, with median

Table I. Characteristics of 1437 patients (therapeutic and cosmetic use) for whom adverse events (serious and nonserious) were reported

	Therapeutic		Cosmetic	
Characteristic	Serious (%) 12/1989-5/2003 N = 217	Nonserious (%) 12/2001-11/2002 N = 189	Serious (%) 12/1989-5/2003 N = 36	Nonserious (%) 12/2001-11/2002 N = 995
Age category, yrs				
<20	31 (14.2)	9 (4.7)	0 (0.0)	0 (0.0)
20-29	13 (6.0)	1 (1.1)	1 (2.8)	10 (1.0)
30-39	25 (11.5)	19 (10.0)	12 (33.3)	88 (8.8)
40-49	26 (11.9)	25 (13.2)	8 (22.2)	145 (14.6)
50-59	34 (15.6)	27 (14.2)	6 (16.7)	114 (11.5)
60-69	36 (16.6)	14 (7.4)	6 (16.7)	31 (3.1)
>70	23 (10.6)	16 (8.4)	1 (2.8)	13 (1.3)
Unknown	29 (13.3)	78 (41.1)	2 (5.6)	594 (59.7)
Sex				
Male	81 (36.0)	33 (17.9)	1 (2.8)	42 (4.2)
Female	132 (60.8)	145 (76.3)	35 (97.2)	812 (81.6)
Unknown	4 (1.8)	11 (5.8)	0 (0.0)	141 (14.2)
Dose, U				
Median	110	100	30	25
Range	12-11,000	3-500	16-92	1-375
Indication for use*				
On-label	74 (34.1)	87 (45.8)	15 (41.7)	532 (53.5)
Facial wrinkle: glabellar	-	-	15	532
Cervical dystonia	54 (73.0)	48 (55.2)	-	-
Blepharospasm	19 (25.3)	37 (42.5)	-	-
Strabismus	2 (2.7)	2 (2.3)	-	-
Possibly on-label†	42 (19.3)	24 (13.2)	11 (30.6)	369 (37.1)
Facial wrinkle: site unknown	-	-	11	369
Spasticity (NOS)	38 (90.5)	20 (84.0)	-	-
Pain (neck, NOS)	3 (7.1)	4 (16.0)	-	-
Off-label	98 (45.0)	83 (43.7)	14 (38.9)	322 (32.4)
Facial wrinkle: not glabellar	-	-	14	322
Spasticity (other than neck)	37 (37.8)	22 (26.5)	-	-
Pain (sites other than neck)	24 (24.5)	14 (16.9)	-	-
Spasmodic dysphonia	6 (6.1)	4 (4.8)	-	-
Migraine	9 (9.2)	30 (36.1)	-	-
Achalasia	10 (10.2)	2 (2.4)	-	-
Other‡	12 (12.2)	13 (15.7)	-	-
Unknown	3 (1.4)	4 (4.8)	0 (0.0)	0 (0.0)

There were two patients with both cosmetic and therapeutic indication among the serious adverse events and 6 patients among the nonserious adverse events. These patients were counted both in the cosmetic and therapeutic categories.
NOS, not otherwise specified.
*More than one indication for use was reported for many patients and, thus, multiple counts per patient is represented.
†From the information reported, it was not possible to clearly determine if botulinum toxin type A was used for an on-label use.
‡Listed in Appendix A.

doses of 25 and 30 U among patients with cosmetic use who reported AEs. In 14 cosmetic cases, patients were reported to have received 100 U or more of BTA in one treatment. Drug dilution modifications were reported frequently with such diluent substitutions as bupivacaine, lidocaine, water, and previously reconstituted BTA, rather than the recommended saline diluent. Administration and potential handling errors included injecting reconstituted product after the recommended 4-hour expiration, freezing or refrigerating reconstituted product for future use, injecting multiple patients with BTA from a vial labeled for single-patient use, or a combination of these. A large proportion of the AE reports mentioned BTA injection into an off-label site.

In summary, our review of 1437 AE reports to the FDA with BTA showed that serious AEs were most common among patients with therapeutic use who

Table II. Description of the serious and nonserious adverse events among therapeutic and cosmetic users of botulinum toxin type A

