頭頸seminar

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SIAXI Sialorrhea in Adults Xeomin Investigation

Placebo-controlled, randomized, double-blind study of incobotulinumtoxinA for sialorrhea

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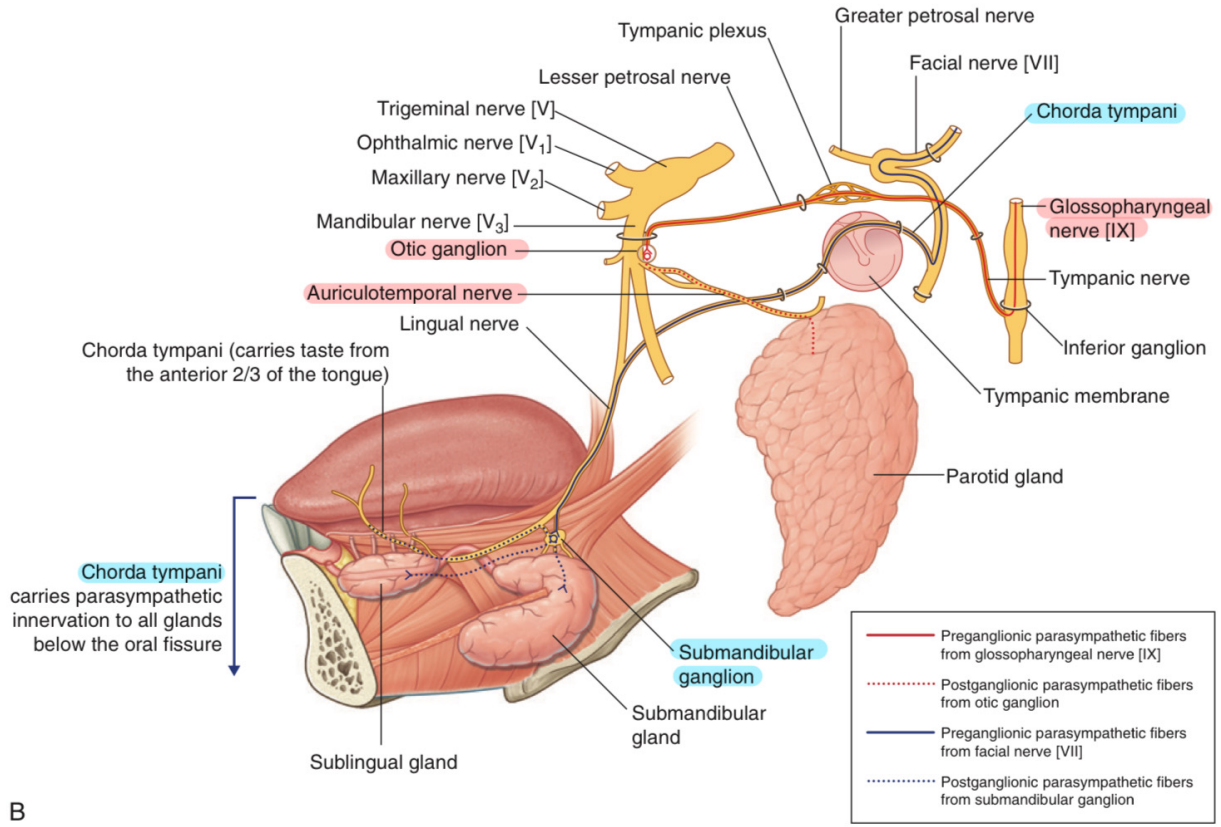
Salivary Gland Anatomy and Physiology

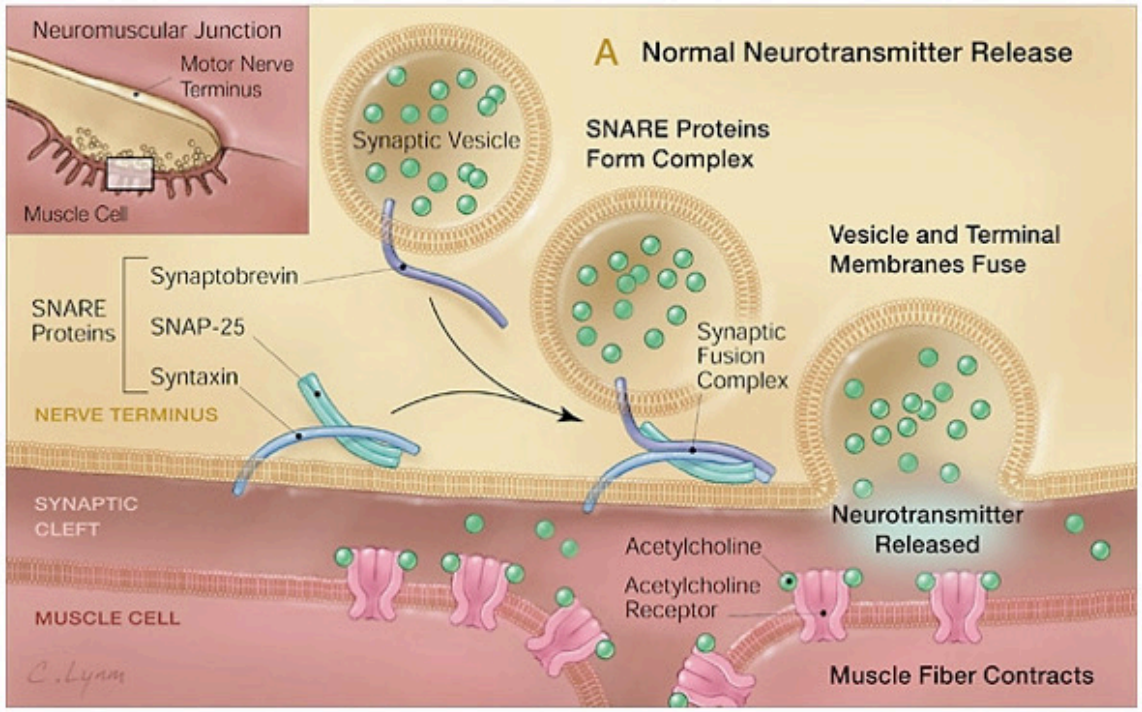
- Major salivary gland
  - Parotid gland-> serous
  - Submandibular gland-> mixed
  - Sublingual gland-> mucous

