IPERATTIVITÀ GHIANDOLARE E SCIALORREA: DIAGNOSTICA NEUROFISIOLOGICA E TOSSINA BOTULINICA

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Fondazione I.R.C.C.S.
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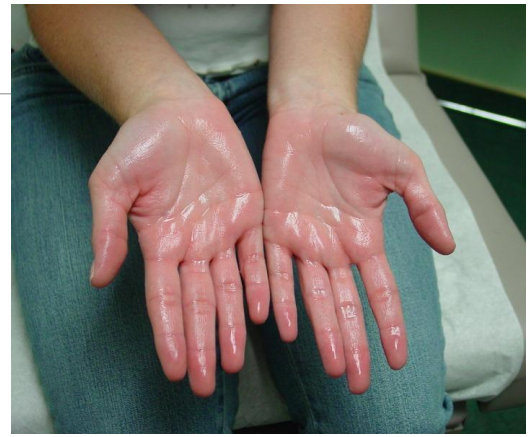
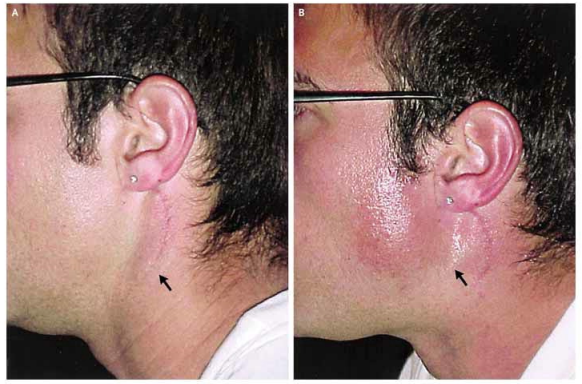
Assenza di conflitto di interessi

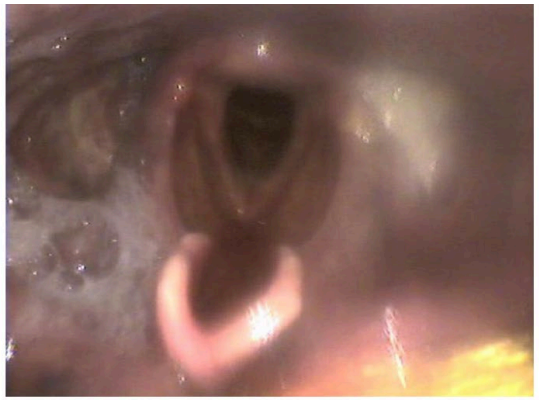
Dichiaro l'assoluta autonomia dei contenuti scientifici di questa presentazione ed indipendenza da interessi economici commerciali con possibili aziende sponsorizzatrici.

Neurogenic hyperactivity

- hyperidrosis
  - Generalized
  - Focal
  - Gustatory sweating
- Increased tearing
  - Crocodile tears syndrome
- hypersalivation
  - hypersalivation

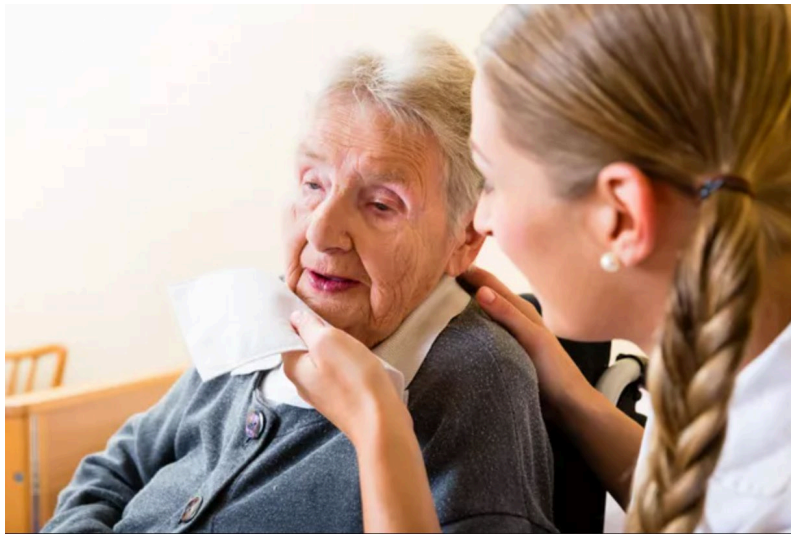


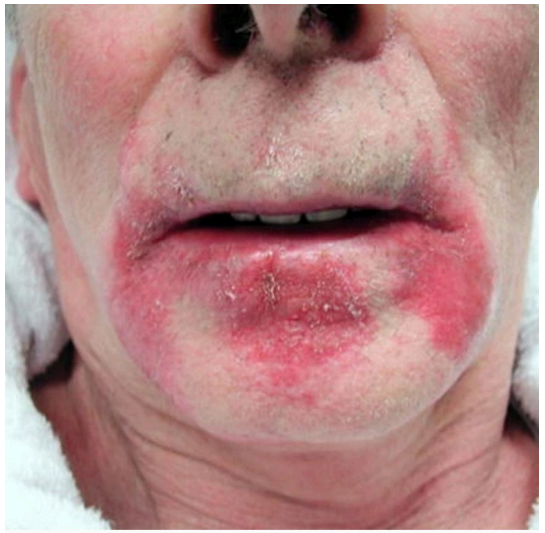


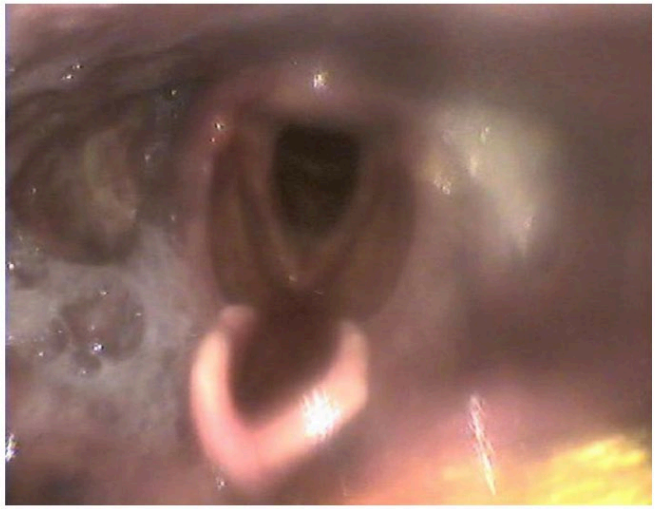


sialorrhea

Hypersalivation (or sialorrhea) refers to the presence of excessive saliva in the mouth, which may cause drooling