	Therapeutic		Cosmetic	
Adverse events*	Serious (%) N = 217	Nonserious (%) N = 189	Serious (%) N = 36	Nonserious (%) N = 995
Respiratory system	33 (15.2)	15 (7.9)	1 (2.8)	18 (1.8)
Respiratory compromise	18 (3.7)	7 (3.7)	1 (2.8)	2 (0.2)
Pneumonia	9 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary embolism	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Vocal cord paralysis	4 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Flu-like syndrome	10 (4.6)	6 (3.2)	2 (5.6)	15 (1.5)
Cough	0 (0.0)	2 (1.1)	0 (0.0)	1 (0.1)
Cardiovascular system	22 (10.1)	0 (0.0)	2 (5.6)	3 (0.3)
Myocardial infarction	6 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)
Arrhythmia	9 (4.1)	0 (0.0)	1 (2.8)	0 (0.0)
Cardiomyopathy	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Congestive heart failure	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac (not otherwise specified)	2 (0.9)	0 (0.0)	1 (2.8)	3 (0.3)
Nervous system	51 (23.5)	47 (24.9)	7 (19.4)	98 (9.8)
Stroke	5 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebral edema	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Myasthenia gravis	2 (0.9)	0 (0.0)	1 (2.8)	0 (0.0)
Focal facial paralysis	6 (2.8)	4 (2.1)	3 (8.3)	21 (2.1)
Muscle weakness/spasm	13 (6.0)	39 (20.5)	2 (5.6)	51 (5.1)
Seizure	17 (7.8)	0 (0.0)	1 (2.8)	1 (0.1)
Psychiatric/behavioral effects	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Motor neuron/Guillain-Barré	4 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Paresthesia/numbness	0 (0.0)	3 (1.5)	0 (0.0)	23 (2.3)
Gastrointestinal system	41 (18.9)	19 (10.1)	3 (8.3)	11 (1.1)
Dysphagia	26 (12.0)	13 (6.8)	2 (5.6)	4 (0.4)
Elevated liver enzymes	2 (0.9)	0 (0.0)	1 (2.8)	0 (0.0)
Ulcerative colitis/cholecystitis/pancreatitis/ enteropareisis/esophageal ulcer	8 (3.7)	0 (0.0)	1 (2.8)	0 (0.0)
Diarrhea	0 (0.0)	6 (3.2)	0 (0.0)	7 (0.7)
Skin/injection site reactions	1 (0.5)	67 (35.4)	2 (5.6)	190 (19.1)
Rash	0 (0.0)	17 (8.9)	0 (0.0)	29 (2.9)
Edema (at injection site)	1 (0.5)	19 (10.0)	2 (5.6)	74 (7.4)
Pain (at injection site)	0 (0.0)	26 (13.7)	0 (0.0)	67 (6.7)
Bruise (at injection site)	0 (0.0)	5 (2.6)	0 (0.0)	20 (2.0)
Eye	1 (0.5)	23 (12.2)	5 (13.9)	141 (14.2)
Diplopia	0 (0.0)	3 (1.5)	0 (0.0)	4 (0.4)
Ptosis	0 (0.0)	12 (6.3)	2 (5.6)	111 (11.1)
Retinal detachment/vitreous/detachment/ optic/nerve atrophy	0 (0.0)	2 (1.1)	3 (8.3)	2 (0.2)
Other eye disorders	1 (0.5)	6 (3.2)	0 (0.0)	24 (2.4)
Miscellaneous				
Trauma during injection	9 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)
Allergic reaction/rash	11 (5.1)	0 (0.0)	2 (5.6)	0 (0.0)
Syncope	7 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	6 (2.8)	5 (2.6)	1 (2.8)	12 (1.2)
Miscarriage	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Electrolyte imbalance	1 (0.5)	0 (0.0)	1 (2.8)	0 (0.0)
Vomiting	2 (0.9)	20 (10.5)	2 (5.6)	17 (1.7)
Fatigue/malaise	3 (1.4)	6 (3.2)	1 (2.8)	5 (0.5)
Headache	1 (0.5)	13 (6.8)	3 (8.3)	46 (4.6)
Renal failure/infection	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Pain (other than injection site)	0 (0.0)	20 (10.5)	0 (0.0)	12 (1.2)

Table II. Cont'd

Adverse events*	Therapeutic		Cosmetic	
	Serious (%) N = 217	Nonserious (%) N = 189	Serious (%) N = 36	Nonserious (%) N = 995
Alopecia	0 (0.0)	2 (1.1)	0 (0.0)	5 (0.5)
Infections (NOS)	0 (0.0)	8 (4.2)	0 (0.0)	6 (0.6)
Tinitus/hearing loss	0 (0.0)	0 (0.0)	2 (5.6)	0 (0.0)
Urinary incontinence	3 (1.4)	1 (0.5)	1 (2.8)	0 (0.0)
Dysphonia	0 (0.0)	7 (3.2)	0 (0.0)	0 (0.0)
Other†	8 (3.7)	17 (8.9)	0 (0.0)	12 (1.2)
Unknown	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Death	28 (12.8)	0 (0.0)	0 (0.0)	0 (0.0)

There were two patients with both cosmetic and noncosmetic indication among the serious adverse events and 6 patients among the nonserious adverse events. These patients were counted both in the cosmetic and therapeutic categories.
NOS, not otherwise specified.
*Multiple adverse event terms can be reported for a single adverse event episode.
†Listed in Appendix B.

received higher doses and had complicated underlying diseases. Indeed, all reported deaths occurred for patients who received BTA for therapeutic purposes. Serious AEs were less commonly reported among cosmetic cases. Most AEs involved risks previously recognized from clinical trials before licensure. We also noted numerous departures from the drug dose, dilution, administration, handling, storage, and site of injection advised in the approved labeling.

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APPENDIX A

AEs for other off-label indications not mentioned in Table I (No.)
Alopecia (1)
Anesthetic reaction (1)
Drooling (1)
Dysphagia (1)
Essential tremor (2)
Facial myokymia (1)
Facial twitch (1)
Gastroparesis (1)
Hemiparesis (1)
Hyperhydrosis (3)
Laterocollis (1)
6th Nerve palsy (1)
Occipital neuralgia (1)
Paralytic scoliosis (1)
Physician test (1)
Sialorrhea (1)
Tardive dyskinesia (2)
Temporomandibular joint pain (1)
Thoracic outlet syndrome (3)

APPENDIX B

List of other AEs not listed in Table II (No.)
Amnesia (1)
Anxiety (2)
Aplastic anemia (1)
Depression (2)
Diabetes mellitus (1)
Earache (1)
Fever (1)
Flushed feeling (1)
Gout (1)
Hypercoagulative state (1)
Indigestion (1)
Inner ear problem requiring shunt (1)
Insomnia (1)
Jittery feeling in stomach (1)
Knee infection (1)
Loss of prodromal warning of migraine (2)
Lumbar pain (1)
Nodule near ear (1)
Pain in the neck (1)
Pancreatic cancer (1)
Postnasal drip (1)
Pruritus (1)
Rectal bleeding (1)
Renal cancer (1)
Road traffic accident (1)
Salty taste in mouth (2)
Stomach cramps (1)
Throat irritation (1)
Toe curling (1)
Typhoid fever (1)
Vasovagal response (1)
Vertical stretch marks from the needle (2)