Supplemental Article

Current Aesthetic Use of AbobotulinumtoxinA in Clinical Practice: An Evidence-Based Consensus Review

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Abstract

The amount and complexity of scientific and clinical evidence for aesthetic use of botulinum neurotoxin type A (BoNT-A) has expanded rapidly in recent years, especially for abobotulinumtoxinA, necessitating reassessment of current knowledge about aesthetic use of abobotulinumtoxinA and other BoNT-A preparations. A committee of 13 plastic surgeons, facial plastic surgeons, and dermatologists engaged in a live discussion of information from a systematic literature review and an Internet-based survey of their beliefs and practices. The committee achieved consensus on most issues. It was concluded that doses of different BoNT-A preparations cannot be interconverted with a fixed ratio. The size of the "field of effect" is difficult to measure, and comparisons between preparations have yielded equivocal results. Nonresponse due to neutralizing antibodies appears exceedingly rare with currently available BoNT-A preparations and of little concern clinically. BoNT-A dose, injection depth, and injection technique should be adjusted according to the anatomic area being treated and each patient's individual characteristics and goals. Aesthetic use of BoNT-A has a good safety profile. Most adverse events are minor and related to the trauma of injection, although special care is needed in certain anatomic areas. Detailed recommendations for treatment of different anatomic areas are presented. BoNT-A products are often used in conjunction with other treatment modalities (eg, fillers and resurfacing), but little agreement was reached on best practices. The findings reported in this consensus document may serve as a practical guide for aesthetic practitioners as they apply the latest knowledge about BoNT-A in providing their patients with optimal care.

Keywords

botulinum toxin, abobotulinumtoxinA, onabotulinumtoxinA, cosmetic medicine

BACKGROUND

In 2002, the United States Food and Drug Administration (FDA) approved the use of botulinum neurotoxin type A (BoNT-A) (onabotulinumtoxinA; Botox Cosmetic; Allergan, Inc, Irvine, California)[1] to diminish glabellar furrows, starting a revolution in noninvasive aesthetic medicine. Since then, new aesthetic uses for BoNT-A have been explored more rapidly than definitive clinical trials have been conducted. As a result, panels of experienced practitioners have convened periodically to debate the current state of clinical knowledge about the aesthetic uses of BoNT-A. The published proceedings of these discussions[2-6] have served as a valuable resource for practitioners who inject BoNT-A.

Today, advances in BoNT-A therapy continue unabated. A second BoNT-A (abobotulinumtoxinA; Dysport; Medicis, Inc, Scottsdale, Arizona) was approved for treatment of glabellar lines in 2009, and a third BoNT-A preparation (incobotulinumtoxinA; Xeomin; Merz Pharmaceuticals, LLC, Greensboro, North Carolina) received FDA approval for this indication in July 2011.[7,8] The amount of information from BoNT-A clinical studies and safety surveillance has expanded, providing a stronger evidence base to

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address issues such as the relative merits of different BoNT-A formulations and outcomes in patients with skin of color. However, due to the complexities of scientific and clinical information, expert consensus remains of value. For example, interpretation of efficacy evidence is challenging because of the use of many different outcome measures, only a minority of which are validated (eg, Glabellar Line Severity Score[9]; Facial Wrinkle Scale for forehead lines[10] and lateral canthal lines[11]). Because several different outcome measures have been used in clinical trials of BoNT-A, comparisons between trials must be made with caution. Moreover, most scales are designed for research use rather than as clinical tools. Conflicting data exist on topics such as the interconversion of doses among distinct BoNT-A products, differences related to unique manufacturing techniques, the impact of reconstitution volume, measuring the field of effect, and the relevance of neutralizing antibodies. For these reasons, translating research findings into clinical practice is not straightforward, and clinician opinion retains a prominent role in shaping the practice of aesthetic BoNT-A therapy.

Arising from a mutually recognized need for a current consensus statement on aesthetic therapy with abobotulinumtoxinA, a consensus committee was formed by the sponsor of this supplement, Medicis, Inc; the committee comprised experienced clinicians who are nationally recognized for their clinical, educational, and research expertise with BoNT-A and included a group of 13 dermatologists, facial plastic surgeons, and plastic surgeons. Committee members were selected based on their experience as BoNT-A investigators, independent research they have performed regarding the use of BoNT-A, publications, and medical education conducted at society meetings. From this group of experienced practitioners, a steering committee of 3 individuals (Corey Maas, MD, FACS; Michael A. C. Kane, MD; Vivian W. Bucay, MD, FAAD) was selected. The steering committee met in July 2011 to provide initial direction for the project. On the basis of a systematic review of the medical literature, the steering committee developed questions for an online survey to gather information from the full consensus committee on clinical areas of fundamental importance. The full committee met in October 2011 to review the medical literature on aesthetic BoNT-A treatment and to discuss the results of the survey. Where the survey results indicated a difference of opinion, the goal of the committee discussion was to discover and document the rationale for divergent points of view, rather than to mandate a uniform consensus on every point. The resulting presentation explores increased US experience with abobotulinumtoxinA considering published clinical evidence, the routine practice of experienced clinicians, and reasoned debate of current areas of controversy.

LITERATURE REVIEW

To provide a foundation for consensus committee discussions, a thorough review of the medical literature was undertaken before the meeting.

Methods

The PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/) was searched using a string of terms that targeted clinically related articles (eg, a trial, meta-analysis, guideline, or case report) published between January 1998 and August 2011 and that addressed any aesthetic use of a botulinum toxin. Review articles were excluded. Initial manual examination of the 475 results eliminated 324 that were about nonaesthetic indications (eg, spasticity, hyperhidrosis, migraine, overactive bladder), leaving 151 articles. Further review eliminated 66 reports that were not in English, were solely about botulinum neurotoxins other than serotype A, described products not available in the United States, or contained only nonapplicable preclinical data. Information was extracted from the remaining 85 articles. Five additional articles known to the authors, but not captured in the automated search, also were reviewed.

Analysis of Results

Information extracted from the 90 compiled articles was categorized and later used to generate questions for an online survey completed by all members of the consensus committee.

The literature search revealed that there was very limited information on incobotulinumtoxinA, owing to its recent marketing approval. There was more information for abobotulinumtoxinA and onabotulinumtoxinA. The abobotulinumtoxinA evidence base has expanded since 2009, when the product was approved for aesthetic use in the United States and also when the last consensus statement was published.[6] Table 1 lists all published clinical studies involving abobotulinumtoxinA for aesthetic use. Seven of the 20 clinical studies listed were published in 2010 or 2011. As described in the literature search

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methods, several botulinum neurotoxin products were not analyzed because they were in development (eg, CosmeTox, DMP Therapeutics, Ancaster, Ontario, Canada; PurTox, Mentor Biologics, Madison, Wisconsin; RT001, Revance Therapeutics, Inc, Newark, California), were not serotype A (eg, Myobloc, Solstice Neurosciences, Inc, Malvern, Pennsylvania), or were not available in the United States (eg, Prosigne, Lanzhou Institute of Biological Products, Lanzhou, Gansu, China). Purification and assay methodologies have been compared previously[12] and were beyond the scope of this clinically oriented consensus committee, although it is important to note that the 3 BoNT-A preparations available in the United States are not considered bioequivalent.[13]

The strength of evidence for efficacy and safety varies dramatically according to the particular anatomic area being considered. Treatment of glabellar lines is the most well-established aesthetic use of BoNT-A and is the first and only aesthetic indication approved by the FDA for each of the 3 available products. At least 22 reports of randomized, blinded clinical studies of abobotulinumtoxinA,[14-21] onabotulinumtoxinA,[22-34] and incobotulinumtoxinA[35] for treatment of the glabella have been published since 1998. Randomized, blinded clinical study evidence for treatment of the forehead (abobotulinumtoxinA,[36-39] onabotulinumtoxinA[25,26,31,36-39]) and lateral canthal lines ("crow's feet"; abobotulinumtoxinA,[40,41] onabotulinumtoxinA,[25,26,31,40-44] incobotulinumtoxinA[42]) also was substantial. No other anatomic areas were associated with clinical studies that were both randomized and blinded. Therefore, objective evidence for treating these areas was weaker, and the clinical experience of practiced injectors played a greater role in developing the recommendations presented in this consensus statement.

Findings from the consensus committee survey and consensus meeting are described according to topic categories of the literature search in the following sections. These categories include reconstitution and handling, the field of effect in clinical studies related to aesthetics and in experimental models such as anhidrotic area, neutralizing antibodies, treatment of specific anatomic areas, and combination of BoNT-A with other aesthetic therapies.

ONLINE SURVEY AND LIVE MEETING OF THE CONSENSUS COMMITTEE

A survey with 13 detailed questions was posted online (SurveyMonkey.com) to garner input from all consensus committee members on the topics of interest identified by literature analysis. These questions were developed and refined in consultation with the steering committee, based on their clinical knowledge as well as an initial systematic review of recent medical literature. Survey responses were tabulated to derive graphical presentations and descriptive statistics. The consensus committee examined the survey results at the live meeting, during which survey questions that generated the greatest divergence of opinion were debated. The committee's interpretations of the data were

Table 1. AbobotulinumtoxinA Clinical Studies

Year Published	Anatomic Area(s)	Total Dose, U (No. of Patients)	
		Abo	Comparator
Placebo-controlled			
2004[17]	GL	25 (34) 50 (34) 75 (34)	NA (17)
2006[21]	GL	30 (73) 50 (73)	NA (37) NA (38)
2007[19]	GL	20 (91) 50 (93) 75 (95)	NA (95)
2009[18]	GL	50, 60, 70 in women 60, 70, 80 in men (544)	NA (272)
2009[20]	GL	50 (171)	NA (84)
2009[80]	GL	50 (105)	NA (53)
2009[40]	LCL	15 (55) 30 (54) 45 (55)	NA (54)
Active-controlled (vs Ona)			
2005[16]	GL	50 (NR[a])	20 (NR[a])
2006[15]	GL	50 (31)	20 (31)
2007[36]	FO	36 (24)	12 (24)
2008[60]	GL[b] FO[b] LCL[b]	63.0 26.2 52.6 (40)	25.2 10.5 21.0 (40)
2010[61]	GL[c] GL, FO, LCL[c] LCL[c]	75 (30) 256 (20) 48 (5)	30 (30) 64 (20) 16 (5)
2011[37-39]	FO	25 (20)	10 (20)
2011[41]	LCL	30 (90)	10 (90)
2011[62]	GL, FO, LCL	30 (5)	12 (5)
Uncontrolled			
2009[79]	GL	50 (768)	NA
2009[81]	GL	50 (1200)	NA
2010[98]	Various facial and platysmal lines	20-160 (500)	NA
2010[88]	GS	5-25 (16)	NA
2010[100]	GL, FO, LCL Same + upper FO	114-163 (20) Same + 36 (20)	NA

Abo, abobotulinumtoxinA; FO, forehead; GL, glabella; GS, gummy smile; LCL, lateral canthal lines; NA, not applicable; NR, not reported; Ona, onabotulinumtoxinA.

*The study included 30 patients, but the number assigned to each treatment group was not reported.

†Mean values for doses were reported.

‡Results from 3 different studies were reported in 1 article.

compiled, summarized, and distributed among the members. This summary formed the basis of the consensus opinion expressed in this article.