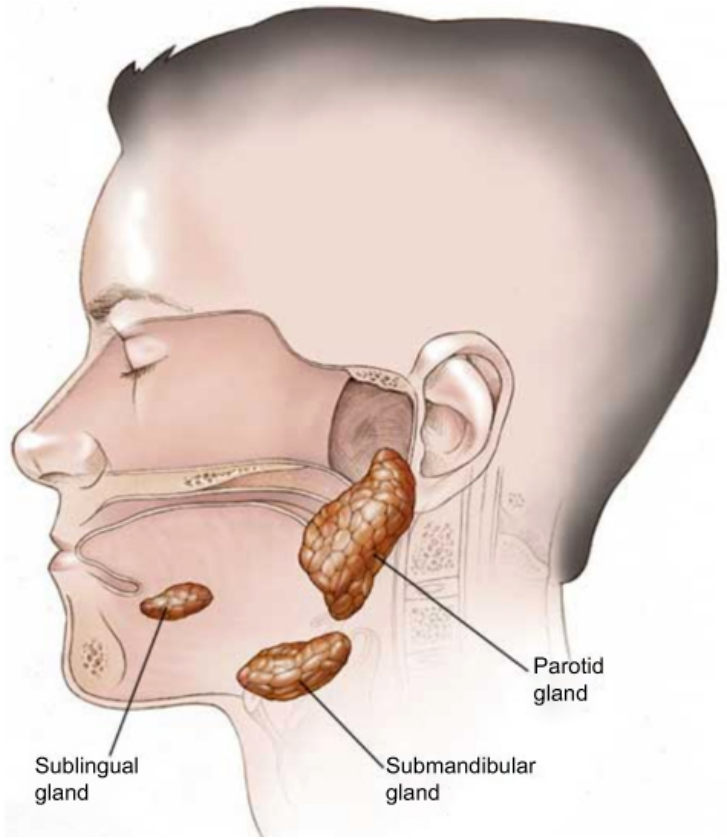






Major salivary glands

- Parotid
- Submandibular
- Sublingual



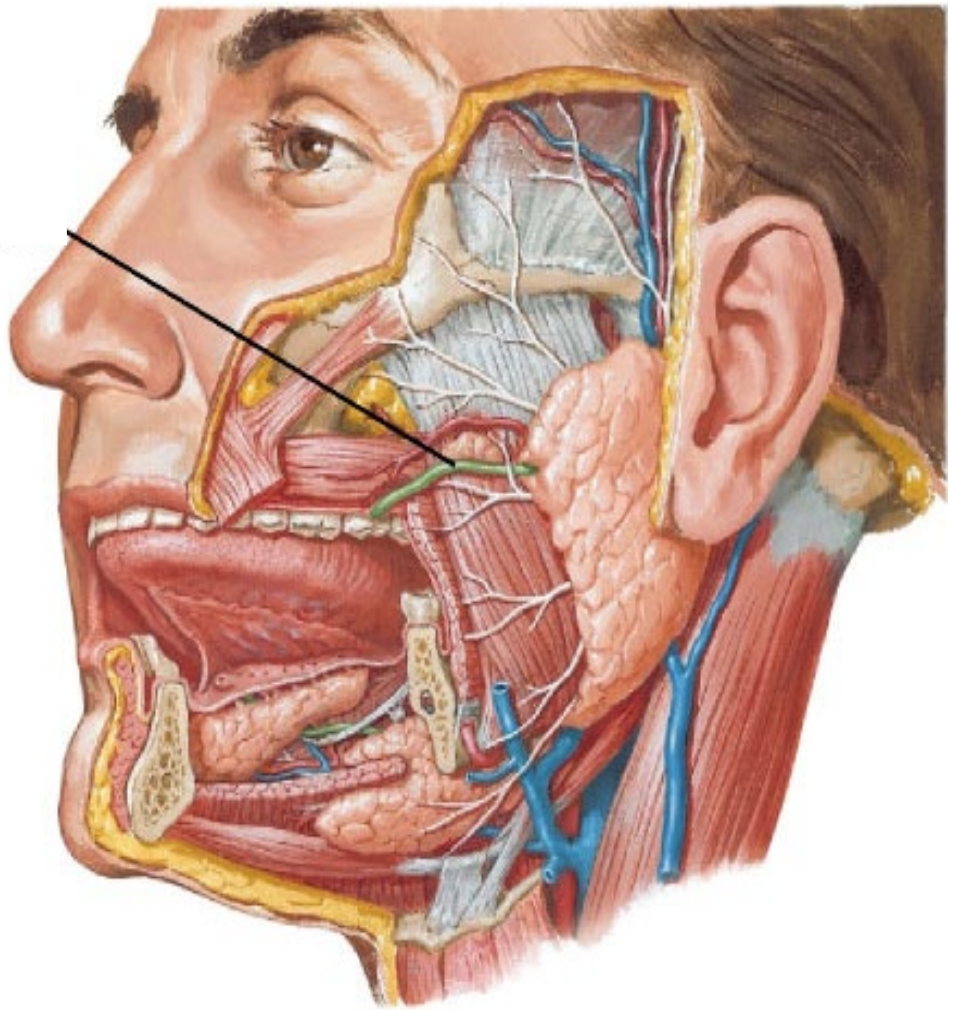
Parotids + submandibular 95% of the total salivary secretion

500-600ml / day
99% water, 1% proteins

TABLE 1 Salivary gland structural features, parasympathetic innervation and contribution to whole saliva volume under unstimulated (in the absence of exogenous stimuli) and under chewing-stimulated conditions[1,10,12-14,40]

	Acinar cell type	Secretory product	Contribution (%) to whole saliva volume	Parasympathetic nerve supply	Ducts to the oral cavity
Major salivary glands					
Parotid glands	Serous	Watery, amylase-rich	Resting: 25% Stimulated: 50%	Glossopharyngeal nerve	Stensen's duct
Submandibular glands	Mixed, mainly serous	Viscous, mucin-rich	Resting: 60% Stimulated: 35%	Facial nerve	Wharton's duct
Sublingual glands	Mixed, mainly mucous	Viscous, mucin-rich	Resting: 7%-8% Stimulated: 7%-8%	Facial nerve	Ducts of Rivinus Bartholin's duct
Minor salivary glands					
Palatinal glands	Mucous	Mucin-rich	Resting: 8% Stimulated: 8%	Facial nerve	Individual small ducts
Buccal glands	Mixed, mainly mucous	Mucin-rich		Facial nerve	
Labial glands	Mixed, mainly mucous	Mucin-rich		Facial nerve	
Lingual glands	Serous	Watery, lipase-rich		Glossopharyngeal	
Retromolar glands	Mucous	Viscous, mucin-rich		Facial nerve/ Glossopharyngeal	

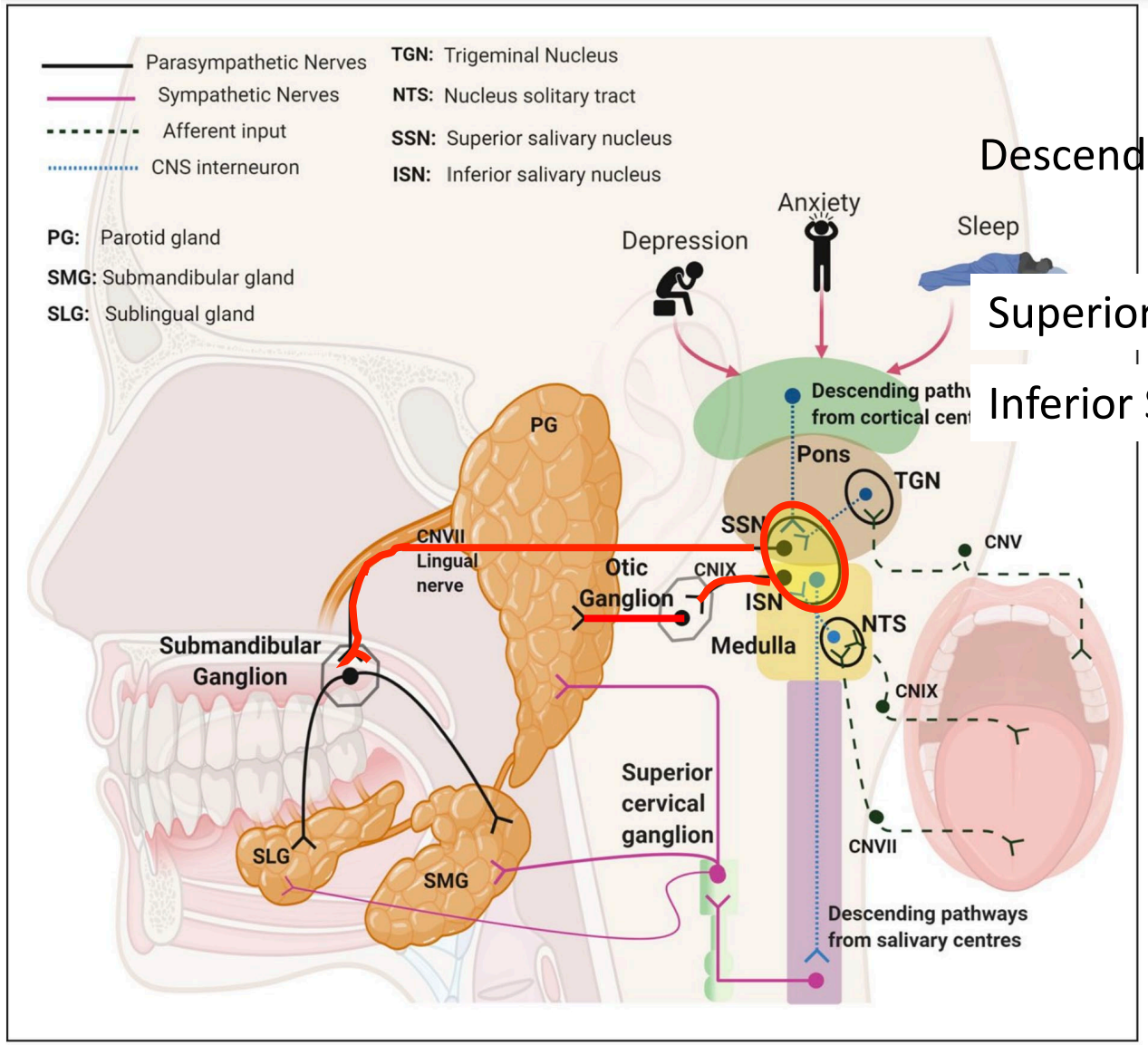
The sympathetic nerve supply is obtained from the superior cervical ganglion. Mixed means that the glands contain both serous and mucous acini, also mucous acini capped with serous demilunes may be seen in these glands.