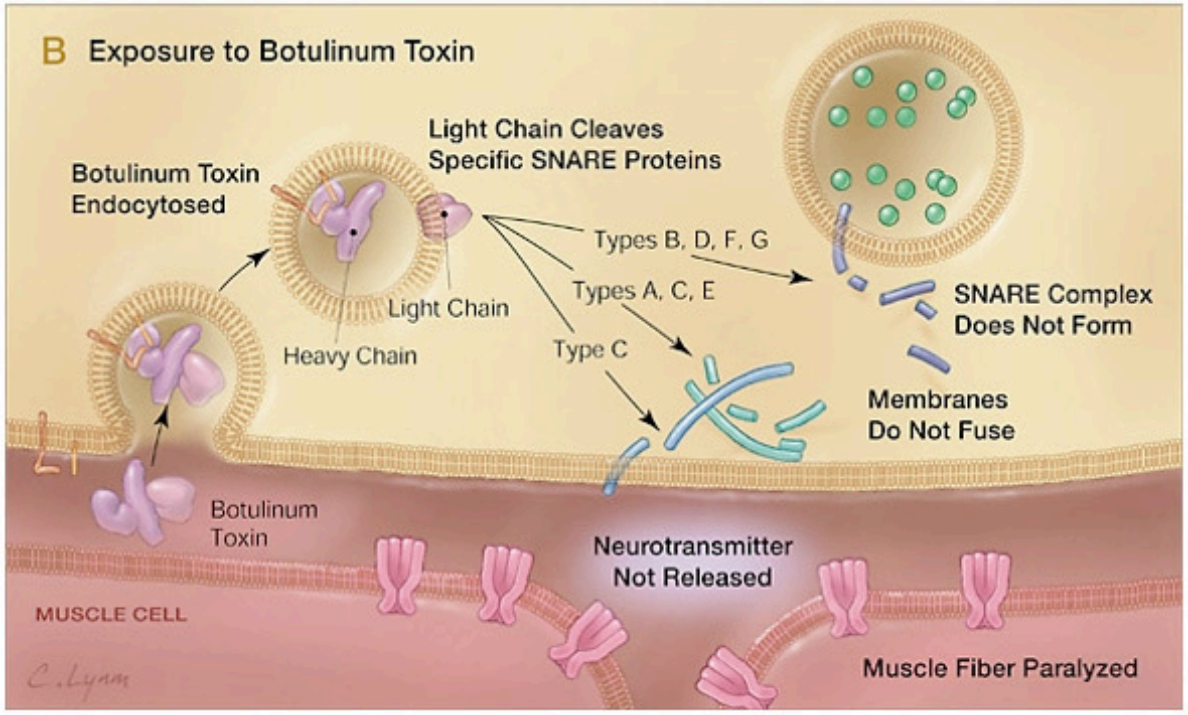


Gray's Anatomy for student, 4th Ed, Fig. 8.150

- Salivary flow rate
  - Stimuli (-) → > 0.1ml/min
  - Stimuli (+) → 0.2-7ml/min
- Daily production: 1000-1500ml
  - Stimuli (-) → submandibular (65%) > parotid (20%) > sublingual (8%) > minor (<10%)
  - Stimuli (+) → parotid (> 50%)

Mechanism of Botulinum Toxins





- Serotype Specificity
  - Botulinum Toxin A →Cleaves SNAP25
  - Botulinum Toxin B →Cleaves VAMP (Synaptobrevin II)
- Result: Prevents ACh vesicle docking → No ACh release

- Xeomin: BoNT/A free from complexing proteins

Introduction

Introduction

Definition: Sialorrhea (intractable drooling) is a disabling symptom resulting from swallowing problems or an inability to retain saliva.

Etiology:

- Frequently associated with underlying neurologic diseases relevant to our practice, including Parkinson Disease (PD), stroke, and Traumatic Brain Injury (TBI)
- The prevalence in PD patients ranges from 32% to 74%

Patient Impact:

- Adverse effects on caregiver and patient quality of life
- Difficulty eating and speaking, severe social and emotional consequences
- Increases risk of morbidity and mortality due to perioral skin breakdown and aspiration pneumonia

Introduction

- **Systemic Agents (e.g., Anticholinergics):**
  - Nonspecific, systemic activity
  - Limited by adverse effects like cognitive impairment, drowsiness, and urinary retention.
- **Botulinum Neurotoxin (BoNT):**
  - Used effectively off-label for years, but lacked high-level, pivotal trial data for a specific formulation.
- **Invasive Options:**
  - Reserved for therapy-resistant cases (e.g., irradiation, salivary gland surgery).

At the time this study was conducted, no pharmacologic agents had US FDA or European Medicines Agency approval for the treatment of chronic sialorrhea in adults.