PATIENT EVALUATION AND COUNSELING

It was agreed by all consensus committee members that patient consent must be obtained and recorded before treatment with abobotulinumtoxinA, in written form, verbally (and charted), or both. In general, the committee members discussed a wider range of issues for new patients considering treatment with abobotulinumtoxinA than for returning patients. Commonly discussed issues included patient experience with different BoNT-A preparations, anticipated onset and duration of effect, the need for posttreatment assessment and retouching, potential adverse events and corrective measures, and options for improving suboptimal aesthetic outcomes. Methods for educating patients on risks were highly variable among the committee members. Some product label warnings (eg, sensitivity to aminoglycosides and cow's milk protein) were discussed only with new patients or not at all, reflecting the rarity of such problems. In terms of patient selection, members of the committee routinely treated patients ≥65 years of age and patients with autoimmune diseases. However, they did not treat women who were pregnant or attempting to conceive. Committee members differed on the value of taking pre- and posttreatment photographs.

Committee members' posttreatment recommendations for patients were mostly related to reducing the risk of bruising associated with minor needle trauma, for example, by instructing patients to avoid bending over or rubbing the treated area. None of the committee members warned their patients about exposure to heat, light, or air travel. Each posttreatment recommendation was based entirely on anecdotal reports or theoretical speculation, some of which were related to possible sequelae of BoNT-A migrating away from the injection site before its uptake was complete. Uptake in an in vitro neuronal cell model takes approximately 150 minutes.[45]

STORAGE, RECONSTITUTION, AND HANDLING

Most committee members (85%) reported having a formal system for maintaining segregation between different BoNT-A products. Commonly, this involved the use of separate storage areas or boxes, different-appearing syringes, or simply employing only a single BoNT-A product. AbobotulinumtoxinA was usually refrigerated before reconstitution, and in some instances, respondents reported freezing the product. Several studies have suggested that properly stored BoNT-A retains clinical activity for substantial periods after reconstitution,[14,46-49] although this is not advised in the product labels. A recently published literature review, released after the consensus meeting, also concluded that BoNT-A products may be more stable than stated on their labels.[50] A recent Internet-based survey of physician members of the American Society for Dermatologic Surgery who administer BoNT-A found that approximately two thirds of the 322 respondents store BoNT-A for 1 week or longer after reconstitution.[51] Although the prolonged storage studies considered clinical efficacy, none formally assayed BoNT-A activity; consequently, it is unknown whether an unmeasured degree of loss of effectiveness may occur and be manifested clinically in ways that were not adequately explored in these studies, such as reduced duration of effect.

The label for abobotulinumtoxinA describes reconstitution of the product with sterile, nonpreserved saline solution; likewise, all pivotal studies specified reconstitution with the same solution. Nonetheless, approximately half of the consensus committee (54%) members used sterile saline solution containing a preservative for reconstitution of abobotulinumtoxinA. The rationale for using preserved saline is to reduce the pain of injection, based on the belief that the benzyl alcohol preservative has a mild local anesthetic effect. Also, it is theoretically possible that microbial growth might occur, in the absence of a preservative, in the large bottles of saline that might be used over prolonged periods in clinical practice to reconstitute BoNT-A.[52] Theoretically, the alcohol preservative could denature the botulinum toxin protein and result in less durable aesthetic clinical effects, but data supporting or refuting this idea have not been published. Although injection of BoNT-A administration is generally considered to be a procedure with little pain,[6] and one study has shown that abobotulinumtoxinA injections are significantly less painful than onabotulinumtoxinA injections,[38] the use of preserved saline for reconstitution has been shown in several studies to significantly decrease the level of pain.[53-56] However, these studies had few patients and the results contradicted the common clinical experience of some of the committee members, which is that discomfort with BoNT-A injections is modest even with nonpreserved saline. Committee members suggested that pain levels may also depend on several other factors, such as injection technique and pH levels of the various BoNT-A products when reconstituted. Reflecting the absence of compelling evidence for use of preserved saline, some of the committee members observed that there has been a shift in their clinics toward reconstitution with preservative-free saline, which in past years was a less common practice.

RELATIVE POTENCY OF BoNT-A PREPARATIONS

For several reasons, the individual BoNT-A products (abobotulinumtoxinA, onabotulinumtoxinA, incobotulinumtoxinA) available in the United States cannot be considered bioequivalent. Production of BoNT-A formulations differs in numerous ways (eg, purification procedure, presence of accessory proteins, and formulation),[1,8,57] although the

clinical significance of these differences has not been established. Given their inherent differences, the methods used to assay neurotoxin potency are specific to each of the 3 manufacturers, and the results are not interchangeable.[1,7,8] Uncertainty exists about the comparability of the *Clostridium botulinum* bacteria used in the fermentations,[12,13,58] although all 3 products are nominally derived from the Hall strain.[1,7,8] Additionally, BoNT-A products have considerable variability in potency within batches from the same manufacturer, which approached 20% for abobotulinumtoxinA in the only published characterization of such variability.[59] Consequently, a fixed ratio between products from different manufacturers cannot be reliably determined. Some committee members reported believing that reconstitution volume can complicate the comparability of conversion ratios between BoNT-A products (ie, clinical comparability of different BoNT-A products may differ at low or high reconstitution volumes). As a result of the numerous confounding factors, the committee consensus was that it is not possible to determine a constant ratio for equipotent doses of different BoNT-A products.

The medical literature does not show a clear pattern for magnitude of effect when comparing abobotulinumtoxinA and onabotulinumtoxinA according to dose ratio and anatomic area.[15,16,36,38,39,41,60-63] Comparative data exist for incobotulinumtoxinA and onabotulinumtoxinA in the treatment of glabellar lines and lateral canthal lines, demonstrating equivalence at a 1:1 dose ratio,[35,42] although this has been disputed.[64] Most of these literature sources arrived at a rough conversion of between 2:1 and 3:1 for abobotulinumtoxinA versus onabotulinumtoxinA, but similar clinical outcomes have been reported with both lower and higher ratios of conversion. The committee suggested that an approximate conversion may be helpful for clinicians experienced with one product to begin gaining experience with another. However, it was agreed that the best outcomes are obtained by following product-specific dosing for each anatomic area based on published studies, expert recommendations, and individual clinician experience with each type of BoNT-A. Table 2 presents the total doses of abobotulinumtoxinA and onabotulinumtoxinA for each anatomic area as recommended by the survey of committee members. For every anatomic area, the median reconstitution volume per 300-U vial of abobotulinumtoxinA was 3.0 mL (range, 1.5-6.0 mL) and per 100-U vial of onabotulinumtoxinA was 2.5 mL (range, 1.0-6.0 mL), except that 1 respondent reconstituted abobotulinumtoxinA in 8.0 mL when treating perioral lines.

FIELD OF EFFECT: MECHANISM OF ACTION, MEASUREMENT, AND CLINICAL RELEVANCE

Neurotoxin Spread and Diffusion

A systematic literature review indicated that there is an ongoing debate in the medical literature on the definition, measurement, and clinical impact of the field of effect of different BoNT-A formulations.[58,65] Field of effect depends on a number of variables, including uniqueness of each product based on specific manufacturing processes; reconstitution volume; total dose; depth, angle, and rate of injection; anatomic area; desired degree of effect (ie, partial vs complete immobility); and patient-specific factors (eg, variation in muscle mass and anatomy).[6] An important first step in clarifying this discussion is a clear understanding of the underlying processes. The field of effect is a function of the active process of "spread" during injection and the passive process of diffusion afterward.[66] Spread occurs rapidly and can be affected by many variables, including the volume, speed, depth, and angle of the injection.[6] Diffusion within the tissues is slower and not dependent on the injection technique.[66] The rate of diffusion is expected to be identical for all BoNT-A products because the core neurotoxin, which is responsible for the therapeutic effect, has the same mass (150 kDa) for each BoNT-A product. Although the core is initially in complex with neurotoxin-associated proteins (as for abobotulinumtoxinA and onabotulinumtoxinA, but not incobotulinumtoxinA), it dissociates almost immediately upon injection as it encounters the neutral pH of the physiologic space.[67] In addition, it may dissociate upon reconstitution, depending on the pH of the saline solution used.

Challenges in Measuring the Field of Effect

Attempts to compare the fields of effect of different BoNT-A products in controlled settings have been limited by the models used, study design, and influence of injection technique. Most data have come from studies that measured inhibition of sweating from the eccrine glands in the forehead.[63,68,69] Unfortunately, the relevance of anhidrosis models to paresis of aesthetically relevant muscles is uncertain. These studies were also limited by the dosing ratios used; in 1 study, larger doses of abobotulinumtoxinA (relative to a fixed dose of onabotulinumtoxinA) had wider areas of anhidrosis,[68] implying that the anhidrotic halo was more a function of dose than of any inherent properties of the BoNT-A. The depth, angle, and volume of injection were not controlled variables and may have influenced the field of effect.

The field of effect, as measured by paresis of facial muscles, is more relevant to aesthetic efficacy than the anhidrotic field of effect in skin, and reproducibly measuring the maximum strength of muscular contraction is more technically challenging than measuring anhidrotic area. Despite this challenge, a recent study that specifically investigated muscular field of effect in 20 subjects and was carefully controlled for other factors found no difference between the field of effect for total doses of 25 U abobotulinumtoxinA and 10 U onabotulinumtoxinA.[70] This conclusion was based on observation of symmetric forehead furrowing, distant from the sites of contralateral frontalis injections, at 14 and 30 days posttreatment; furthermore, there was no brow ptosis with either treatment.[38] Volume might play a significant role in diffusion;

Table 2. Usual Doses and Reconstitution Volumes for AbobotulinumtoxinA and OnabotulinumtoxinA by Anatomic Area Treated

Anatomic Area[a]	AbobotulinumtoxinA Median (Range) Dose, U[b]	OnabotulinumtoxinA Median (Range) Dose, U[b]
Glabella	52.5 (30-70)	20 (12-25)
Forehead	30 (15-75)	11.75 (5-30)
Lateral canthal lines	50 (25-70)	20 (6-30)
Lower eyelids	10 (3-20)	4 (1.5-8)
Bunny lines	22 (5-40)	6 (2-12)
Nasal tip	5 (3-20)	2 (1-5)
Perioral lines	15 (4.5-30)	5 (2-12)
Marionette lines	17.5 (6-25)	6 (2-10)
Gummy smile	15 (4-40)	5 (2-10)
Chin dimple	15 (9-25)	5 (3-10)
Masseter hypertrophy	100 (50-150)	32.5 (20-60)
Platysmal bands	75 (40-150)	30 (10-50)

Abbreviation: U, units.
[a]For symmetrical areas, the total dose indicates the entire amount injected on the left and right sides together.
[b]Units of abobotulinumtoxinA and onabotulinumtoxinA are not interchangeable.

a recent study investigating the field of effect in 10 subjects found a larger field of effect (ie, mean wrinkle reduction, 794.1 vs 486.6 mm^2) when a larger reconstitution volume was used.[71]

Clinical Relevance of the Field of Effect

Survey responses from the consensus committee provided further insights into the topic of field of effect as relevant to the efficacy and safety of aesthetic BoNT-A therapy. Slightly more than half of the committee (54%) believed that abobotulinumtoxinA had a larger field of effect than onabotulinumtoxinA, whereas the rest believed that the field of effect was the same (31%) or felt that evidence was not conclusive (15%). The majority of respondents believed that abobotulinumtoxinA had a faster onset of effect (69%), and approximately half believed that it had a longer duration of effect (54%) than onabotulinumtoxinA; these clinical observations are supported by recently reported results of a blinded contralateral clinical trial.[38,39] All members of the expert committee had observed no more adverse events with abobotulinumtoxinA than with onabotulinumtoxinA, with 92% of respondents indicating that abobotulinumtoxinA did not cause more eyelid ptosis than onabotulinumtoxinA. Adverse events related to the field of effect have been infrequently observed in large, randomized controlled studies, as reflected in low incidences of eyelid ptosis in pivotal clinical trials (abobotulinumtoxinA, 2%; onabotulinumtoxinA, 3%),[1,8] and are not indicative of greater diffusion with abobotulinumtoxinA than with onabotulinumtoxinA, thus supporting the personal observations of the committee members.