The salivary reflex

parasympathetic

sympathetic



Descending pathways

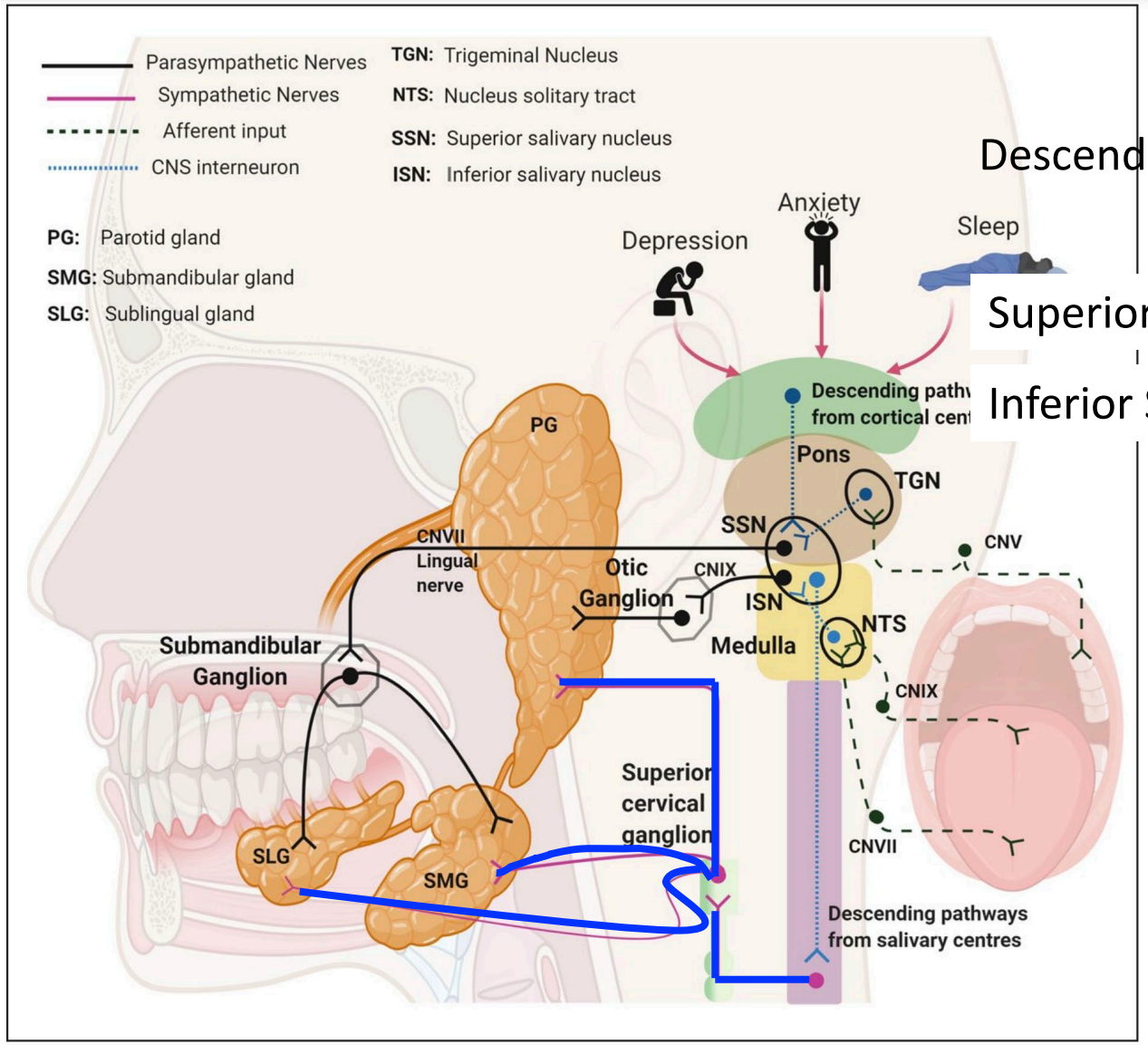
Superior Salivary Nucleus

Inferior Salivary Nucleus

The salivary reflex

parasympathetic

sympathetic



Descending pathways

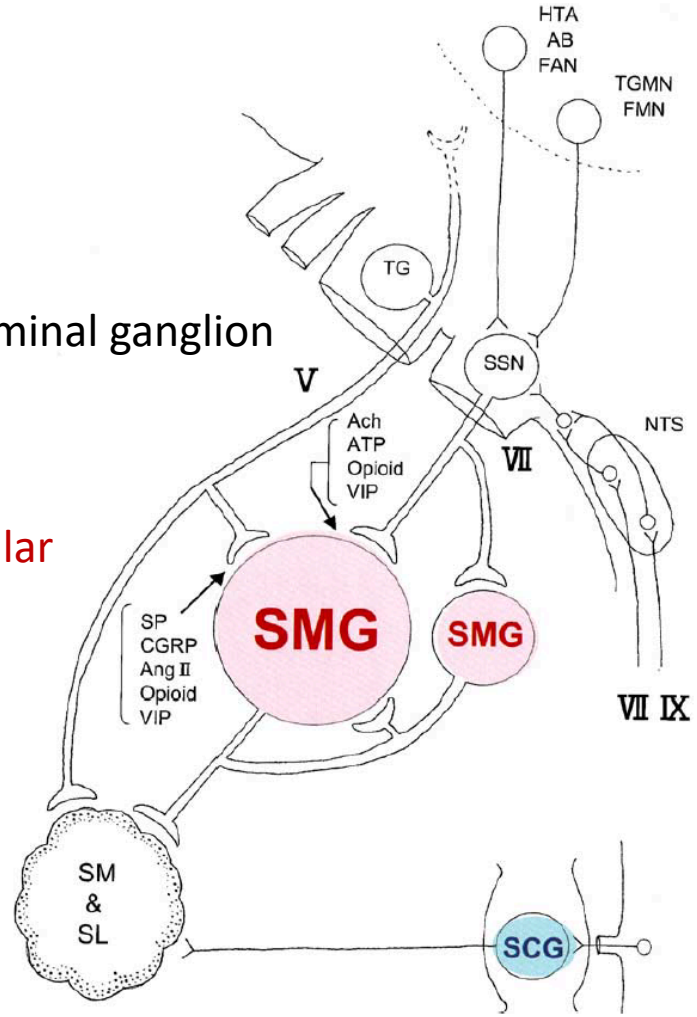
Superior Salivary Nucleus

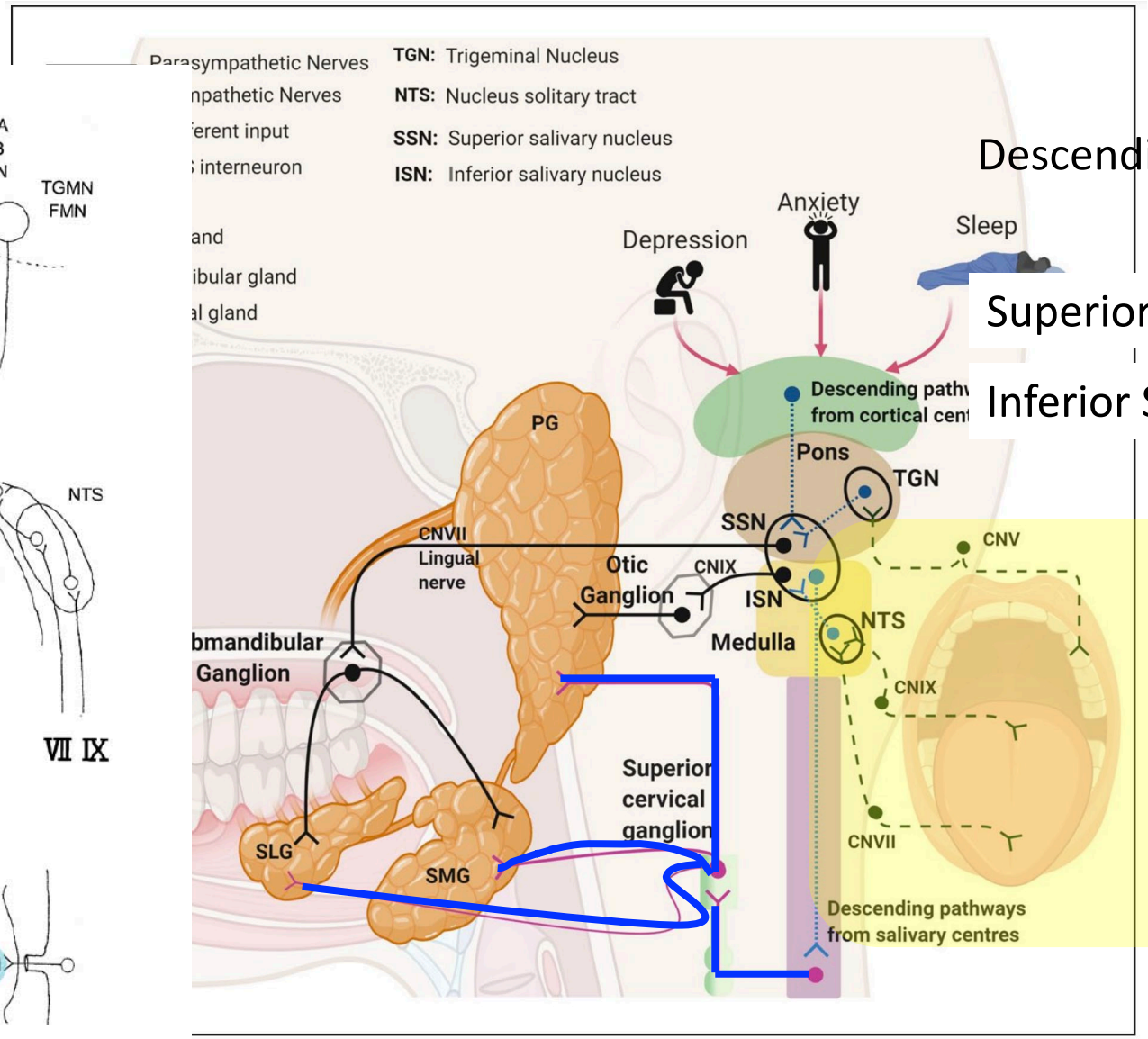
Inferior Salivary Nucleus

The salivary reflex

Trigeminal ganglion

submandibular ganglion (SMG)