The SIAXI Trial's Design

- Study Objective: To investigate the efficacy and safety of incobotulinumtoxinA for treating chronic sialorrhea.
- Study type: Pivotal phase III, prospective, Randomized, Double-Blind, Placebo-controlled, multicenter study conducted over 33 sites (12 sites in Germany and 21 sites in Poland)
- Evidence classification: This study was designed to provide Class I evidence

Methods

Study population

Inclusion:

- Adults with chronic (≥3 months) troublesome sialorrhea due to:
  - Parkinson Disease
  - Atypical Parkinsonism
  - Stroke
  - Traumatic Brain Injury (TBI)
- Drooling Severity and Frequency Scale (DSFS) sum score of ≥6
- modified Radboud Oral Motor Inventory for Parkinson's Disease (mROMP) score drooling ≥3 points, swallowing items A ≤2, items C ≤3

DSFS	Drooling severity	Drooling frequency
1	Never drools, dry	No drooling
2	Mild-drooling, only lips wet	Occasionally drools
3	Moderate- drool reaches the lips and chin	Frequently drools
4	Severe- drool drips off chin & onto clothing	Constant drooling
5	Profuse- drooling off the body and onto objects (furniture, books)	

Study population

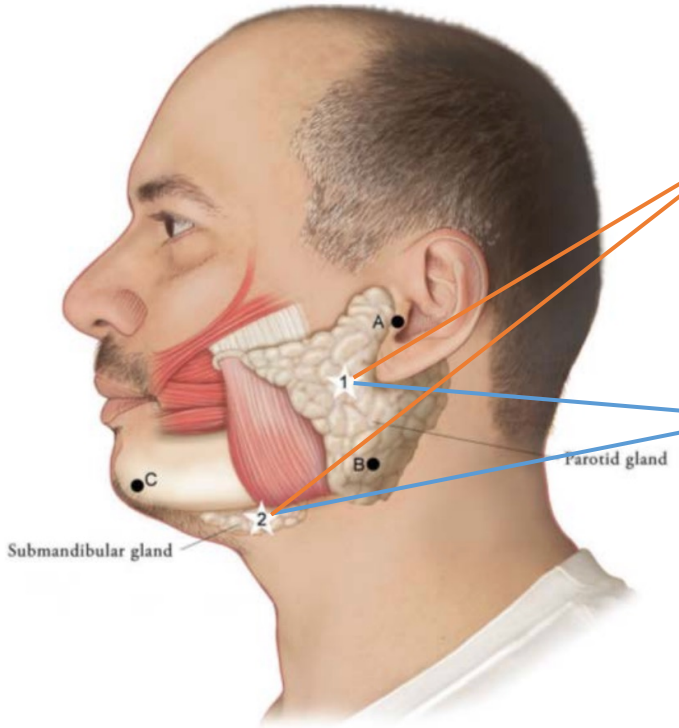
Exclusion:

- Secondary causes of sialorrhea
- Use of drug treatment for sialorrhea within 4 weeks
- Unstable concomitant medications that may affect sialorrhea
- Changes in antiparkinsonian medication within 4 weeks prior to screening
- History of recurrent aspiration pneumonia
- Prior recent botulinum toxin (BoNT) treatment or hypersensitivity to BoNT
- Previous or planned surgery for the treatment of sialorrhea

Study design

- Treatment groups
  - Patients were randomized in a 2:2:1 ratio
  - IncobotulinumtoxinA 75 U
  - IncobotulinumtoxinA 100 U
  - Placebo
- Main Period(MP):16wks
- Treatment schedule: 3 additional treatments
- Total observation period: 64 weeks
- Injection Protocol: 4 total injections, one into each parotid and submandibular gland, bilaterally
- Guidance: Ultrasound or Anatomical Landmarks

Figure 1: Glands for Injection in Chronic Sialorrhea in Adult Patients



75U Group:
22.5U(Parotid) (0.6 mL)
+15U (Submandibular) (0.4 mL)

100U Group:
30U (Parotid) (0.6 mL)
+20U (Submandibular) (0.4 mL)

Placebo Group:
- Equivalent volumes were injected into each gland.
- Placebo contained excipients of incobotulinumtoxi A injection, sucrose, and human serum albumin

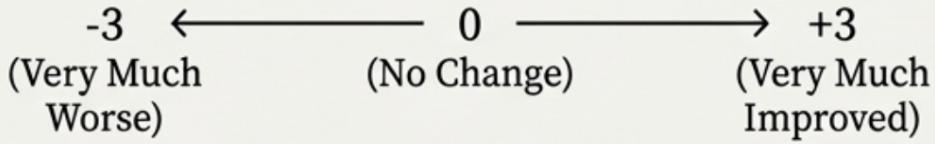
Outcome measurement: The Co-Primary Endpoints at Week 4

Endpoint 1: Change in unstimulated Salivary Flow Rate (uSFR)

- Prepare:
  - 1 hour before, the patient's teeth were brushed and the patient was not allowed to eat or smoke
  - 30 minutes before, patients were offered a drink of mineral water
- Swab method:
  - 4 adsorbent swabs placed at gland orifices for 5 minutes.
  - Weight increase calculated in g/min.
  - Repeated after 30 minutes and the average of 2 results was calculated

Endpoint 2: Patients' and carers' Global Impression of Change Scale (GICS)

- A 7-point Likert scale
  - For patients: "Compared to how you were doing just before the last injection... what is your overall impression of how you are functioning now?"
  - For caregivers: "Compared to how the patient was doing just before the last injection into his/her salivary gland, what is your overall impression of how he/she is functioning now as a result of this treatment?"