NEUTRALIZING ANTIBODIES

Neutralizing antibodies are immunoglobulins whose binding to an antigen prevents its therapeutic effect. Only antibodies against the core botulinum neurotoxin (as opposed to accessory proteins), which is present in all BoNT-A preparations, would be expected to be neutralizing. This is true whether the BoNT-A is "naked" (as with incobotulinumtoxinA) or formulated with neurotoxin-associated proteins (as with abobotulinumtoxinA and onabotulinumtoxinA), because these latter complexes dissociate almost immediately upon injection, thus freeing the core neurotoxin.[67]

Slightly more than half of the consensus committee (54%) believed that neutralizing antibodies are potentially clinically relevant in aesthetic indications of BoNT-A products, although this may be a remote risk as neutralizing antibodies have never been found in a large clinical trial. On the more specific question of whether neutralizing antibodies are of clinical importance with abobotulinumtoxinA, most respondents (77%) answered "no," and 23% believed that there was not yet conclusive evidence. The committee concluded that "nonresponse" to BoNT-A (sometimes called "resistance") might be a more practical term for apparent absence of therapeutic effect with BoNT-A, because the presence of neutralizing antibodies is rarely tested.

It was important to the committee that a distinction be made between primary nonresponders, who had never been successfully treated with BoNT-A, and secondary nonresponders, for whom BoNT-A treatment was initially effective but later became completely or largely ineffective. Most committee members (75%) had encountered patients who presented as primary nonresponders to BoNT-A after therapy attempted at other clinics.[72] All committee members who answered this survey question (n = 12) had been able to effectively treat patients who had presented to them as primary nonresponders. In these cases, it appears that underdosing or other technique errors may have caused the previous lack of response. In other cases, primary nonresponse was associated with a known history of botulism (ie, poisoning by the *C botulinum* bacterium, as opposed to injection of purified BoNT-A), which presumably had resulted in development of neutralizing antibodies.

Endogenous neutralizing antibody production due to botulism has been observed previously.[73] Another possible cause of resistance was subclinical botulism—for example, via food, which conceivably could be common.

There has been speculation about this possibility,[74] but no confirmatory data are available. Finally, some military personnel have been vaccinated in anticipation of botulinum neurotoxin–based biological warfare[75]; antibodies produced in response to this vaccination could interfere with BoNT-A therapy.

Several committee members stated that in their experience, secondary nonresponse was less common than primary nonresponse and, likewise, may in some cases have been attributable to environmental factors other than the BoNT-A injections themselves. Case reports of nonresponse to aesthetic therapy have appeared for abobotulinumtoxinA, incobotulinumtoxinA, and onabotulinumtoxinA.[76,77] Conversely, clinical studies[35,78-81] found no confirmed evidence of neutralizing antibodies for any of the 3 products. Furthermore, a large (1554 patients) integrated review of abobotulinumtoxinA clinical trials found only 5 patients who had a positive screening result for neutralizing antibodies (ie, formation of antibody-ligand complexes using an ^{125}I-labeled recombinant C-terminal fragment of the botulinum toxin heavy chain) using a radioimmunoprecipitation-competition assay protocol, but none of the positive findings were confirmed upon additional testing with the more specific mouse protection assay.[82] Additionally, all patients with a positive screening result were clinical responders to treatment.

In summary, the committee's consensus was that nonresponse due to neutralizing antibodies resulting from aesthetic BoNT-A therapy appears to be a rare event and of little clinical concern, regardless of whether the BoNT-A preparation contains neurotoxin-associated proteins or is "naked."

TREATMENT OF ANATOMIC AREAS

Treatment with BoNT-A must be considered differently in each anatomic area for a variety of reasons. The threshold for an effective dose will be greater in areas with greater muscular mass and strength. The optimal injection depth and angle will depend on the position of the target muscles between the skin and bony structures. Although certain localized adverse effects, such as pain, swelling, and bruising, are common to all injections, the risk of other adverse effects is heightened in specific areas (eg, weakened bite strength when injecting the masseter). Objective evidence cannot always be synthesized across anatomic areas because the methods and assessment tools used to evaluate efficacy differ between clinical trials, which also lack consistency in their reporting of adverse events. Furthermore, robust studies have not been performed in a number of areas in which BoNT-A is often injected, so the levels of evidence are not comparable with those in well-studied areas, such as the glabella, forehead, and lateral canthal lines.

Members of the consensus committee provided separate survey input for 13 anatomic areas in terms of usual doses, means of determining individualized doses and location of injection points, reconstitution practices, and injection techniques. All respondents routinely treated the glabella, forehead, and lateral canthal lines with BoNT-A. Other areas were treated somewhat less frequently. The décolleté area was treated by the lowest number (46%) of committee members; this area is poorly represented in the literature, and some committee members had not observed efficacy. Additional treatments described by committee members included treatment of facial asymmetry and the zygomaticus muscles. This panel of leading experienced practitioners often treated areas they consider technically challenging, which may not reflect practice within all segments of the broader aesthetic medicine community. Notably, the forehead, lower eyelids, perioral lines, and marionette lines (or downturned oral commissures) were commonly treated areas, although it may be challenging to consistently achieve optimal results and avoid complications in these areas. The committee advised that specific training for each anatomic area is necessary even for areas where treatment is relatively straightforward, such as the glabella. The more advanced the indication, the more focused the training needs to be to avoid adverse events.

Committee member responses to survey questions on dosing and reconstitution are presented in Table 2. It was felt that muscle mass, the desired outcome, and the duration of effect were predominant factors when considering dosing and injection technique. The smallest median total doses were to the nasal tip, followed in ascending order by the lower eyelids; perioral lines, gummy smile, and chin dimples (equally); marionette lines and bunny lines; the forehead; lateral canthal lines and glabella; platysmal bands; and the masseter. This pattern is likely attributable to considerations of muscle mass and more conservative dosing in anatomic areas that have a greater risk of complications. Variations in total dose (ie, range divided by median value) were smallest for the glabella and consistently large for the forehead and nasal tip. Greater variation may reflect a lack of consensus on methods for injecting areas that are more challenging to treat, as well as variability among patients in terms of anatomy or muscle mass. Individual committee members did not vary their preferred reconstitution volume for either abobotulinumtoxinA or onabotulinumtoxinA to treat distinct anatomic areas, but the preferred reconstitution volume differed among members.

In general, it was concluded that the dose of BoNT-A should be adjusted in different anatomic areas depending mostly on muscle mass (contracted vs resting) and the desired degree and duration of effect. Facial proportions may be an important consideration, for example, when injecting the frontalis to treat forehead lines. Other factors exist and may be interrelated; for example, wrinkle severity increases with age, and men usually have larger muscle mass than women. Observed muscle action was the most important method for locating injection points in almost every anatomic area, followed by superficial landmarks. Anatomic diagrams, bony landmarks, and muscle palpation were generally considered less important.

Intramuscular injection was the most frequently chosen depth of abobotulinumtoxinA delivery in all anatomic areas, although in some areas (forehead, lateral canthal

lines, lower eyelids, bunny lines, and perioral lines), many committee members recommended deep subdermal or subcutis injections. Superficial injections, including deep subdermal or subcutaneous routes, were considered useful in areas such as the periorbital region to avoid adverse events. When used at low doses, superficial injections can yield "mini toxin effects," resulting in preservation of underlying movement while softening wrinkle lines. The angle of injection was usually perpendicular to the skin, but a shallower angle was sometimes adopted, for example, in treating the lateral canthal lines, lower eyelids, bunny lines, and perioral lines. Committee members mostly preferred thinner (32- or 31-gauge) versus thicker (30- or 29-gauge) needles and were approximately evenly split on a preference for larger (1.0 mL) or smaller (0.5 or 0.3 mL) syringes.

Consensus committee findings are presented in the following sections for each anatomic area. Figures are provided to illustrate the general approach for treating each anatomic area.

Glabella

Glabellar lines form as the result of frowning and may also persist in repose as approximately vertical, static lines between the eyebrows (Figure 1). Consistent with the large concentration of clinical knowledge about treatment of the glabella,[14-35] committee members concluded that this area may be treated by the "novice" injector, although a basic degree of training is needed before injecting in any area. Injection points for the glabella are best determined by observing muscle contraction, although palpation of the muscles and making reference to superficial landmarks sometimes can be useful, as can bony landmarks and anatomic diagrams, to a lesser extent (Figure 1). The targets of injection are the procerus and corrugators and depressor supercilii muscles, the latter of which are highly variable in angle of insertion and length. Among committee members, the median total dose injected in the glabellar region was 52.5 U abobotulinumtoxinA or 20 U onabotulinumtoxinA (Table 2), in close agreement with the labeled dose recommendations.[1,8] According to the committee's survey responses, the standard dose should be adjusted according to the individual patient's glabellar muscle mass (contracted vs resting), wrinkle severity, and the desired magnitude and duration of effect. Many patients desire complete immobilization of the glabellar complex to abolish all dynamic wrinkles, although some may wish to retain partial function. Injections should be made intramuscularly and usually perpendicular to the skin surface. Care should be used to avoid injecting superior to the target muscles, which can cause brow ptosis by weakening the frontalis. Injecting within 1 cm of the bony margin of the orbit or near the supraorbital notch can cause eyelid ptosis by weakening the levator palpebrae superioris; this complication can be alleviated with apraclonidine eye drops.[1,6-8] If the frontalis is not weakened at the same time as the glabella, excessive brow elevation can occur. This effect, variously called "Spock," "Joker," or "Mephisto" eyebrow, can be reversed by injecting approximately 5 U abobotulinumtoxinA or 2 U onabotulinumtoxinA into the frontalis above the point of highest eyebrow elevation.[6]

Forehead

Horizontal lines on the forehead appear when the frontalis muscle is contracted to raise the eyebrows (Figure 2). Clinical trial evidence of the efficacy and safety of BoNT-A in treating the forehead is substantial.[25,26,31,36-39] All committee members treat this area but felt that it required more training, experience, and skill than the glabella because of the risk of brow ptosis and the need to consider the action of adjacent muscle groups. Observed muscle action and, to a lesser degree, superficial landmarks are important for locating injection points (Figure 2). Muscle mass and desired effects are the main considerations for dosing, but facial proportions also play a role. Complete immobilization of the forehead is often not desired, even if some lines remain, because it can prevent normal facial expression. Because of variation in the anatomy and strength of the frontalis between patients, conservative initial dosing is suggested, especially for new patients or those with small or weak frontalis muscles. The median total dose for the forehead according to survey responses from the committee members was 30 U abobotulinumtoxinA or 11.75 U onabotulinumtoxinA (Table 2). Half of the committee members injected the target area intramuscularly, but 25% injected deep subdermally and 25% injected superficially. Injections were usually perpendicular (75%). Brow ptosis was the complication of primary concern; this "caveman droop" is difficult to fully correct because the frontalis is the only muscle that can elevate the brows. Injecting the lower part of the forehead should be avoided for this reason, and an additional safety margin can be gained by treating only the upper half of the forehead.