Descending pathways

Superior Salivary Nucleus

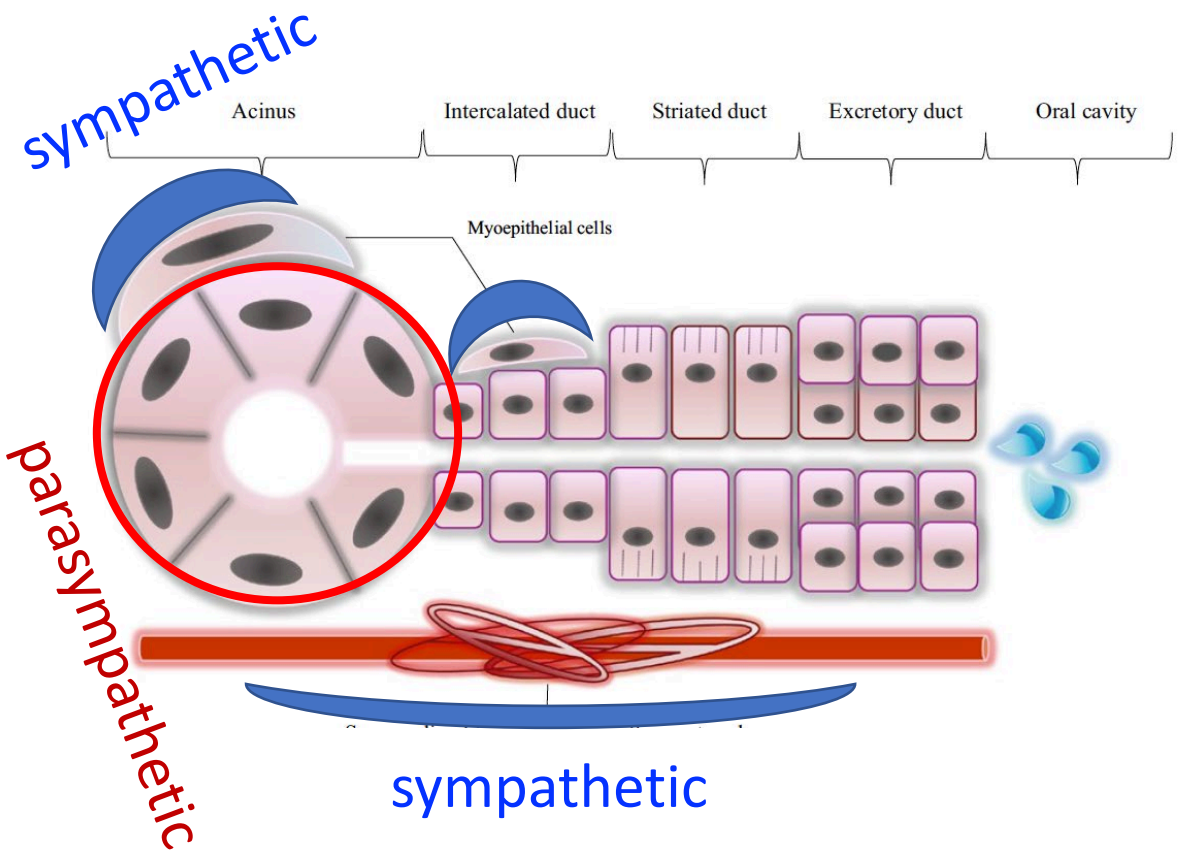
Inferior Salivary Nucleus

afferents

TRPV1

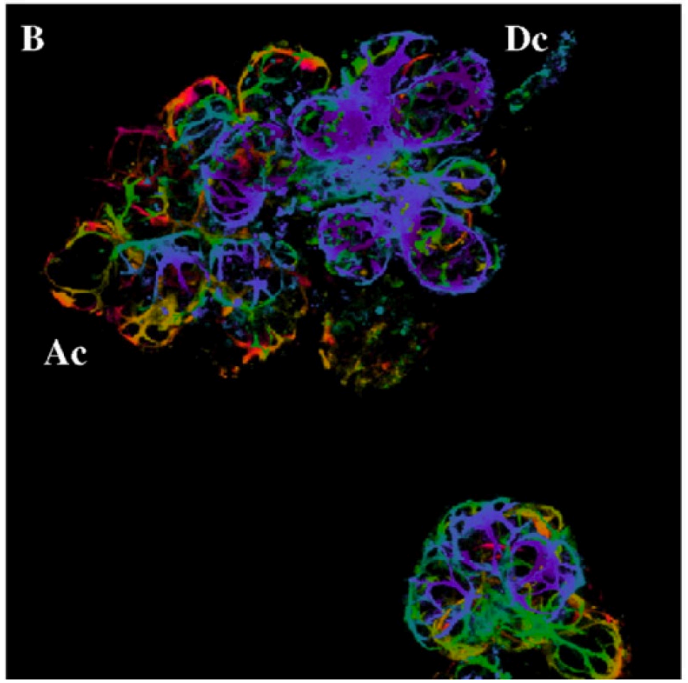
TRPM8

TRPA1

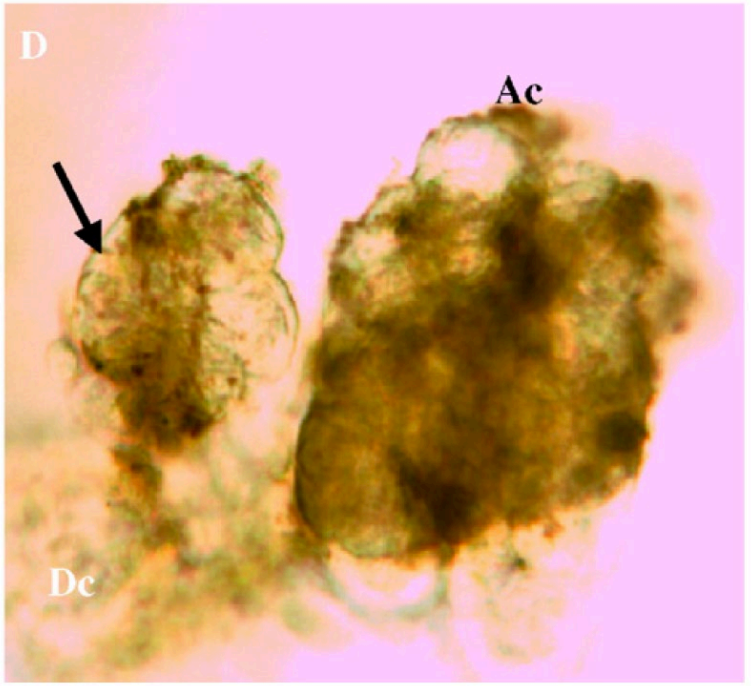


Parasympathetic stimulation
1) Is mediated mainly by acetylcholine in combination with NANC peptides (e.g. VIP) 2) Evokes most of the salivary fluid secreted. Mainly acts through M3 and to a lesser extent M1 muscarinic cholinergic receptors 3) Causes variable degrees of exocytosis from salivary cells but is responsible for most mucin secretion by mucous glands 4) Induces contraction of myoepithelial cells 5) Increases glandular blood flow as part of the salivary reflex

Sympathetic stimulation
1) Is mediated mainly by noradrenaline and acts essentially on cells receiving parasympathetic impulses, which tends to produce synergistic effects, but exerts little effect on mucous gland secretion 2) Often does not cause much mobilization of fluid but DOES NOT inhibit salivary secretion 3) Tends to modulate the composition of saliva by increasing exocytosis from salivary cells 4) Induces contraction of myoepithelial cells 5) Exerts control on glandular blood flow but NOT as part of the salivary reflex



Myoepithelial cells surrounding acinar groups demonstrated by actin staining



Cholinesterase staining of parasympathetic nerves surrounding the acinar units

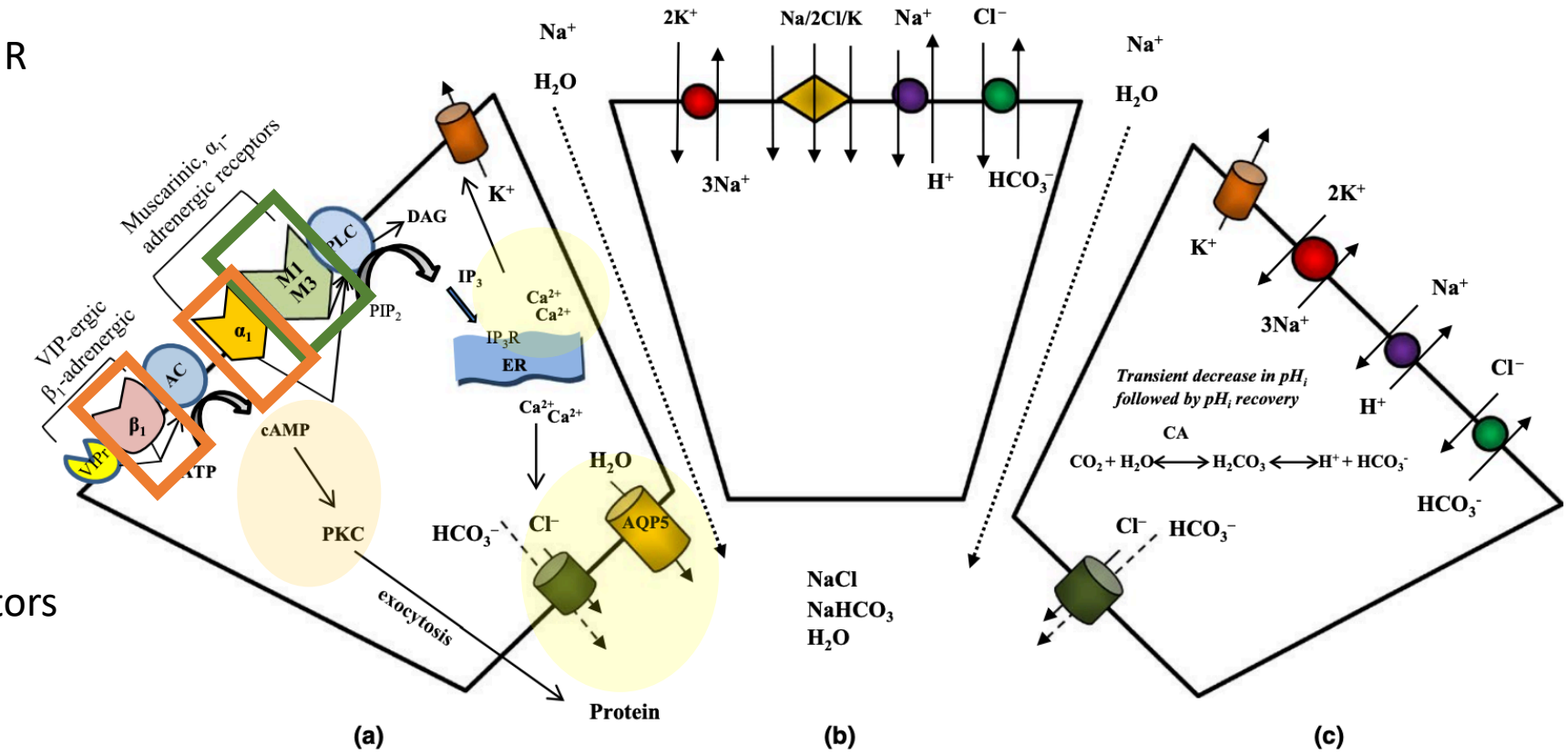
Acini (Ac) and ducts (Dc)