Other Key Measures: Efficacy was also assessed at weeks 8, 12, and 16 to evaluate duration of effect

Other endpoints

- Drooling Severity and Frequency Scale (DSFS):
  - Drooling severity: a 5-point Likert scale from 1 (dry; never drools) to 5 (profuse; hands, tray, and objects wet)
  - Drooling frequency : a 4-point Likert scale from 1 (never) to 4 (constantly)

- The occurrence of adverse events (AEs), AEs related to treatment, AEs of special interest (AESIs)

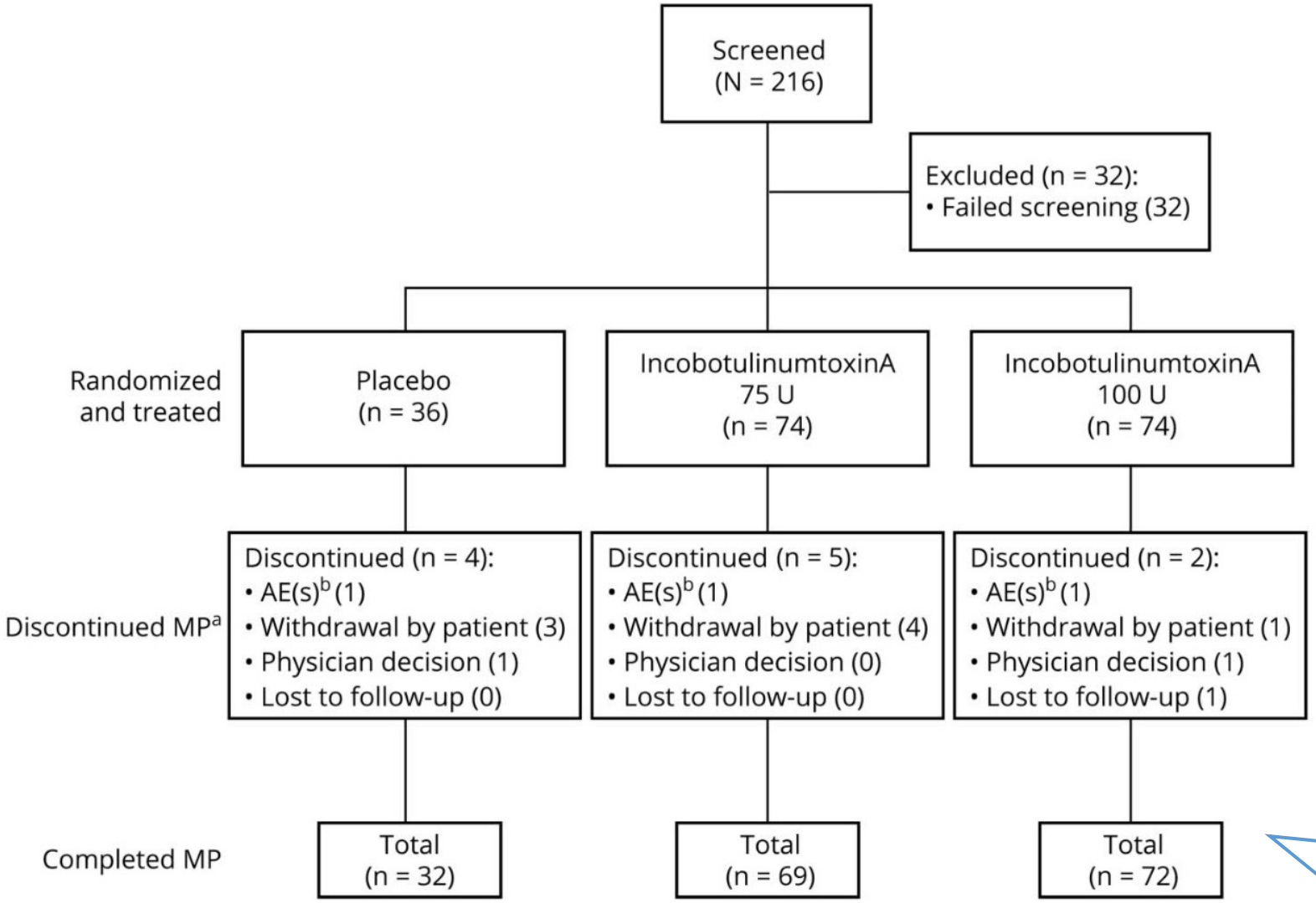
	Drooling severity	Drooling frequency
1	Never drools, dry	No drooling
2	Mild-drooling, only lips wet	Occasionally drools
3	Moderate- drool reaches the lips and chin	Frequently drools
4	Severe- drool drips off chin & onto clothing	Constant drooling
5	Profuse- drooling off the body and onto objects (furniture, books)	

Statistical analysis

- **Analysis Sets:**
  - Full Analysis Set (Efficacy): all patients treated who had at least a baseline uSFR value.
- **Testing Procedures:**
  - Fixed-sequence test procedure: The 100 U group was compared with placebo first; the 75 U group was compared only if the first test was significant.
- **Statistical Models:**
  - MMRM Analysis: Mixed model repeated measurement was used to assess changes from baseline in primary and secondary variables.
  - Independent Variables:
    - fixed factors: treatment group, etiology, ultrasound guidance, country, and sex,
    - Interaction term: visit*treatment
    - repeated factor: visit
  - Confirmatory and Sensitivity Analyses: Used least squares means (LS-means) comparison from the MMRM model

Results

Disposition of patients



Low Discontinuation(6.0%): Overall, 173 of 184 patients (94.0%) completed the main period