Lateral Canthal Lines (Crow's Feet)

Lateral canthal lines appear bilaterally upon smiling in a fan-shaped pattern that may extend as far as the temporal hair line (Figure 3). A significant evidence base of clinical study data for treatment of lateral canthal lines with BoNT-A exists in the medical literature.[25,26,31,40-44] This area is routinely treated by all committee members, although they felt that specific training should be obtained by injectors who are not already experienced, because there is significant risk of hitting small blood vessels and causing bruises and a low risk of lower lid ectropion or bagginess if the skin is too lax. Care should be taken to avoid injecting patients with dry eyes, morning eyelid edema, or poor skin elasticity, and patients should have a positive "snap test."[5] Injection points are located based on observed muscle action and superficial landmarks; bony landmarks

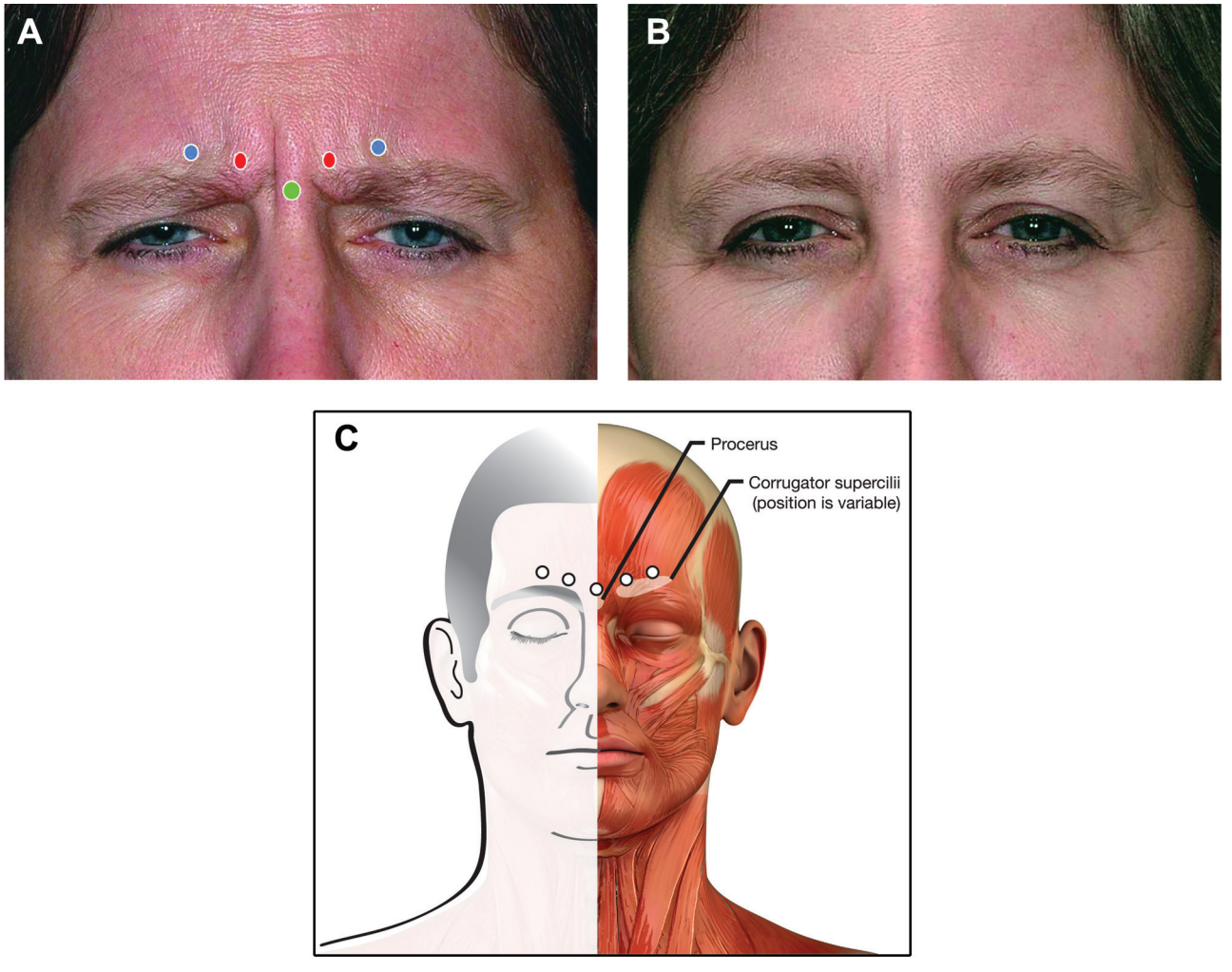

Figure 1. Treatment of glabellar lines with botulinum neurotoxin type A (BoNT-A). (A) This 52-year-old Caucasian woman with preexisting low brows who did not desire a brow shape change sought BoNT-A treatment to achieve a more relaxed appearance and a less angry look. She had not been previously treated with BoNT-A. She is shown at maximum contraction (ie, frowning). For this patient, 10 units of abobotulinumtoxinA were injected at each point shown on the photo. (B) Thirty-two days posttreatment, also at maximum contraction. (C) The diagram illustrates the underlying muscles to be injected (labels). The locations of typical injection points are denoted with circles. Images used with permission from Paradigm Medical Communications, LLC. © 2010. All rights reserved.

and anatomic diagrams also may be useful (Figure 3), but muscle palpation is of little value. Care should be used to stay 1 cm from the lateral canthus in most indications and over the lateral orbit as opposed to injecting over the eye adnexa. Median total doses (ie, for both sides of the face together) used by the committee members for lateral canthal lines are 50 U abobotulinumtoxinA or 20 U onabotulinumtoxinA (Table 2). Dose should be adjusted for desired degree of effect and the expanse and number of wrinkles. The usual injection depth for this area varied among the committee members: 42% of respondents injected intramuscularly, 25% deep subdermally, and 33% superficially. Likewise, the injection angle varied from perpendicular (42%) to 60 degrees (17%), 45 degrees (25%), and parallel (17%).

Lower Eyelids

Fine lines beneath the eyes can form as a result of smiling but should be distinguished from wrinkles that are due to lax skin. Although clinical trials on treatment of lower eyelid wrinkles were not found, most members of the committee treated this anatomic area routinely, and all treated it at least occasionally. Treating the lower eyelids is not for the novice injector, due to the delicacy of the area, but is effective with experience and reasonable skill; however, committee members indicated that consistently successful treatment can be challenging even for very experienced injectors. Observed muscle action and superficial landmarks guide the choice of injection sites (Figure 4). Bony landmarks and muscle palpation are not relevant. A “snap test” to measure

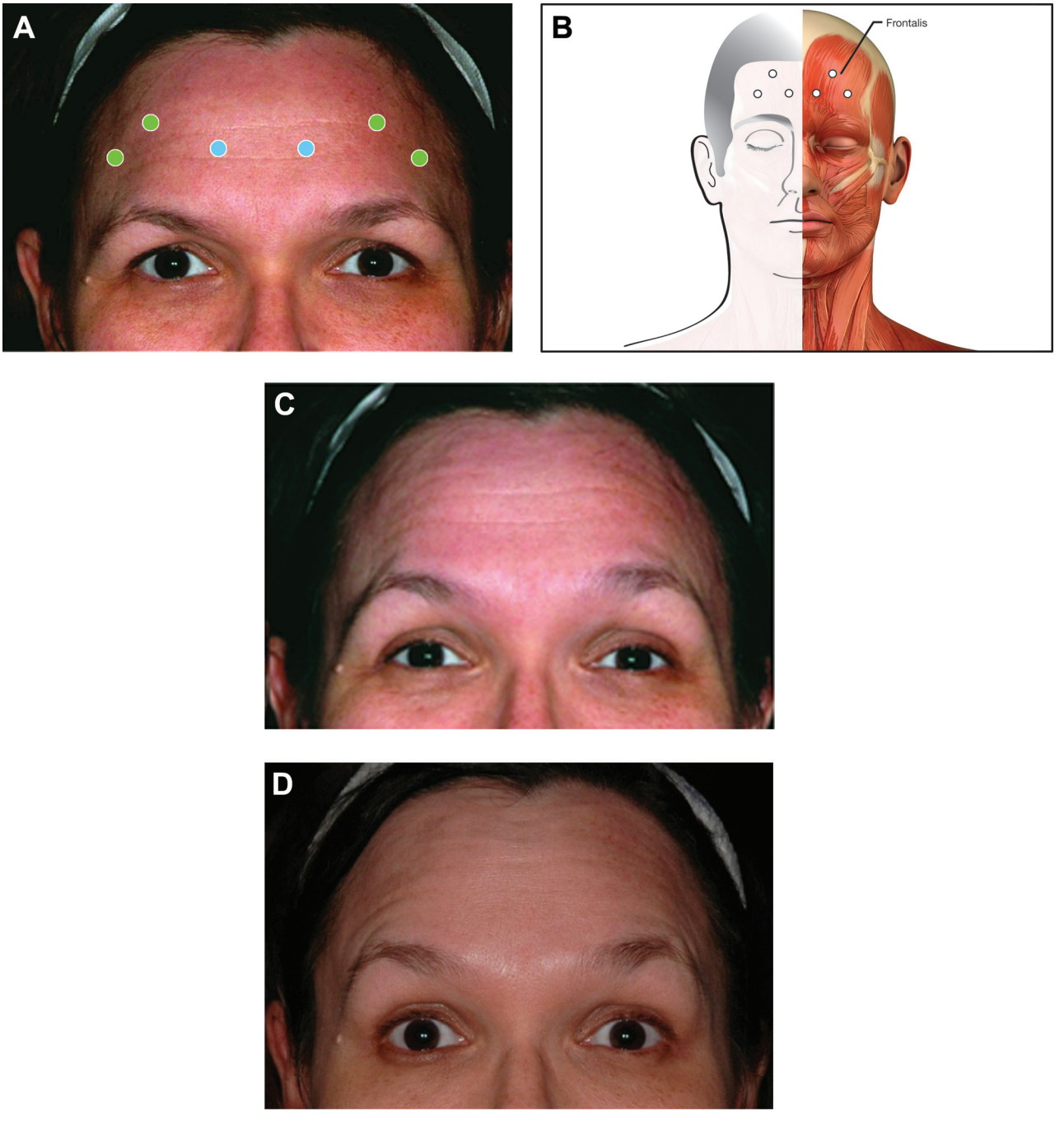

Figure 2. Treatment of forehead lines with botulinum neurotoxin type A (BoNT-A). (A, B) This Caucasian woman, approximately 45 to 49 years old, sought BoNT-A treatment to balance brow elevation with forehead smoothing. She had received previous treatment with BoNT-A 2 years before presentation. She is shown at repose and maximum contraction. The blue circles indicate that 5 units of abobotulinumtoxinA were injected, and the green circles indicate that 2.5 units were injected. (C) Thirty-three days posttreatment, at maximum contraction. (D) The diagram illustrates the underlying muscles to be injected (label). The locations of typical injection points are denoted with circles. Images used with permission from Paradigm Medical Communications, LLC. © 2010. All rights reserved.