Proctor, 2007

Parasympathetic and sympathetic nerves: synergic function

M1, M3- Ach – R
α1-adrenergic
ß1-adrenergic
VIP-r

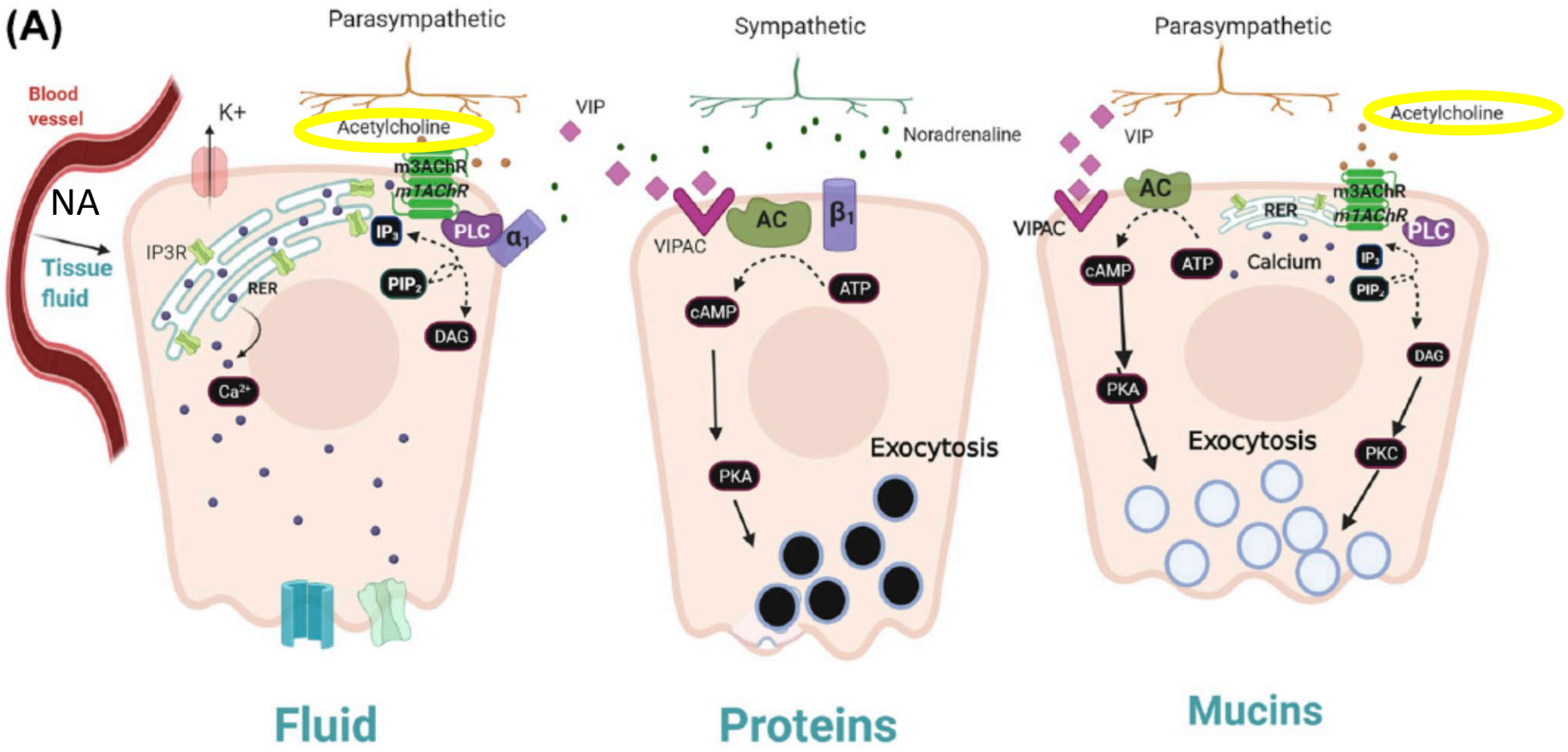
Purinergic receptors



Cross-talk neuropeptides and neurotransmitters

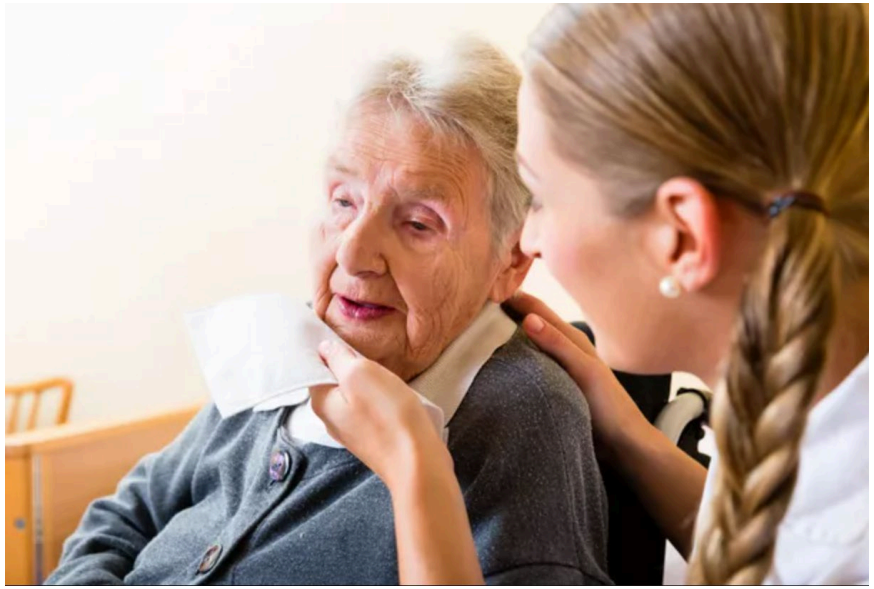
Salivar production

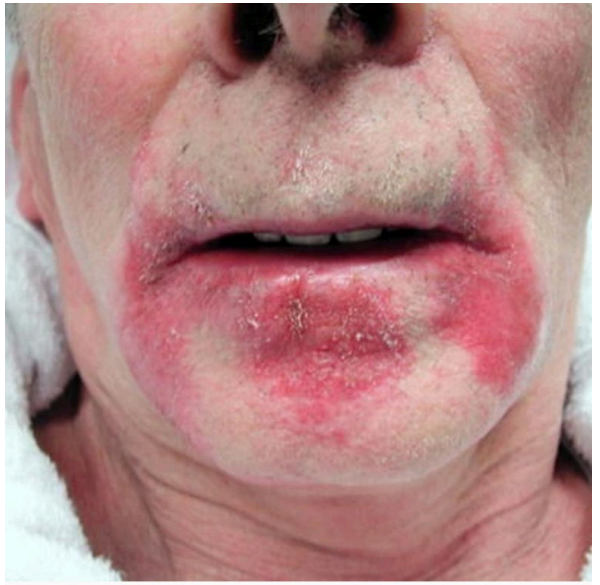
Pedersen, 2018

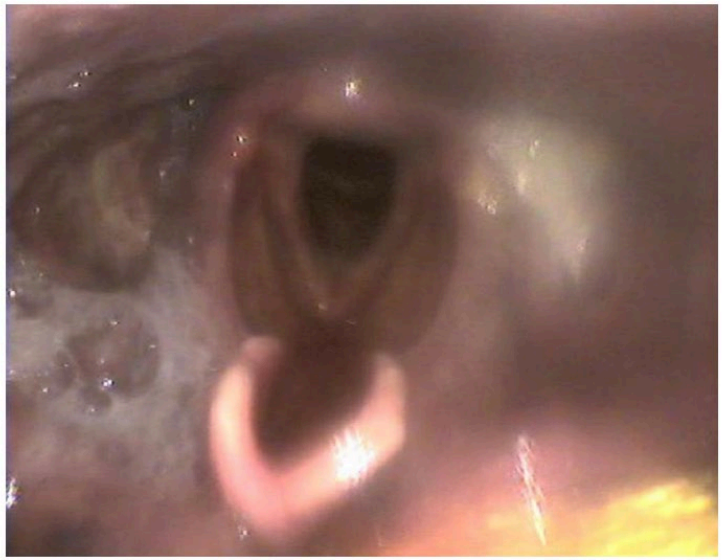


- Resting flow rate (0.3-0.4ml/min, during sleep 0.1ml/min)
- Stimulater flow rate (parotids)
- Different kind of stimuli change the proteoma

Sialorrhea







Sialorrhea

Table 5: Some drugs known to be associated with drug-induced drooling or sialorrhea.

Direct cholinergic/ muscarinic agonists	Bethanechol, pilocarpine, arecoline, cevimeline
Indirect cholinergic/ muscarinic agonists (acetylcholinesterase inhibitors)	Edrophonium, neostigmine, physostigmine, pyridostigmine, metrifonate, donepezil, galantamine, rivastigmine, tacrine
Antipsychotics	Typical (first generation) antipsychotics: haloperidol, fluphenazine Atypical (second generation) antipsychotics: clozapine, risperidone, olanzapine Reserpine
Sedative medications	Anticonvulsants-antiepileptics Benzodiazepines
Adrenergic antagonists (peripheral)	Yohimbine
Medications irritating the esophagus	Doxycycline, tetracycline, iron preparations, quinidine, potassium, nonsteroidal anti-inflammatory drugs
Poisons and toxins	Heavy metals: arsenic, manganese, mercury (inorganic volatile), thallium Organophosphates: insecticides, nerve gases (sarin, tabun, soman, VX) Food poisoning: *Amanita muscaria* Illicit drugs: phencyclidine (PCP)
Herbal and fruit preparations	Betel nut, jaborandi, yohimbine, citric acid, red pepper

Table 4: Main causes underlying drooling or sialorrhea.