Table 1 Patient demographics and baseline characteristics

Characteristic	Placebo (n = 36)	IncobotulinumtoxinA 75 U (n = 74)	IncobotulinumtoxinA 100 U (n = 74)	Total (N = 184)
Sex, n (%)				
Male	28 (77.8)	50 (67.6)	52 (70.3)	130 (70.7)
Female	8 (22.2)	24 (32.4)	22 (29.7)	54 (29.3)
Age, y, mean (SD)	63.5 (10.6)	65.2 (11.7)	66.0 (11.6)	65.2 (11.4)
Weight, kg, mean (SD)	80.6 (16.4)	78.4 (17.1)	79.8 (14.0)	79.4 (15.7)
BMI, kg/m^2, mean (SD)	28.5 (6.0)	26.7 (5.2)	27.7 (3.8)	27.5 (4.9)
Drooling etiology, n (%)				
PD	26 (72.2)	51 (68.9)	53 (71.6)	130 (70.7)
Atypical parkinsonism	3 (8.3)	8 (10.8)	5 (6.8)	16 (8.7)
Stroke	6 (16.7)	13 (17.6)	14 (18.9)	33 (17.9)
Traumatic brain injury	1 (2.8)	2 (2.7)	2 (2.7)	5 (2.7)
UPDRS section III score, mean (SD) [n]	29.2 (12.7) [29]	33.1 (17.2) [59]	30.3 (15.1) [58]	31.2 (15.6) [146]
uSFR, g/min, mean (SD)	0.38 (0.23)	0.42 (0.28)	0.40 (0.27)	0.40 (0.26)
DSFS score, mean (SD)	6.97 (1.06)	6.88 (0.91)	6.78 (0.90)	6.86 (0.93)
Concomitant anti-PD medication, n (%)[a]				
Dopaminergic agents	28 (77.8)	57 (77.0)	58 (78.4)	143 (77.7)
Anticholinergic agents[b]	0 (0.0)	2 (2.7)	2 (2.7)	4 (2.2)
Injection guidance, n (%)				
Ultrasound-guided	18 (50.0)	45 (60.8)	41 (55.4)	104 (56.5)
Anatomical landmark–guided	18 (50.0)	29 (39.2)	33 (44.6)	80 (43.5)

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Baseline characteristics (age, sex, drooling etiology) were similar across the three treatment groups, ensuring a valid comparison.

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Unified Parkinson's Disease Rating Scale section III "motor examination" score: **31.2 (15.6)** at baseline
-> indicating moderate to severe impairment

- uSFR: 0.40 (0.26) g/min
- DSFS score: 6.86 (0.93)

-> moderate to severe troublesome sialorrhea on average

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uSFR, g/min, mean (SD)	0.38 (0.33)	0.43 (0.28)	0.40 (0.27)	0.40 (0.26)
DSFS score, mean (SD)	6.97 (1.06)	6.88 (0.91)	6.79 (0.00)	6.86 (0.93)
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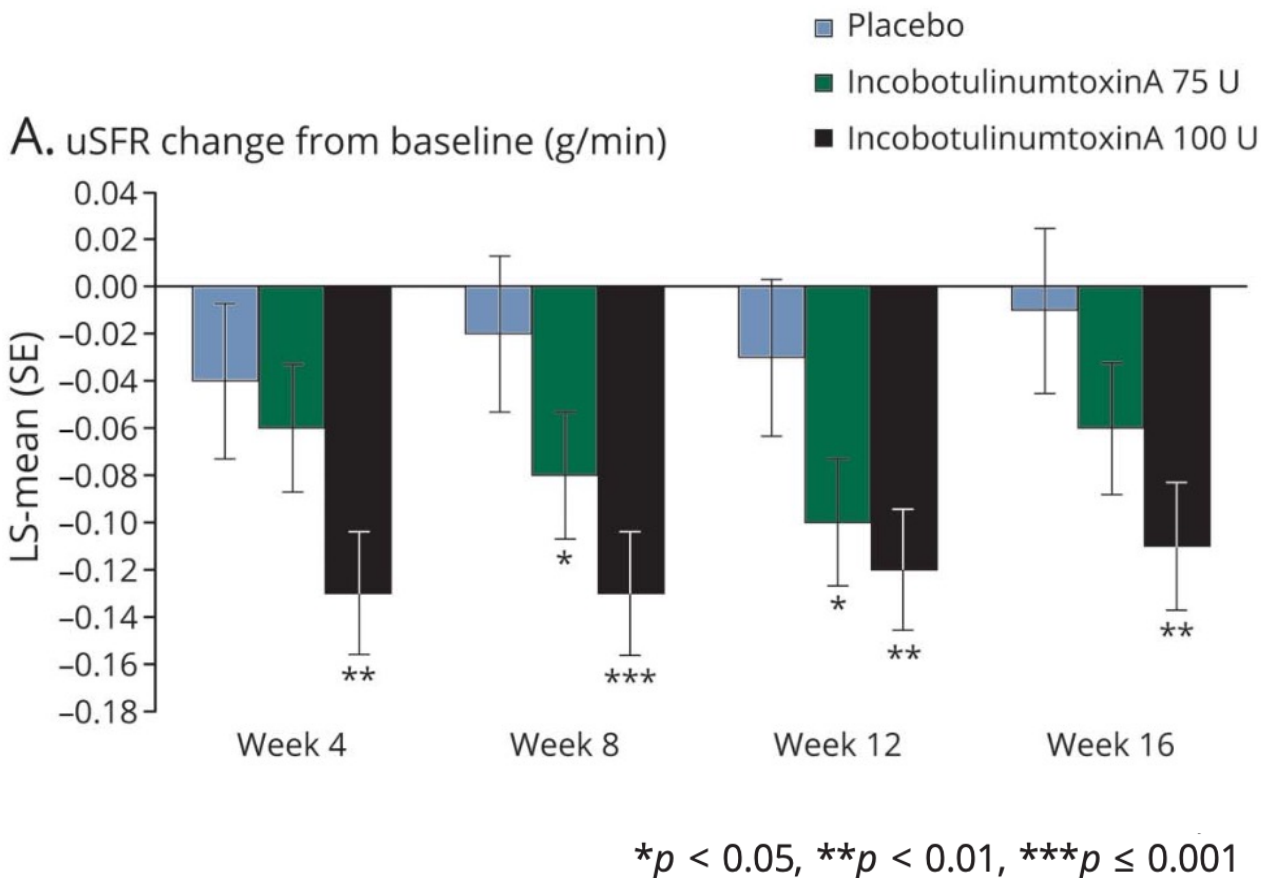
- Ultrasound guidance: 56.5% of and at least 50.0% in each treatment group
- Anatomical landmark–guided: 43.5%