lower lid skin laxity should be performed because a poor response can be expected if the skin does not snap back into place after downward tugging. Committee members reported injecting a median total dose (ie, for both lower eyelids considered together) of 10 U abobotulinumtoxinA or 4 U onabotulinumtoxinA (Table 2). Dosing was adjusted

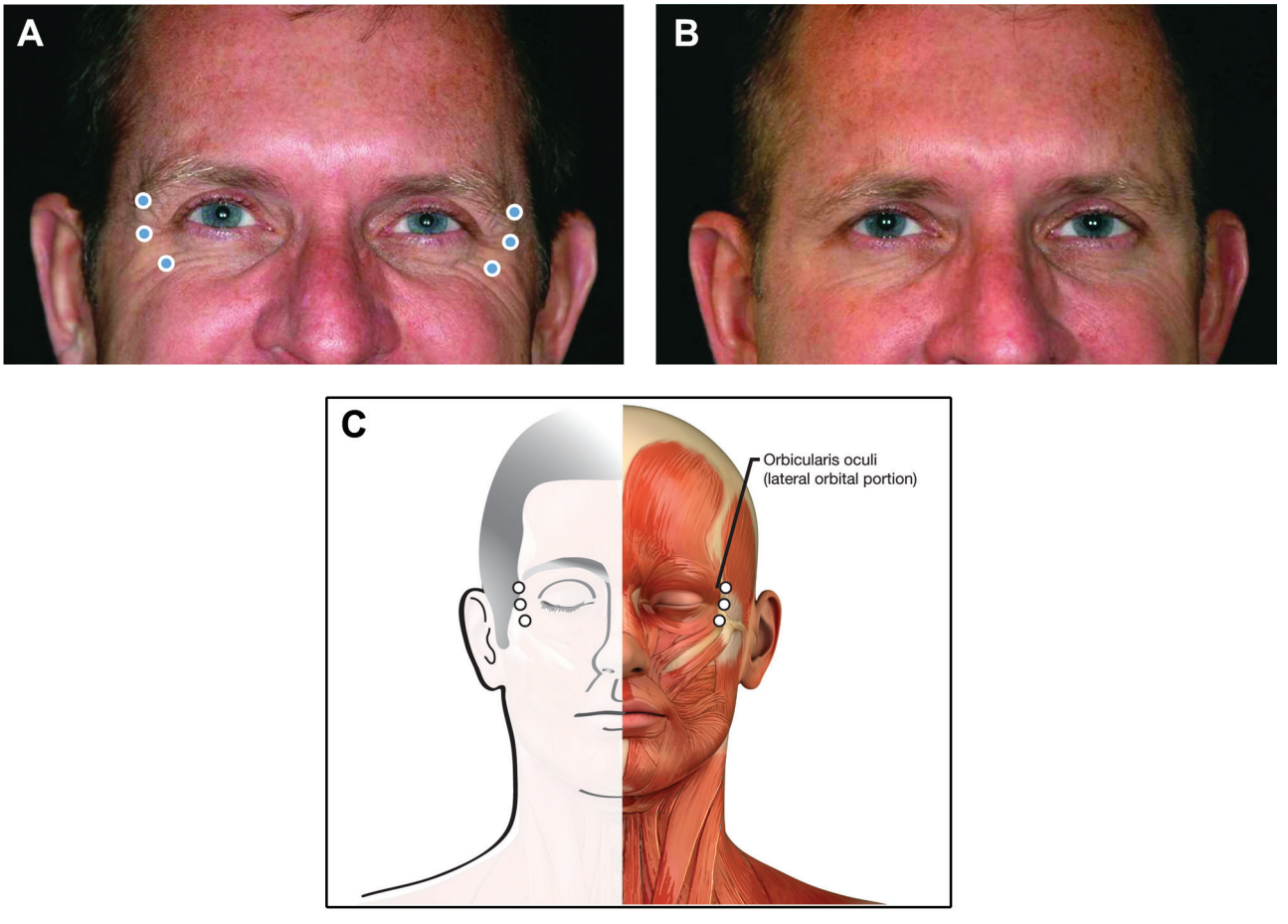

Figure 3. Treatment of lateral canthal lines (crow's feet) with botulinum neurotoxin type A (BoNT-A). (A) This 47-year-old Caucasian man sought BoNT-A treatment to reduce crow's feet wrinkles when smiling. He had been previously treated with BoNT-A. He is shown at maximum contraction (ie, smiling). For this patient, 15 units of abobotulinumtoxinA were injected at each point. (B) Seventeen days posttreatment, also at maximum contraction. (C) The diagram illustrates the underlying muscles to be injected (label). The locations of typical injection points are denoted with circles. Images used with permission from Paradigm Medical Communications, LLC. © 2010. All rights reserved.

based on muscle mass (thick muscles produce deeper lines and thin muscles produce finer although not necessarily fewer lines), desired degree of effect, wrinkle severity, and function of adjacent muscles. Injections were normally made intramuscularly (50% of committee members) or superficially (42%), but rarely deep subdermally (8%). The angle of injection could be perpendicular (42%), 60 degrees (17%), 45 degrees (25%), or parallel (17%). Total is 101%

Bunny Lines

So-called horizontal "bunny lines" form across the bridge of the nose due to contraction of the transverse nasalis muscle (Figure 5) and often become more prominent after BoNT-A treatment of the glabella. The literature lacks studies on the treatment of bunny lines, although all committee members performed this procedure. Most members (69%) recommended specific training before treating bunny lines because of the risk of asymmetry or accidental injection of the levator labii superioris alaeque nasi, which can lead to upper lip ptosis. Observed muscle action was considered most important for locating injection points; other factors were much less important. Committee members injected median total doses of 22 U abobotulinumtoxinA or 6 U onabotulinumtoxinA to treat bunny lines (Table 2). Wrinkle severity, muscle mass, degree and duration of effect, and adjacent muscle function were the main considerations in adjusting dose. Most committee members injected intramuscularly (58%), but several targeted a deep subdermal (25%) or superficial (17%) depth. Most respondents injected perpendicularly (58%), but some injected at 45 degrees (25%) or 30 degrees (17%).

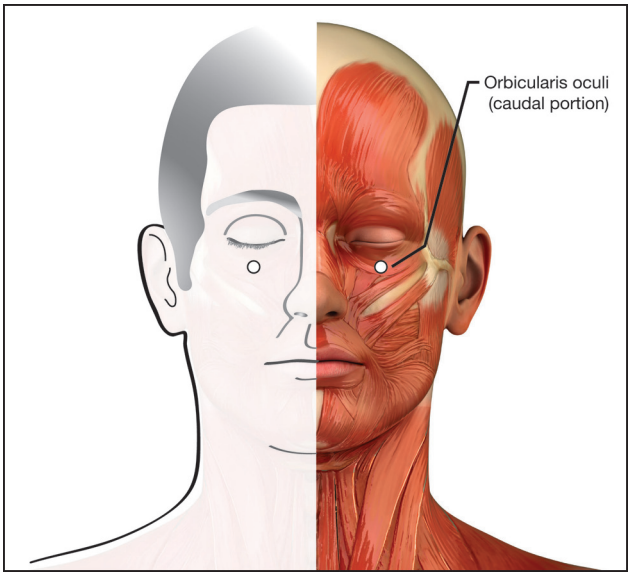

Figure 4. Treatment of lower eyelid lines with botulinum neurotoxin type A (BoNT-A); this represents alternative injection positioning for treatment of lateral canthal lines. The diagram illustrates the underlying muscles to be injected (label). The locations of typical injection points are denoted with circles. Images used with permission from Paradigm Medical Communications, LLC. © 2010. All rights reserved.

Nasal Tip

A ptotic or drooping nasal tip may result from overactivity of the depressor septi nasi muscle (Figure 6) and can be exacerbated by smiling. One article[83] described relieving ptosis of the nasal tip by paresis of the depressor septi nasi (and also the levator labii superioris alaeque nasi). All but 1 member of the consensus committee treated this area at least rarely. Respondents agreed that injector experience and skill are preferable, but specific training is required before injecting this area because of the risks of asymmetry and upper lip ptosis. Superficial landmarks are of the most importance (Figure 6), followed by observed muscle action; bony landmarks and anatomic diagrams are of lesser importance, and muscle palpation is not useful. The nasal tip had the smallest median dose of any anatomic area among committee members, with total values of 5 U abobotulinumtoxinA or 2 U onabotulinumtoxinA (Table 2). The dose is adjusted based on desired degree and duration of correction, facial proportions, observed muscle action, and adjacent muscle function. Nearly all of the committee members (82%) injected intramuscularly and perpendicularly.

Perioral Lines

Perioral lines form chiefly superior to the mouth as the result of pursing the lips (Figure 7). These rhytides may also be called "smoker's lines." Treatment of perioral lines with BoNT-A was mentioned in several articles, but only as adjunctive therapy with dermabrasion[84] or a soft-tissue filler.[85] Most of the committee members treated perioral lines routinely (54%) or infrequently (38%), with 1 member never treating this area. Most committee members felt that experience and skill are required (46%) or that treatment is challenging even for very experienced injectors (38%). Skill is needed because overdosing can produce perioral muscle weakness, lip elevation, or lip depression, and slight differences in injection depth or placement on either side of the midline can lead to facial asymmetry.[86] This procedure was frequently accompanied by injection of a hyaluronic acid dermal filler.[87] Muscle action and superficial landmarks (Figure 7) were recommended for location of injection points. The median total dose for perioral lines used by committee members was 15 U abobotulinumtoxinA or 5 U onabotulinumtoxinA (Table 2). Considerations for dose adjustment included muscle mass, wrinkle severity, desired degree and duration of effect, and function of adjacent muscles. Half of the expert committee injected intramuscularly (50%); others used an intradermal or subdermal (25%) or superficial injection depth (17%). Most injected perpendicularly (58%), but others used shallower angles ranging from 0 to 45 degrees.