Drugs	See table 5
Neurological diseases	Myasthenia gravis Cerebral palsy Facial paralysis Guillain-Barré syndrome Motor neuron disease, notable amyotrophic lateral sclerosis (ALS) Moebius syndrome Cerebrovascular accidents Parkinson's disease Congenital suprabulbar palsy Hydrocephalus Hypoxic encephalopathy Freeman-Sheldon syndrome Psychosis Brain tumors Seizures Severe mental retardation, Down syndrome Worster-Drought syndrome Landau-Kleffner syndrome Encephalitis Angleman syndrome
Systemic diseases	Nasal obstruction Heavy metal poisoning Hyperhydration Digestive pathologies: Oesophageal spasms, tumors and ulcerations, gastric disorders accompanied by nausea and vomiting, pancreatitis, bladder processes, intestinal infections
Oral conditions	Mucosal ulcerations Teething Ulcerative lichen planus Herpetic ulceration Traumatic ulceration Oral pain: pulpitis, periodontitis, stomatitis Pharynx and tonsilar Inflammation, irritative and ulcerative lesions

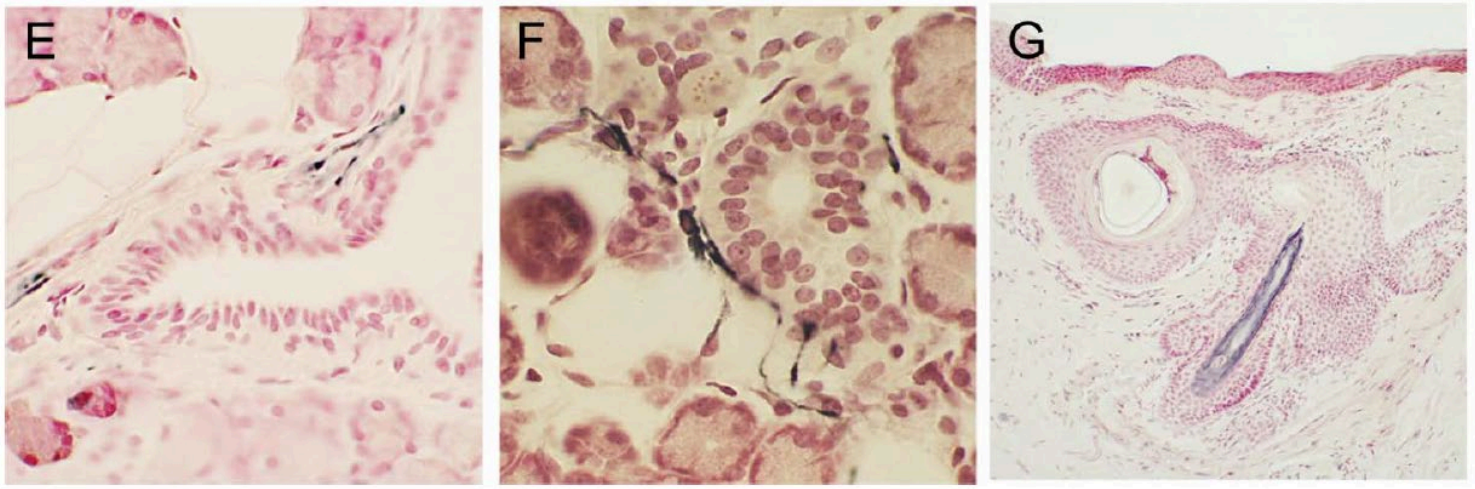
Neurological diseases

Myasthenia gravis
Cerebral palsy
Facial paralysis
Guillain-Barré syndrome
Motor neuron disease, notable amyotrophic lateral sclerosis (ALS)
Moebius syndrome
Cerebrovascular accidents
Parkinson's disease
Congenital suprabulbar palsy
Hydrocephalus
Hypoxic encephalopathy
Freeman-Sheldon syndrome
Psychosis
Brain tumors
Seizures
Severe mental retardation, Down syndrome
Worster-Drought syndrome
Landau-Kleffner syndrome
Encephalitis
Angleman syndrome

Sialorrhea due to loss of muscular control rather than hypersalivation

Sialorrhea in Parkinson Disease

- Prevalence 10-84%
- Lewy pathology have been found in the submandibular glands
- Saliva production seems unchanged or even depressed in PD, indicating excessive salivation is not a crucial factor



Adler, Neurology, 2014

- Risk factor for **drooling**: dysphagia, orofacial rigidity/hypomimia, lingual bradykinesia, cognitive status, male gender and more advanced disease stage, non-tremor dominant PD phenotype
- The relationship between drooling and L-Dopa / DBS is still *controversial*

Sialorrhea

ALS

- Prevalence 20-25%
- not increased production of saliva but inability to swallow secretions (spasticity, weakness, loss of oropharyngeal coordination,…)

Cerebral Palsy

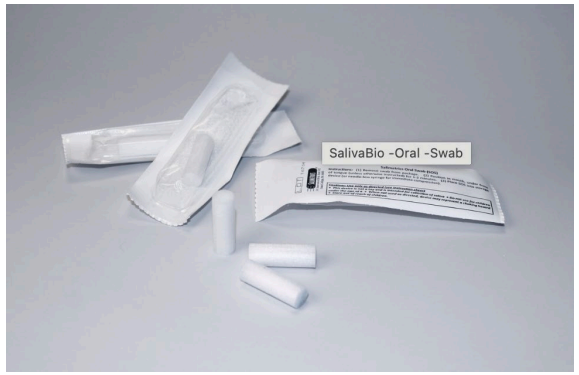
- 10% of patients with CP and post-traumatic encephalopathy

Young, Cochrane Library 2011 Adler, Neurology, 2014

Methods to quantify

- ✓ Swab method
- ✓ Sialometry
  - ✓Unstimulated salivary flow rate (uSFR)

    gr/min
- ✓Clinical score
  - ✓DSFS (PD, Parkinsonisms, ALS)
  - ✓Sialorrhea Scoring Scale (ALS)
  - ✓Global Impression of Change Scale GICS

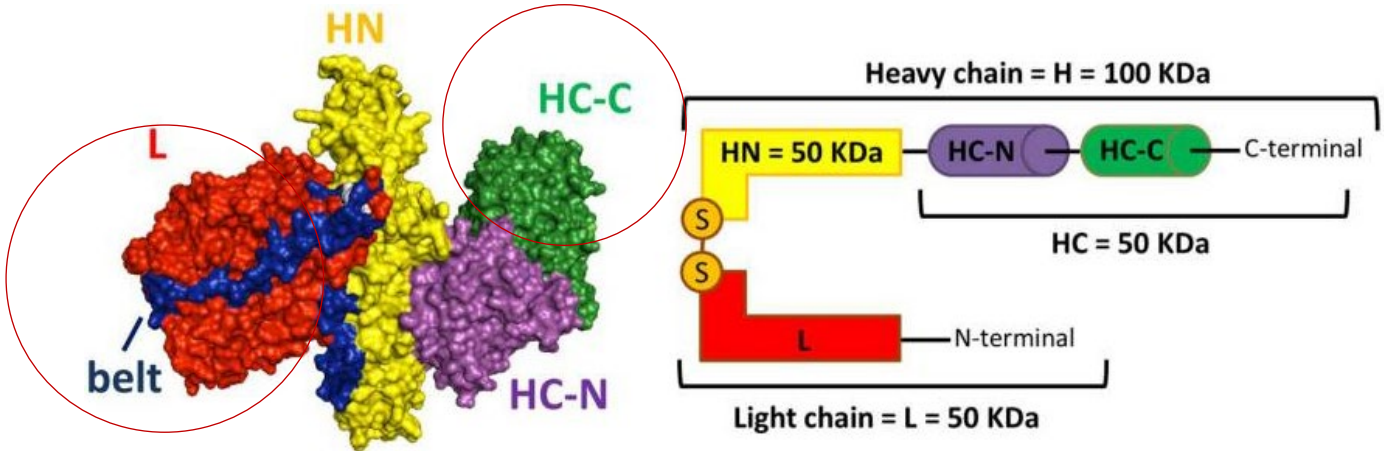


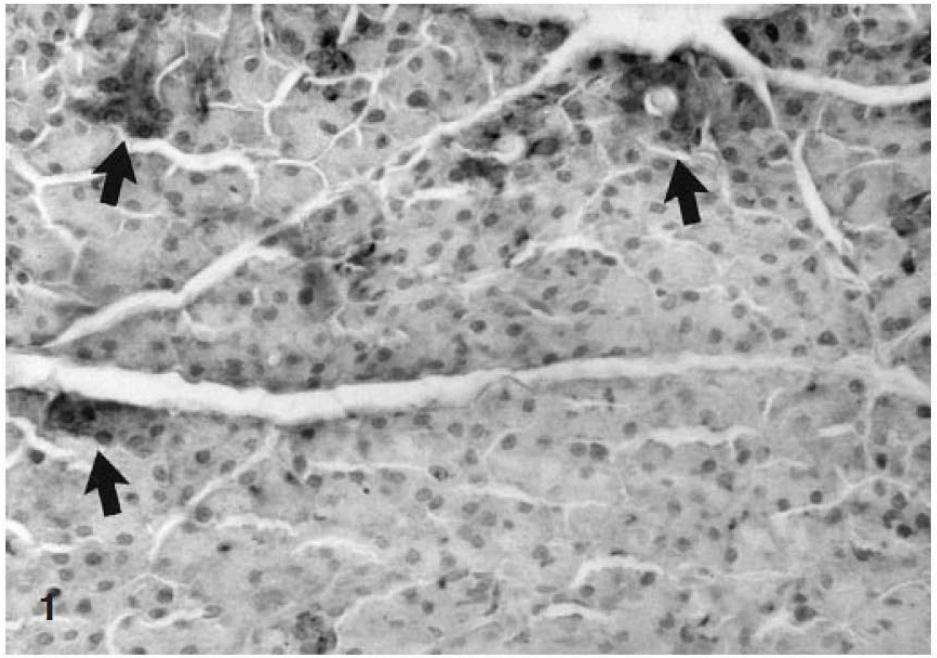
Treatment options

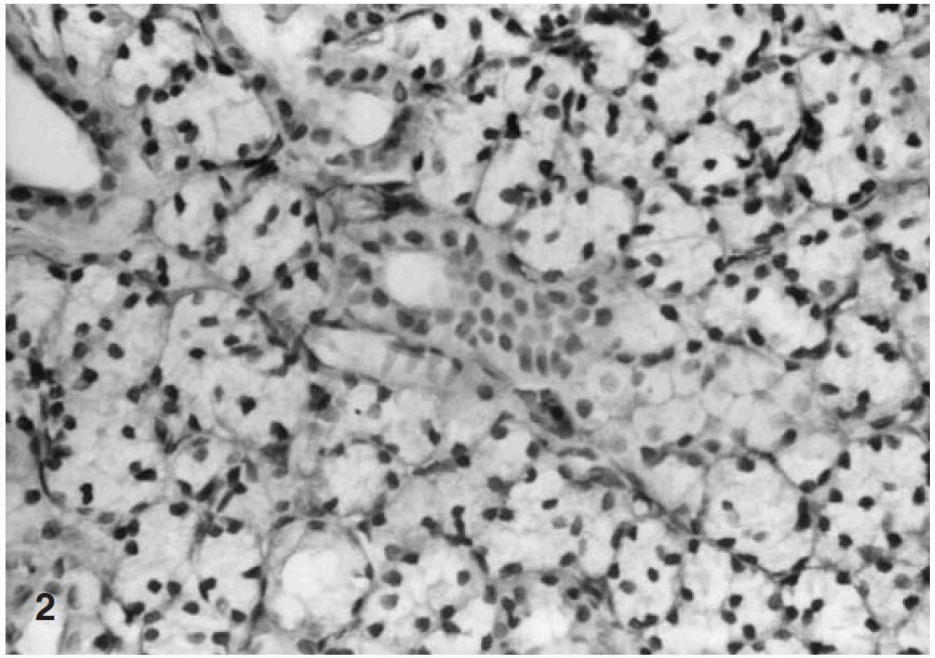
- Anticholinergic drugs
- **Botulinum Toxin**
- Radiotherapy
- Surgery