-> with no difference in baseline demographics or severity of sialorrhea

Results: uSFR change from baseline



LS-mean (standard error [SE]) difference
Primary Endpoint (Week 4):

- **100U group** vs. placebo **:** −0.09 (0.031; p = 0.004) -> Statistically significant reduction
- **75U group** vs. placebo**:** −0.02 (0.030; p = 0.542) -> No significant difference

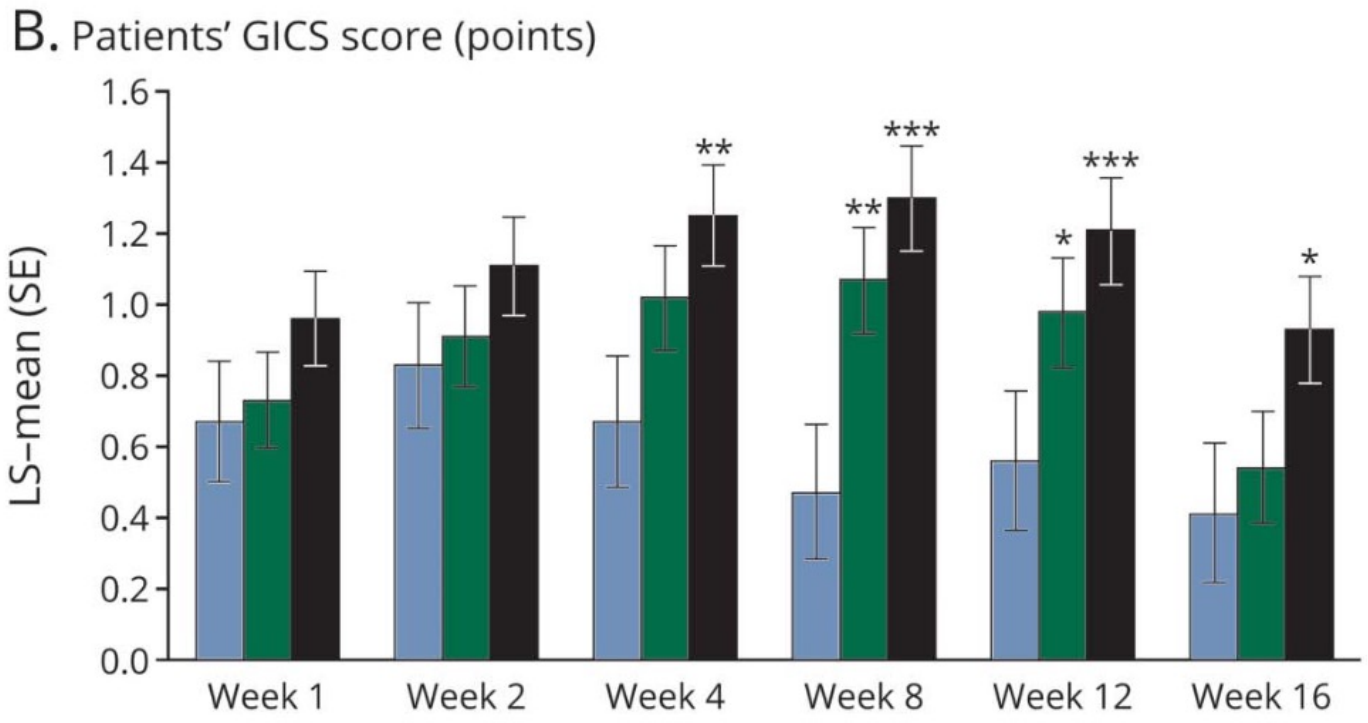
Week8, 12:

- Both 75U and 100U reached statistical significance

Durability (Week 16):

- **100U group:** −0.10 (0.033; p = 0.002) -> Effect is sustained, remaining significant at 16 weeks post-injection

Results: Patients' GICS score



LS-mean (standard error [SE]) difference
Primary Endpoint (Week 4):

- **100U group** vs. placebo **:** 0.58 (0.183; p = 0.002) -> Statistically significant
- **75U group** vs. placebo**:** 0.35 (0.181; p = 0.055) -> No significant difference