Marionette Lines

Marionette lines extend downward from downturned oral commissures due to contraction of the depressor anguli oris, giving an aged appearance (Figure 8). Treatment of marionette lines or downturned oral commissures with BoNT-A has been studied only as part of overall lower facial rejuvenation in combination with soft-tissue filler augmentation (eg, large-particle hyaluronic acid gel).[86] All committee members injected patients at least occasionally for treatment of marionette lines, and most felt that it requires experience and skill (69%). Observed muscle action was most important for locating injection points, whereas superficial landmarks (Figure 8) played a secondary role. Marionette lines were injected with median total doses of 17.5 U abobotulinumtoxinA or 6 U onabotulinumtoxinA (Table 2). Dosing was adjusted based nearly equally on muscle mass and adjacent muscle function, as well as wrinkle severity to a lesser degree. Nearly all committee members injected intramuscularly (92%) and perpendicularly (92%). Muscle weakness and an asymmetric smile secondary to diffusion into the depressor labii inferioris were possible complications when injecting in this area. It was agreed that careful, symmetric placement of injections away from the oral commissures (ie, at least halfway from the mouth corners to the jawline), along with proper dosing, can minimize the risk of adverse effects on oral function. The lower third of the depressor anguli oris should be targeted to avoid injecting the depressor labii inferioris.[6]

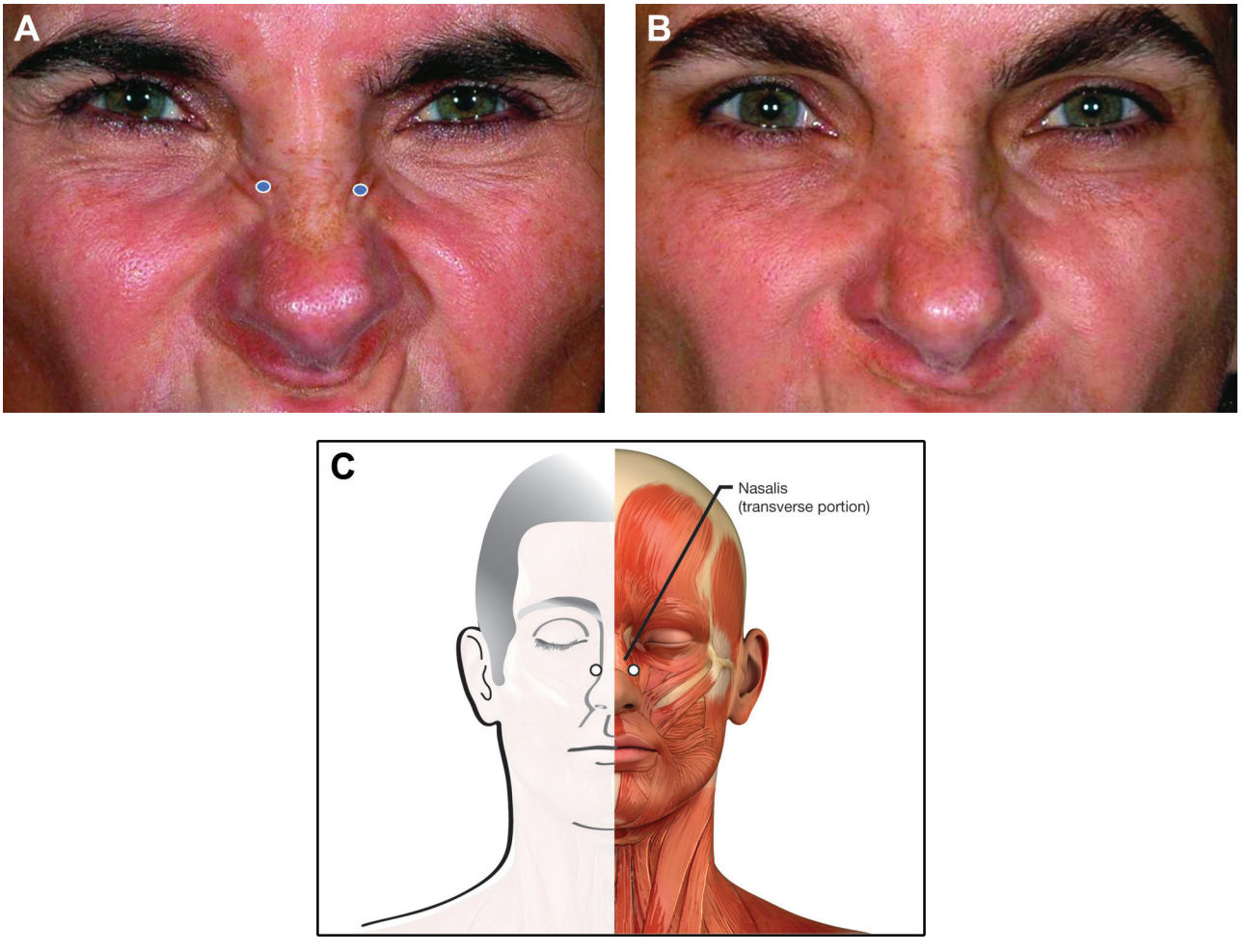

Figure 5. Treatment of bunny lines with botulinum neurotoxin type A (BoNT-A). (A) This 46-year-old Hispanic woman sought treatment to reduce bunny lines when smiling. Her previous BoNT-A treatment history was unknown. She is shown at maximum contraction. For this patient, 10 units of abobotulinumtoxinA were injected at each point. (B) Seventeen days posttreatment. (C) The diagram illustrates the underlying muscles to be injected (label). The locations of typical injection points are denoted with circles. Images used with permission from Paradigm Medical Communications, LLC. © 2010. All rights reserved.

Gummy Smile

A gummy smile exposes excessive gingival area as the upper lip is raised, due to overactivity of the levator labii superioris alaeque nasi muscle, and may also be asymmetric (Figure 9). Injection of BoNT-A can diminish elevation of the upper lip and improve symmetry, as several studies have established, albeit with a low level of evidence.[88-91] All but one committee member treated gummy smile at least occasionally. Slightly more than half the committee stated that treatment was challenging even for very experienced practitioners (54%), whereas the remaining members stated that it requires experience and skill (46%). Injection points were determined equally by observed muscle action and superficial landmarks (Figure 9), whereas dose adjustment is based on adjacent muscle function, desired degree and duration of effect, facial proportions, and muscle mass. The median total doses reported by the committee members were 15 U abobotulinumtoxinA or 5 U onabotulinumtoxinA (Table 2). The emphasis on adjacent muscle function for dosing reflects the risk of producing an asymmetric smile or difficulty in smiling.[88] The committee members nearly always injected intramuscularly (83%) and perpendicularly to the skin (78%).

Chin Dimple

A dimpled appearance of the skin due to mentalis muscle contraction is also known as pebbled, cobblestone, or golf ball chin (Figure 10). The level of evidence for treating chin dimples is low, with only 2 published studies in which other facial areas also were treated simultaneously

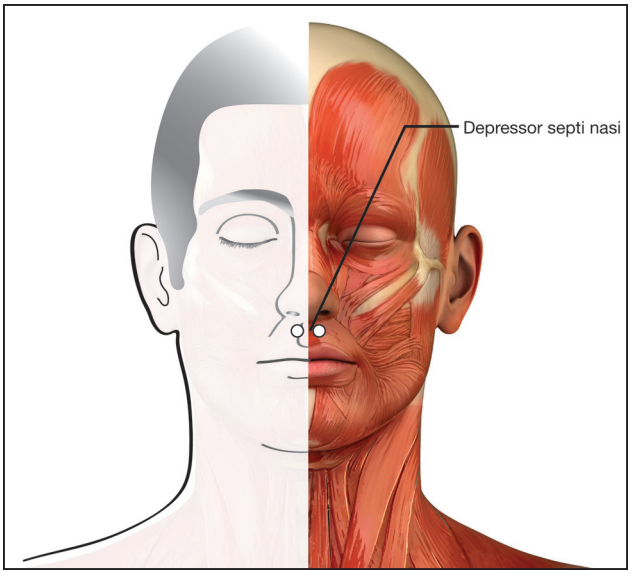

Figure 6. Adjustment of a drooping nasal tip position with botulinum neurotoxin type A (BoNT-A). The diagram illustrates the underlying muscles to be injected (label). The locations of typical injection points are denoted with circles. Images used with permission from Paradigm Medical Communications, LLC. © 2010. All rights reserved.

and results were not separated by anatomic area.[86,92] Nonetheless, all committee members treated chin dimple either routinely (54%) or infrequently (46%), although they felt it was not for the novice injector, instead requiring specific training (54%) or skill and experience (46%) to avoid risks of asymmetry as a result of diffusion to the depressor labii inferioris or difficulties with eating and drinking, such as drooling. Injection points were located mostly by observed muscle action but also based on superficial landmarks (Figure 10). Injections typically are made at 1 or 2 points, the number depending in part on whether bifurcation of the mentalis is seen on animation. Committee members injected median total doses of 15 U abobotulinumtoxinA or 5 U onabotulinumtoxinA (Table 2). Muscle mass, adjacent muscle function, desired degree and duration of effect, and wrinkle severity were all important when adjusting the usual dose. Most committee members inject intramuscularly (83%) and perpendicular to the skin (75%).

Masseter Hypertrophy

Masseter hypertrophy creates a "square-jawed" profile that may be considered unattractive (Figure 11), especially by women and in certain cultures. Unlike most other aesthetic uses of BoNT-A, which diminish wrinkles or correct asymmetry, treatment of the masseter is intended to reduce muscle mass by atrophy, thus slimming the jawline. Five studies described use of onabotulinumtoxinA for this purpose, although none of these studies were

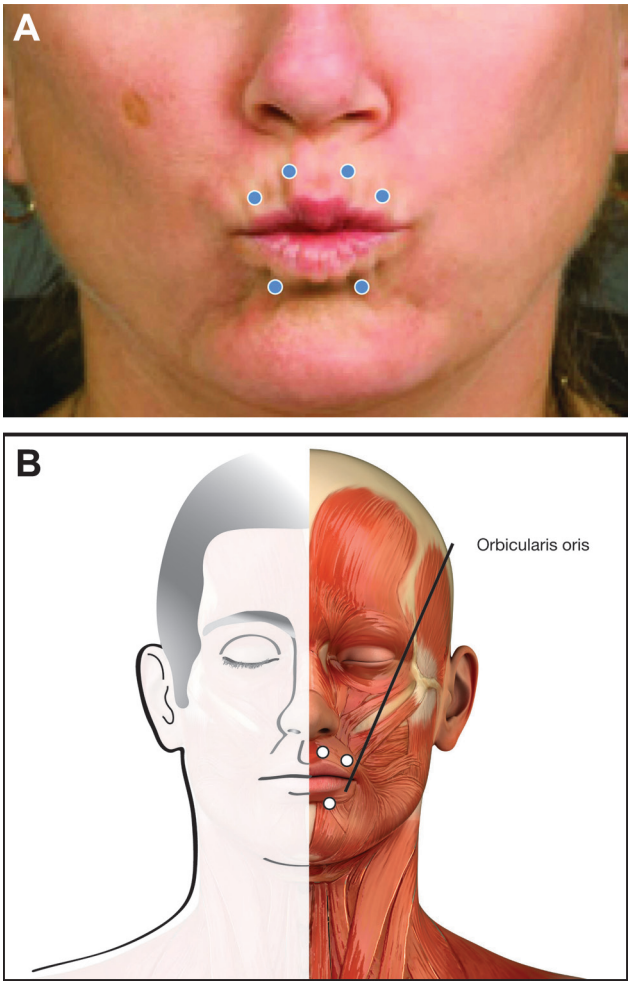

Figure 7. Treatment of perioral lines with botulinum neurotoxin type A (BoNT-A). (A) This 45-year-old Caucasian woman sought treatment to reduce lines around her mouth that were worsening with age. No history of previous treatment with BoNT-A was reported. The patient is shown at maximum contraction, pretreatment. The diagram (B) illustrates the underlying muscles to be injected (label). The locations of typical injection points are denoted with circles. Photograph is from Gordon RW. BOTOX Cosmetic for lip and perioral enhancement. *Dent Today*. 2009;28(5):94-97. Reprinted with permission from *Dentistry Today*, © 2009 *Dentistry Today*.

randomized or blinded; Asian patients (particularly Koreans) made up large portions or all of the population in most studies.[93-97] Adverse events reported with treatment of masseter hypertrophy included those that would be expected when a major functional muscle of the face is weakened (decreased mastication force,[93,95-97] changes in facial expression,[93,95] and speech disturbance[96]), as well as dysgeusia[93] and transient muscle bulge.[95]