BotulinumToxin

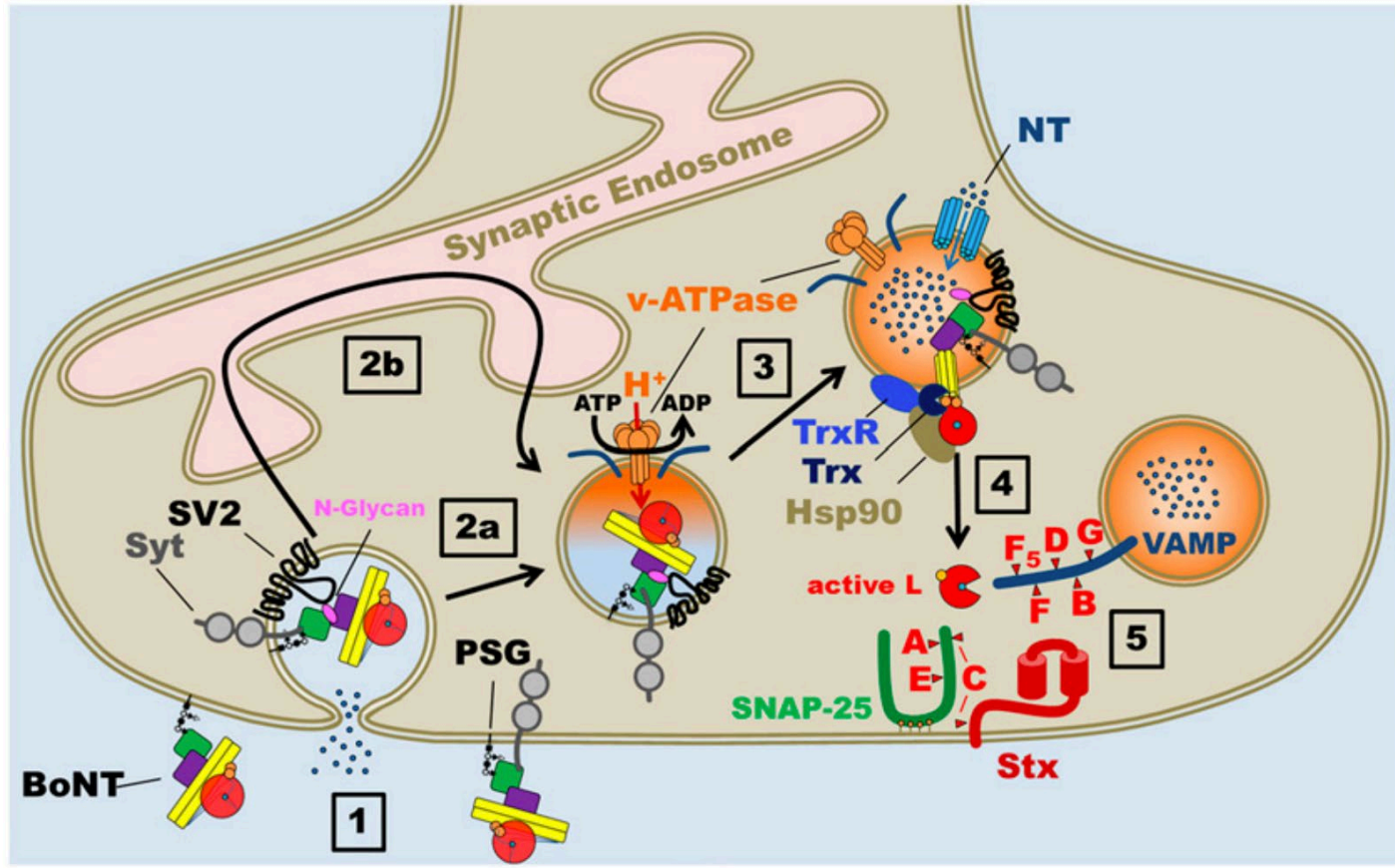
- Selective block of presynaptic release of acetylcoline from the cholinergic endings supplying eccrine salivary glands.
- Botulinum Toxin injection for excessive drooling was first reported in 1997 and, in the last years, BoNT has emerged as a safe and effective treatment.
- Both serotype A and type B were used (onabotulinumtoxinA, abobotulinumtoxinA and incobotulinumtoxinA, rimabotulinumtoxinB.
- Incobotulinum is **licenced** for chronic sialorrhea in adults.

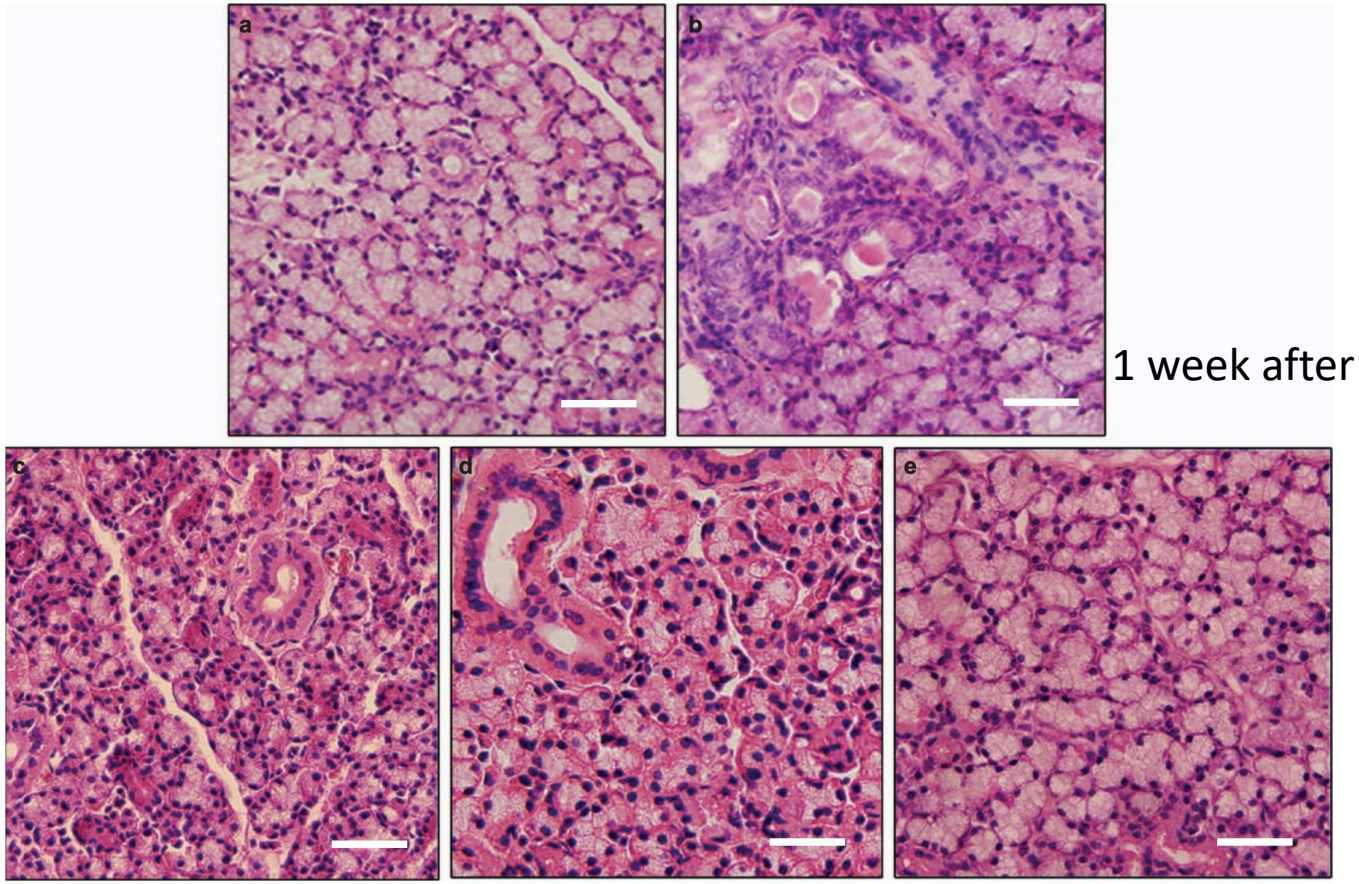






Ellis, Eur Arch Otorhinolaryngol (1999)


Synaptic Endosome
NT
v-ATPase
2b
3
ATP
H+
ADP
TrxR
Trx
Hsp90
4
SV2
Syt
N-Glycan
2a
VAMP
F5 D G
active L
F B
5
PSG
A
E
C
SNAP-25
Stx
BoNT
1