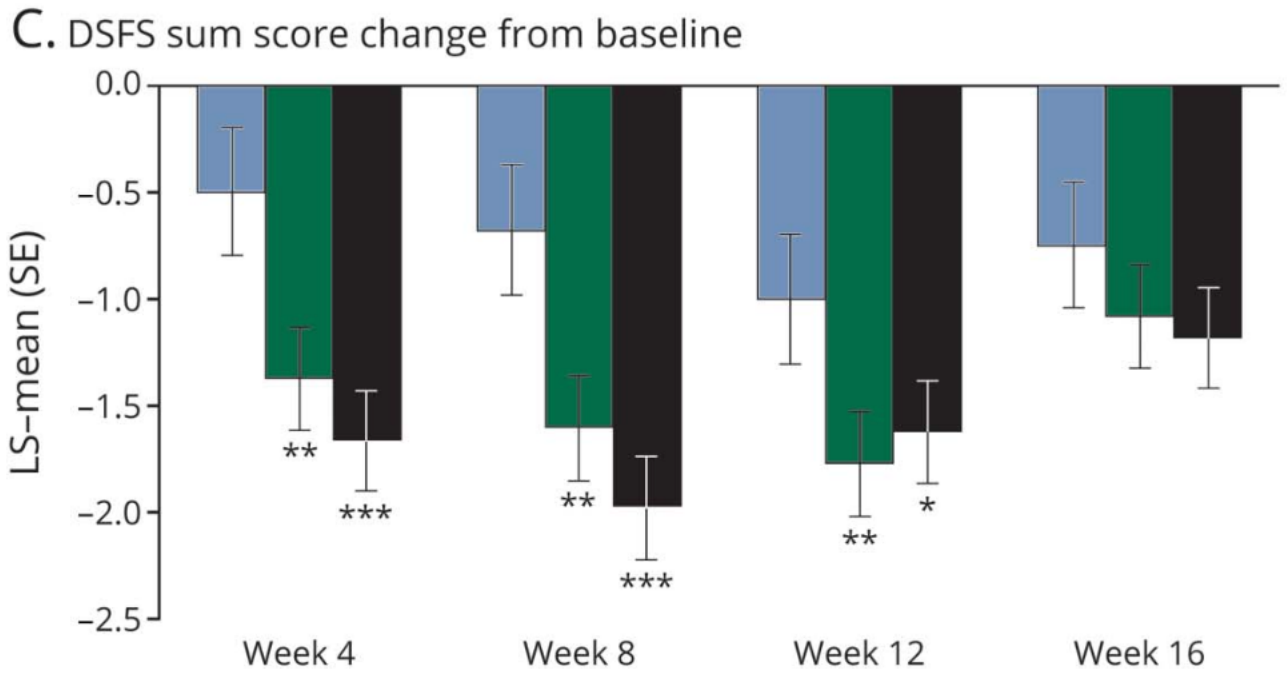
Week8, 12:

- Both 75U and 100U showed statistical significance

Durability (Week 16):

- **100U group:** 0.52 (0.203, p = 0.011) -> maintained a significant improvement at the final observation point

Results: DSFS sum score change from baseline



LS-mean (standard error [SE]) difference
Primary Endpoint (Week 4):

- **100U group** vs. placebo **:** -1.17 (0.278, p < 0.001) -> significant improvements
- **75U group** vs. placebo**:** -0.88 (0.275, p = 0.002 -> significant improvements

Week8, 12:

- Both 75U and 100U showed significant improvements

Safety

Table 2 Summary of AEs

Patients	Placebo (n = 36)	IncobotulinumtoxinA, 75 U (n = 74)	IncobotulinumtoxinA, 100 U (n = 74)	Total incobotulinumtoxinA (N=148)
Any AE	15 (41.7)	32 (43.2)	34 (45.9)	66 (44.6)
Any treatment-related AE	3 (8.3)	7 (9.5)	6 (8.1)	13 (8.8)
Any AESI[a]	0 (0.0)	5 (6.8)	5 (6.8)	10 (6.8)
Any treatment-related AESI	0 (0.0)	3 (4.1)	1 (1.4)	4 (2.7)
Any SAE	3 (8.3)	6 (8.1)	9 (12.2)	15 (10.1)
Any treatment-related SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any AE leading to discontinuation[b]	0 (0.0)	1 (1.4)	1 (1.4)	2 (1.4)
			0 (0.0)	0 (0.0)
			0 (0.0)	0 (0.0)
			0 (0.0)	0 (0.0)

- All treatment-related events were nonserious and of mild or moderate intensity

Dry mouth	Dysphagia
75U Group: 5.4% (4 patients)	75U Group: 2.7% (2 patients)
100U Group: 2.7% (2 patients)	100U Group: 0.0% (0 patients)

Safety

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Any SAE	3 (8.3)	6 (8.1)	9 (12.2)	15 (10.1)
Any treatment-related SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any AE leading to discontinuation[b]	0 (0.0)	1 (1.4)	1 (1.4)	2 (1.4)
Any treatment-related AE leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any fatal AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any fatal treatment-related AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

- AESIs occurring in the incobotulinumtoxinA 75 U and 100 U groups, respectively, were as follows:
  - dysphagia (n = 3 [2 related], n = 0); dry mouth (n = 0, n = 2 [1 related]); dysarthria (n = 0, n = 1); speech disorder (n = 1 [related], n = 0);
  - dysphonia (n = 0, n = 2); bradycardia (n = 1, n = 0); and eyelid ptosis (n = 1 [related], n = 0)
- dry mouth considered to be severe, serious, or irreversible were reported as AESIs

Safety

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Any AESI	2 (5.6)	5 (6.8)	6 (8.1)	13 (8.8)
Any treatment-related AESI	0 (0.0)	5 (6.8)	5 (6.8)	10 (6.8)
Any SAE	0 (0.0)	3 (4.1)	1 (1.4)	4 (2.7)
Any treatment-related SAE	3 (8.3)	6 (8.1)	9 (12.2)	15 (10.1)
Any AE leading to discontinuation[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any AE leading to discontinuation[b]	0 (0.0)	1 (1.4)	1 (1.4)	2 (1.4)
Any treatment-related AE leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any fatal AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any fatal treatment-related AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Discontinuations and Fatalities:

- 2 patients discontinued due to AEs (pneumonia in the 75 U group; gastrointestinal obstruction in the 100 U group); neither was treatment-related.
- No fatal events occurred during the study