Most of the committee treated masseter hypertrophy at least occasionally (77%), but a minority had never treated this area (23%). Most stated that skill and

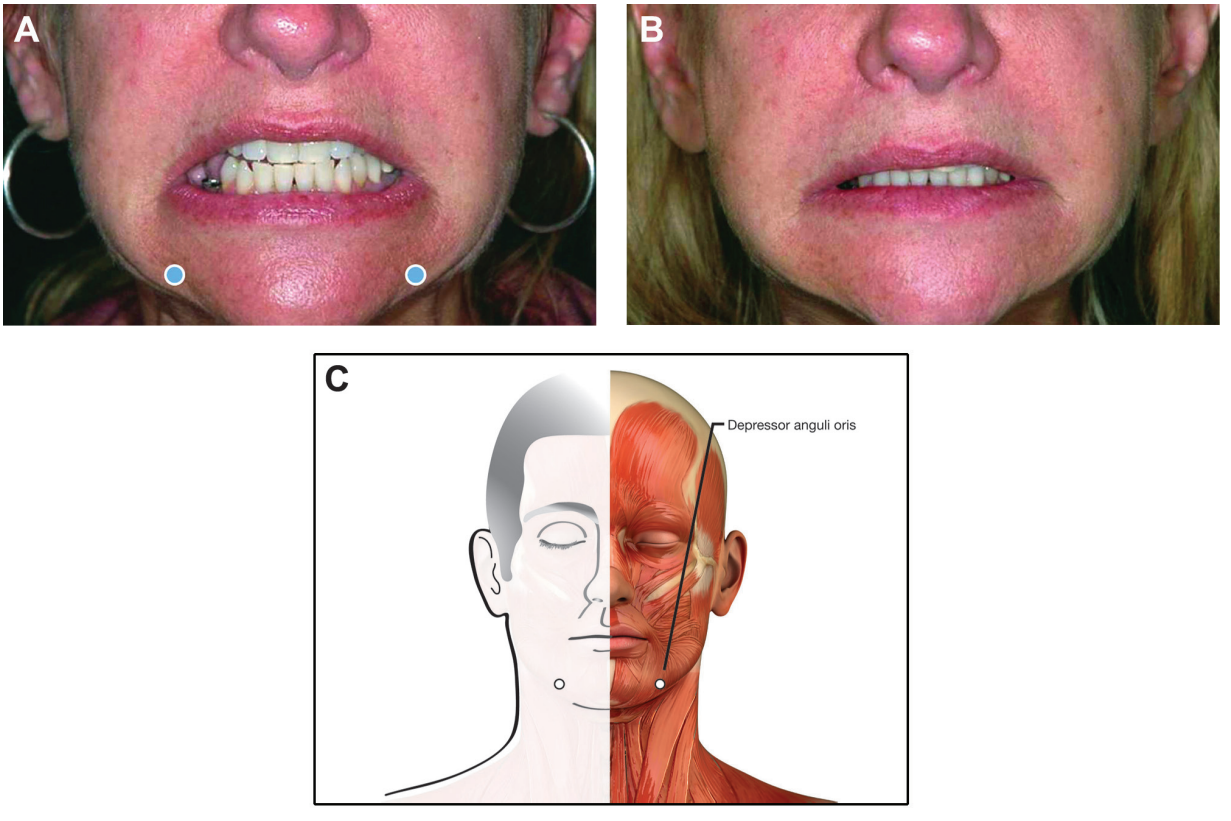

Figure 8. Treatment of marionette lines with botulinum neurotoxin type A (BoNT-A). (A) This 52-year-old Caucasian woman sought treatment to soften marionette lines. Her previous treatment history with BoNT-A was unknown. The patient is shown at maximum contraction (ie, grimacing). For this patient, 10 units of abobotulinumtoxinA were injected at each point. (B) Twenty-eight days posttreatment, also at maximum contraction. The diagram (C) illustrates the underlying muscles to be injected (label). The locations of typical injection points are denoted with circles. Images used with permission from Paradigm Medical Communications, LLC. © 2010. All rights reserved.

experience are required or that treatment is challenging even for those who are very experienced (42%). Committee members stated that observed muscle action and muscle palpation were most important for locating injections, with minor roles for superficial landmarks and anatomic diagrams. The median total dose injected to reduce masseter hypertrophy was the largest of any anatomic area, with values of 100 U abobotulinumtoxinA or 32.5 U onabotulinumtoxinA (Table 2). Muscle mass and the desired degree and duration of effect were the predominant factors to consider when deciding upon a dose. Injections were always made intramuscularly and usually perpendicularly (77%).

Platysmal Bands

The platysma muscle, which is a thin, flat sheet covering the lower face, throat, and upper chest, can raise bands on the neck upon contraction (Figure 12). These dynamic bands should be distinguished from flaps of lax skin. Injection of the platysma has been reported in the literature, but without description of efficacy or safety.[98] The majority of the expert committee treated platysmal bands routinely (62%). Most felt that it required specific

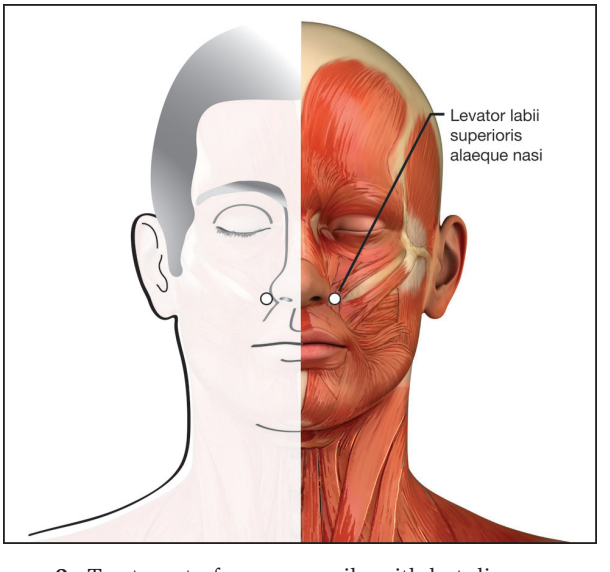

Figure 9. Treatment of gummy smile with botulinum neurotoxin type A (BoNT-A). The diagram illustrates the underlying muscles to be injected (label). The locations of typical injection points are denoted with white circles. Images used with permission from Paradigm Medical Communications, LLC. © 2010. All rights reserved.

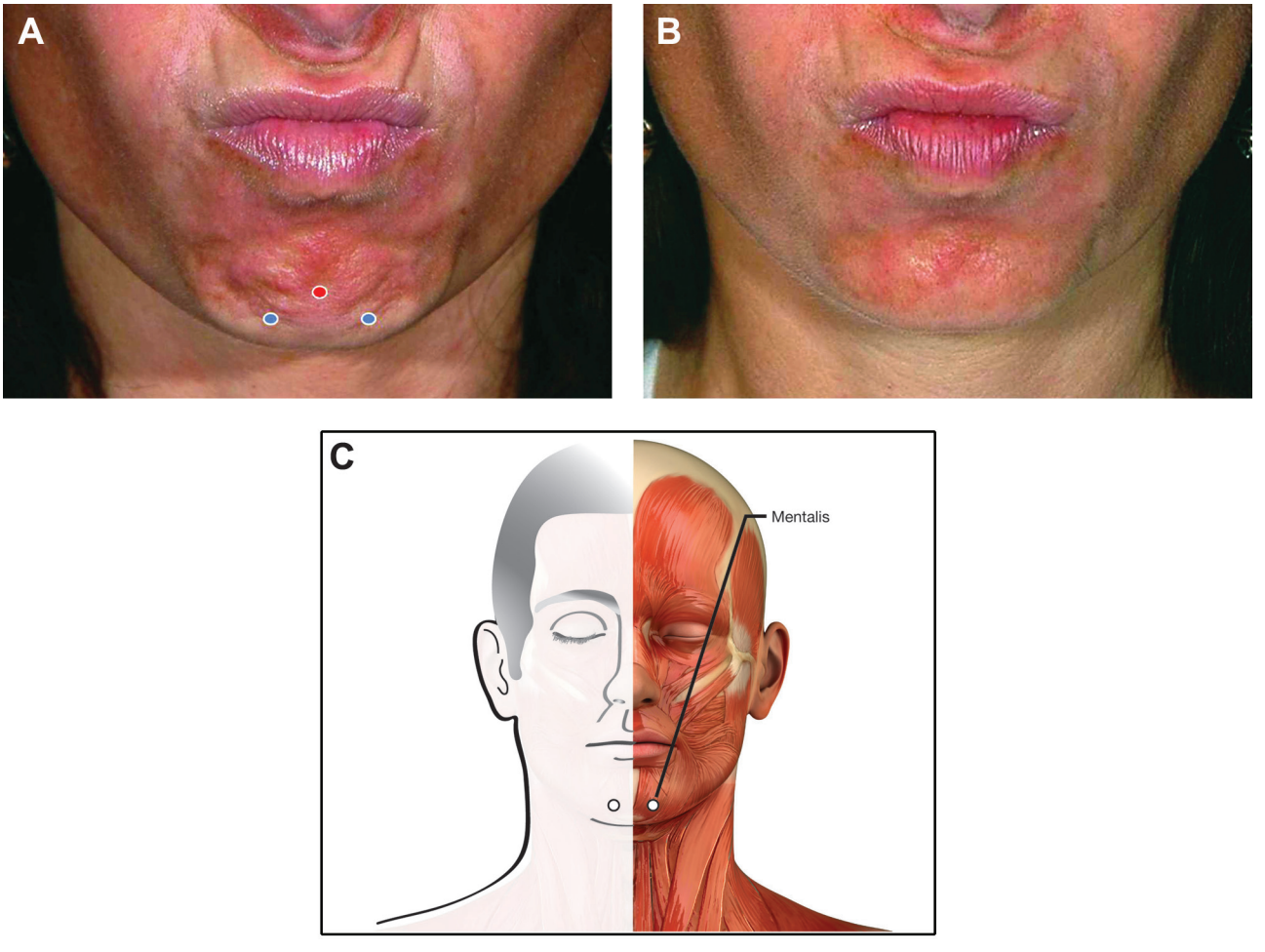

Figure 10. Treatment of chin dimple with botulinum neurotoxin type A (BoNT-A). (A) This 46-year-old Hispanic woman sought treatment to reduce chin dimpling. Her previous treatment history with BoNT-A was unknown. The patient is shown at maximum contraction. For this patient, the blue circles indicate that 10 units of abobotulinumtoxinA were injected and the red circle indicates that 5 units were injected. (B) Seventeen days posttreatment, also at maximum contraction. The diagram (C) illustrates the underlying muscles to be injected (label). The locations of typical injection points are denoted with circles. Images used with permission from Paradigm Medical Communications, LLC. © 2010. All rights reserved.

training or experience and skill (74%), although a few found it challenging even for the very experienced injector (15%), because of the risks of difficulty swallowing, neck weakness, and asymmetric smile from accidental injection of the depressor anguli oris. Observed muscle action mostly determined the location of injections; superficial landmarks, muscle palpation, and anatomic diagrams may also be useful (Figure 12). The median total dose used by committee members was 75 U abobotulinumtoxinA or 30 U onabotulinumtoxinA (Table 2). Dose was adjusted based on muscle mass; less important factors may include desired degree and duration of effect, wrinkle severity, and adjacent muscle function. Panel members usually made injections intramuscularly (80%) and directly into to the bands (90%).