Safety

Table 2 Summary of AEs

Patients	Placebo (n = 36)	IncobotulinumtoxinA, 75 U (n = 74)	IncobotulinumtoxinA, 100 U (n = 74)	Total incobotulinumtoxinA (N=148)
Any AE	15 (41.7)	32 (43.2)	34 (45.9)	66 (44.6)
Any treatment-related AE	3 (8.3)	7 (9.5)	6 (8.1)	13 (8.8)
Any AESI[a]	0 (0.0)	5 (6.8)	5 (6.8)	10 (6.8)
Any treatment-related AESI	0 (0.0)	3 (4.1)	1 (1.4)	4 (2.7)
Any SAE	3 (8.3)	6 (8.1)	9 (12.2)	15 (10.1)
Any treatment-related SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any AE leading to discontinuation[b]	0 (0.0)	1 (1.4)	1 (1.4)	2 (1.4)
Any treatment-related AE leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any fatal AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any fatal treatment-related AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

- No new safety concerns were reported
- Serious AEs were rare and not deemed related to treatment
- The 100U dose showed an exceptionally favorable profile regarding dysphagia.

Discussion

- **Evidence and Efficacy of 100 U Dose:**
  - The study provides **Level I evidence** that incobotulinumtoxinA is an effective targeted treatment for chronic sialorrhea in adults.
  - The 100 U group reached statistical significance for both coprimary endpoints at week 4
  - Efficacy for the 100 U dose was further confirmed by secondary and other endpoints.
- **Safety and Tolerability:**
  - Both the 75 U and 100 U doses were well tolerated.
  - The most frequent treatment-related AEs were dry mouth and dysphagia, both occurring at a low frequency.
- **Comparison with Conventional Treatments:**
  - Traditional Approaches: speech therapy, swallowing training, oral anticholinergics
  - Resistant Cases: Surgical relocation of salivary ducts or irradiation were used in therapy-resistant cases.
  - Limitations of Anticholinergics: non-specific systemic activity often causes side effects such as cognitive impairment, drowsiness, and urinary retention, limiting their long-term use for chronic conditions.

A Critical Appraisal: Study Strengths and Limitations

Strengths

- Randomized, double-blind, placebo-controlled methodology
- Included two active dose groups, allowing for dose-response evaluation
- Comprehensive Endpoints: Utilized both objective (uSFR) and patient- reported (GICS) primary outcomes
- Sufficient Power: A large sample size (N=184) for a trial of this nature

Limitations

- Etiology Imbalance: The study initially aimed for at least 20% representation from each etiologic subgroup. However, the patient population was predominantly PD (70.7%).

JAMA Neurology | Original Investigation

Safety and Efficacy of RimabotulinumtoxinB for Treatment of Sialorrhea in Adults
A Randomized Clinical Trial

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IMPORTANCE RimabotulinumtoxinB (RIMA) may be preferable as an anti-sialorrhea treatment compared with current oral anticholinergic drugs in people with neurological disorders.

OBJECTIVE To assess the safety, efficacy, and tolerability of RIMA injections for the treatment of sialorrhea in adults.

DESIGN, SETTING, AND PARTICIPANTS This randomized, parallel, double-blind, placebo-controlled clinical trial of RIMA 2500 U and 3500 U was conducted from November 14, 2013, to January 23, 2017. A total of 249 adult patients with troublesome sialorrhea secondary to any disorder or cause were screened. Of them, 13 refused further participation in the study or were lost to follow-up and 49 did not fulfill the criteria for participation; 187 were ultimately enrolled. Patients had to have a minimum unstimulated salivary flow rate (USFR) of 0.2 g/min and a minimum Drooling Frequency and Severity Scale score of 4.

EXPOSURES Patients were randomized 1:1:1 to RIMA, 2500 U (n = 63); RIMA, 3500 U (n = 64); or placebo (n = 60).

MAIN OUTCOMES AND MEASURES Primary outcomes were the change in USFR from baseline to week 4 and the Clinical Global Impression of Change (CGI-C) at week 4. The CGI-C scores were recorded on a 7-point scale ranging from very much improved to very much worse. Adverse events were recorded throughout the trial period.

RESULTS Of 187 patients enrolled (147 men [78.6%]; mean [SD] age, 63.9 [13.3] years), 122 patients had Parkinson disease (65.2%), 13 (7.0%) were stroke survivors, 12 had amyotrophic lateral sclerosis (6.4%), 6 had medication-induced sialorrhea (3.2%), 4 had adult cerebral palsy (2.1%), and 30 had sialorrhea owing to other causes (16.0%). A total of 176 completed the study. Treatment with both doses of RIMA significantly reduced USFR at week 4 vs placebo (mean treatment difference, −0.30 g/min [95% CI, −0.39 to −0.21] for both doses vs placebo, $P < .001$). The CGI-C scores were statistically significantly improved at week 4 for both treatment groups vs placebo (−1.21 [95% CI, −1.56 to −0.87] for 2500 U, −1.14 [95% CI, −1.49 to −0.80] for 3500 U, both $P < .001$). Treatment benefits were seen as early as 1 week after injection and were maintained over the treatment cycle of approximately 13 weeks. The RIMA injections were well tolerated compared with placebo. The most common adverse events were self-limited mild to moderate dry mouth, dysphagia, and dental caries.

CONCLUSIONS AND RELEVANCE Treatment with RIMA (2500 U and 3500 U) in adults was well tolerated and reduced sialorrhea, with the onset of the effect at 1 week after the injection. These data support the clinical use of RIMA in the management of sialorrhea in adults.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01994109

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Thanks for listening