COMBINATION OF BoNT-A TREATMENT WITH OTHER THERAPIES

Treatment with injectable fillers, chemical or laser peels, and dermabrasion was commonly combined with abobotulinumtoxinA therapy, but there was little consensus on the timing of these adjunctive treatments relative to abobotulinumtoxinA injection. Fillers were implanted most often in the glabella, perioral lines, and marionette lines; strong trends for use of resurfacing procedures according to anatomic area were not apparent. The results suggest that individual clinical judgment is still paramount in this area, for which the medical literature is sparse. One report recommended that when treating the upper face, BoNT-A should be injected before the filler is implanted to retain

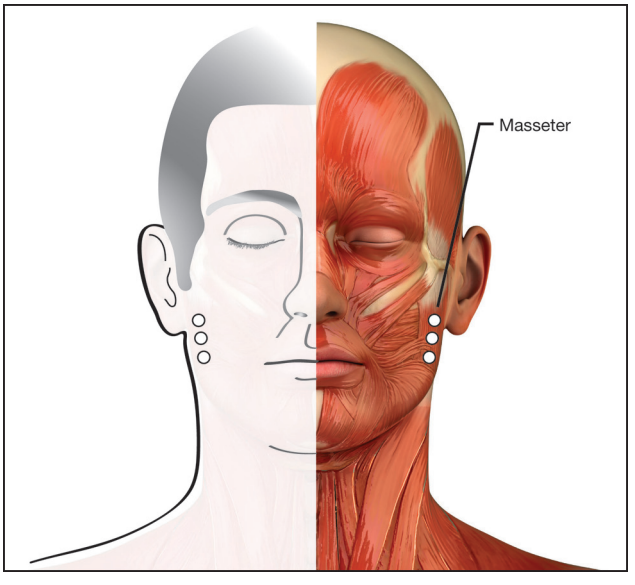

Figure 11. Treatment of masseter hypertrophy with botulinum neurotoxin type A (BoNT-A). The diagram illustrates the underlying muscles to be injected (label). The locations of typical injection points are denoted with circles. Images used with permission from Paradigm Medical Communications, LLC. © 2010. All rights reserved.

the ability to palpate muscles and injection points; however, for the lower face, it was recommended that the filler be injected first.[6] The committee also noted that BoNT-A injection has been reported to minimize scarring after Mohs surgery by immobilizing the resected area.[99]

CONCLUSIONS

The committee of 13 experienced practitioners of BoNT-A aesthetic treatment achieved consensus on most issues by critically synthesizing published literature, results of an online survey of their usual practices, and an extensive live discussion of their collective clinical experience. Treatment of the glabella, forehead, and lateral canthal lines with BoNT-A has now become routine and is represented by a substantial amount of clinical research. Despite gaps in published evidence for other anatomic areas, most committee members treated a variety of these areas with BoNT-A at least infrequently or rarely; these areas included the lower eyelids, bunny lines, ptotic nasal tip, perioral lines, marionette lines, gummy smile, chin dimple, hypertrophic masseter, and platysmal bands. Some aspects of BoNT-A use were consistent across anatomic areas but varied among committee members, suggesting that these personal preferences (such as the volume of diluent in which BoNT-A is reconstituted) are not critical for treatment success. On the other hand, adjusting the dose of BoNT-A based on observed muscle action and mass is held to be important for nearly all anatomic areas. The safety of the 2 most well-established BoNT-A products, abobotulinumtoxinA and onabotulinumtoxinA, is very similar in the experience of the committee. The incidence of nonresponse due to neutralizing antibodies acquired as a result of aesthetic BoNT-A therapy is exceedingly rare and essentially negligible in clinical practice.

As expected, consensus was not reached on all issues. Additional high-quality research may be helpful in providing data to resolve differing expert opinions. Approximately equal numbers of committee members used preserved and nonpreserved saline for reconstitution; strong evidence for or against the use of preservative is lacking. Consistent objective evidence is also lacking in measuring fields of effect with abobotulinumtoxinA and onabotulinumtoxinA and determining whether differences between the two exist. Related to this is the inability of research to determine a uniform, fixed ratio for equipotent doses of the 3 currently available BoNT-A products. Experience with abobotulinumtoxinA and onabotulinumtoxinA in the United States is now more mature than in 2009 and has evolved since the first BoNT-A was approved for aesthetic use in 2002; members of the committee have optimized the use of each product independently for their patients. However, given that incobotulinumtoxinA was only recently approved, experience with this BoNT-A is too limited to adequately assess the optimal aesthetic use of this product. The findings reported in this consensus document, considered in conjunction with the labeling for each of the BoNT-A products, may serve as a practical guide for aesthetic practitioners as they apply the latest knowledge about BoNT-A to provide their patients with optimal care.

Disclosures

Dr Maas is a paid researcher for Colbar LifeScience Ltd, Allergan Inc (Irvine, California), Medicis Inc (Scottsdale, Arizona), and Mentor LLC (Santa Barbara, California); a consultant for Merz Aesthetics Inc (San Mateo, California) Aesthetics Inc (San Mateo, California), Allergan Inc (Irvine, California), Mentor LLC (Santa Barbara, California), and Johnson & Johnson Inc (New Brunswick, New Jersey); a member of the speakers bureau for Merz Aesthetics Inc (San Mateo, California), Allergan Inc (Irvine, California), Integra Life Science Inc (Plainsboro, New Jersey), Lumenis Inc (Santa Clara, California) Inc (Santa Clara, California), Medicis Inc (Scottsdale, Arizona), and Johnson & Johnson Inc (New Brunswick, New Jersey); and a stockholder of Merz Aesthetics Inc (San Mateo, California), Allergan Inc (Irvine, California), Lumenis Inc (Santa Clara, California) Inc (Santa Clara, California), Medicis Inc (Scottsdale, Arizona), Mentor LLC (Santa Barbara, California), and Johnson & Johnson Inc (New Brunswick, New Jersey); Dr Kane is a paid advisor or consultant for Allergan Inc (Irvine, California) Inc, Merz Aesthetics Inc (San Mateo, California), Medical Inc, Medicis Inc (Scottsdale, Arizona), QMed LLC (Charlotte, North Carolina), and Stiefel Laboratories Inc (Triangle Park, North Carolina) Laboratories; a speaker or member of a speakers bureau for Allergan Inc (Irvine, California), Medicis Inc (Scottsdale, Arizona), QMed LLC (Charlotte, North Carolina), and sanofi-aventis Inc (Bridgewater, New Jersey); and a paid researcher for Coapt Systems Inc (Palo Alto, California), Medicis Inc (Scottsdale, Arizona), and Revance

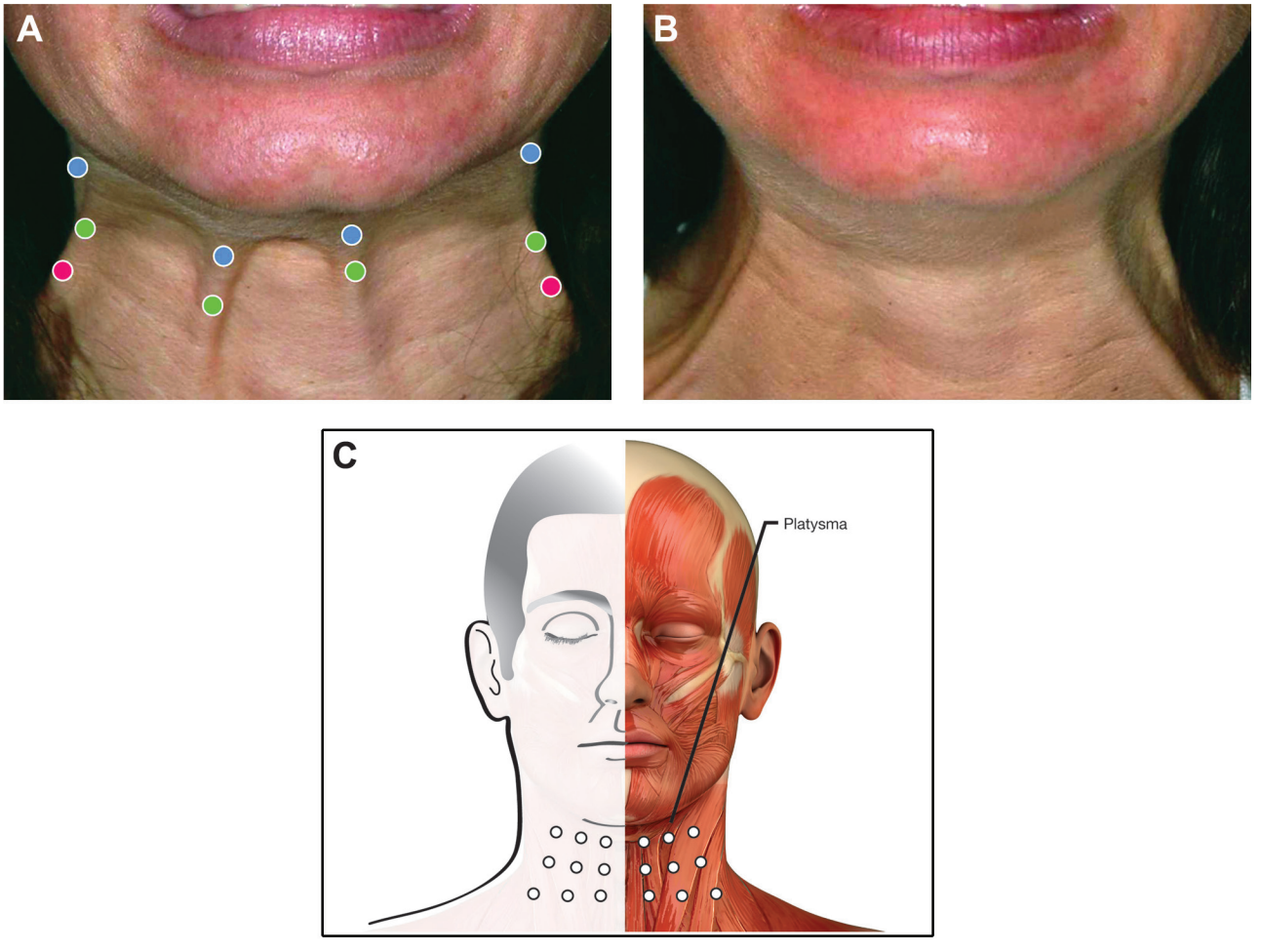

Figure 12. Treatment of platysmal bands with botulinum neurotoxin type A (BoNT-A). (A) This 46-year-old Hispanic woman sought treatment to reduce the size of the visual platysmal bands. Her previous treatment history with BoNT-A was unknown. She is shown at maximum contraction (note the banding). For this patient, the blue circles indicate that 5 units of abobotulinumtoxinA were injected, the green circles indicate that 2.5 units were injected, and the red circles indicate that 2 units were injected. (B) Seventeen days posttreatment, also at maximum contraction. The diagram (C) illustrates the underlying muscles to be injected and the placement of injections (label); the actual number of injections needs to be individualized. The possible locations of typical injection points are denoted with circles; note that these circles represent potential sites, but these should never be used all at the same time for safety reasons. Images used with permission from Paradigm Medical Communications, LLC. © 2010. All rights reserved.

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