1 week after 5 U BTXA injection

2 weeks

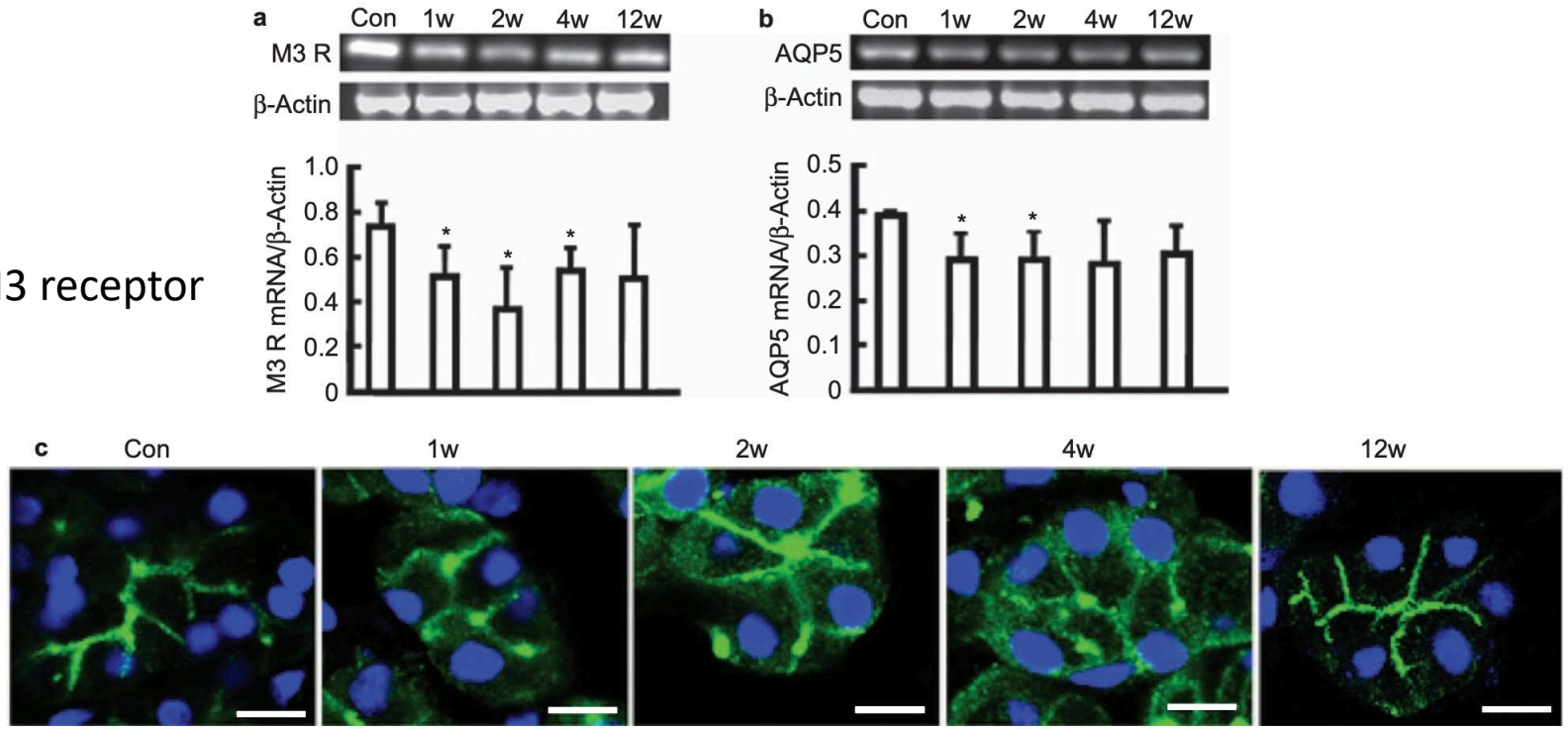
4 weeks

12 weeks

Shan, 2013

M3 receptor

AQP5



Shan, 2013

Botulinum Toxin in Sialorrhea

- Efficacy and safety
- Doses
- Selection of salivary glands
- Use of guidance technique (US vs anatonical landmarks)
- Outcome measures
- Long term treatment of chronic scialorrhea

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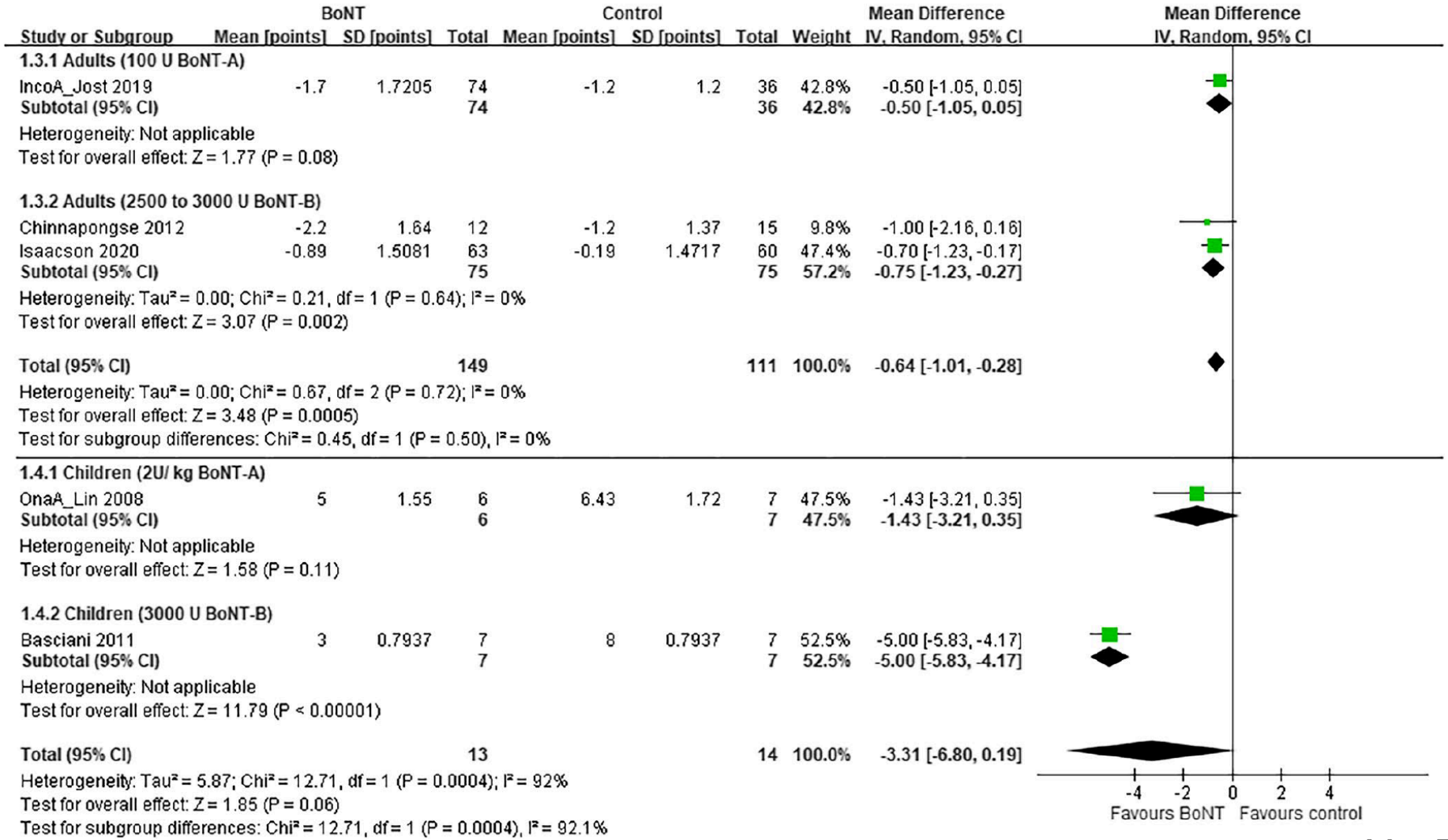
Efficacy and safety

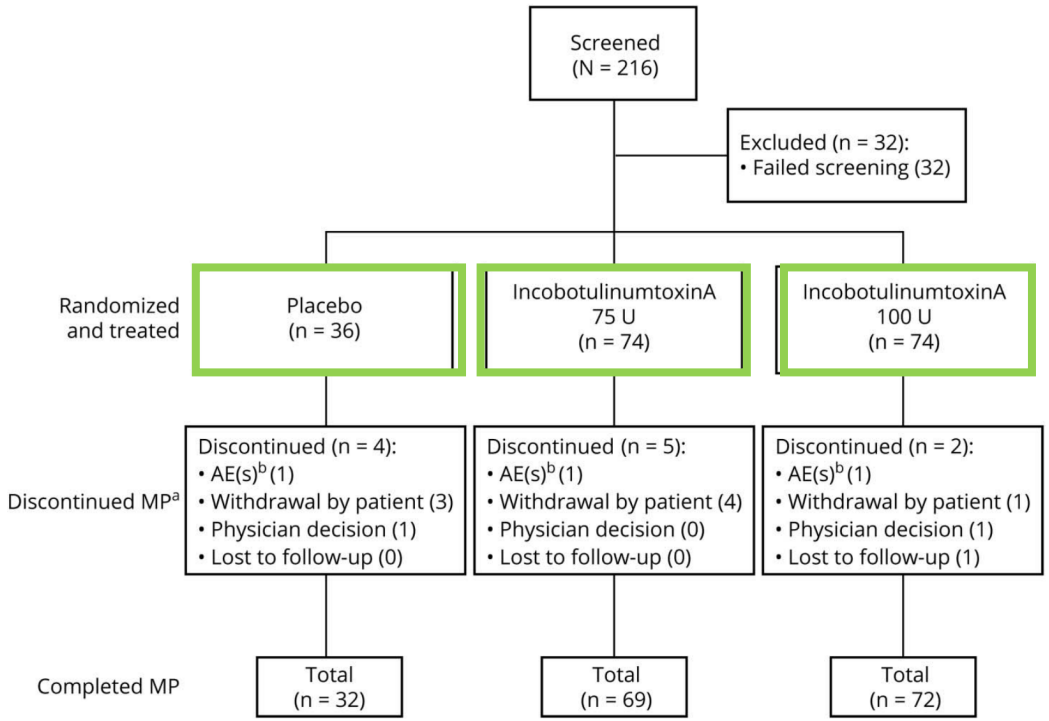
Efficacy and safety of botulinum toxin for treating sialorrhea: A systematic review and meta-analysis



Yu, Eur J Neurol. 2022

SIAXI

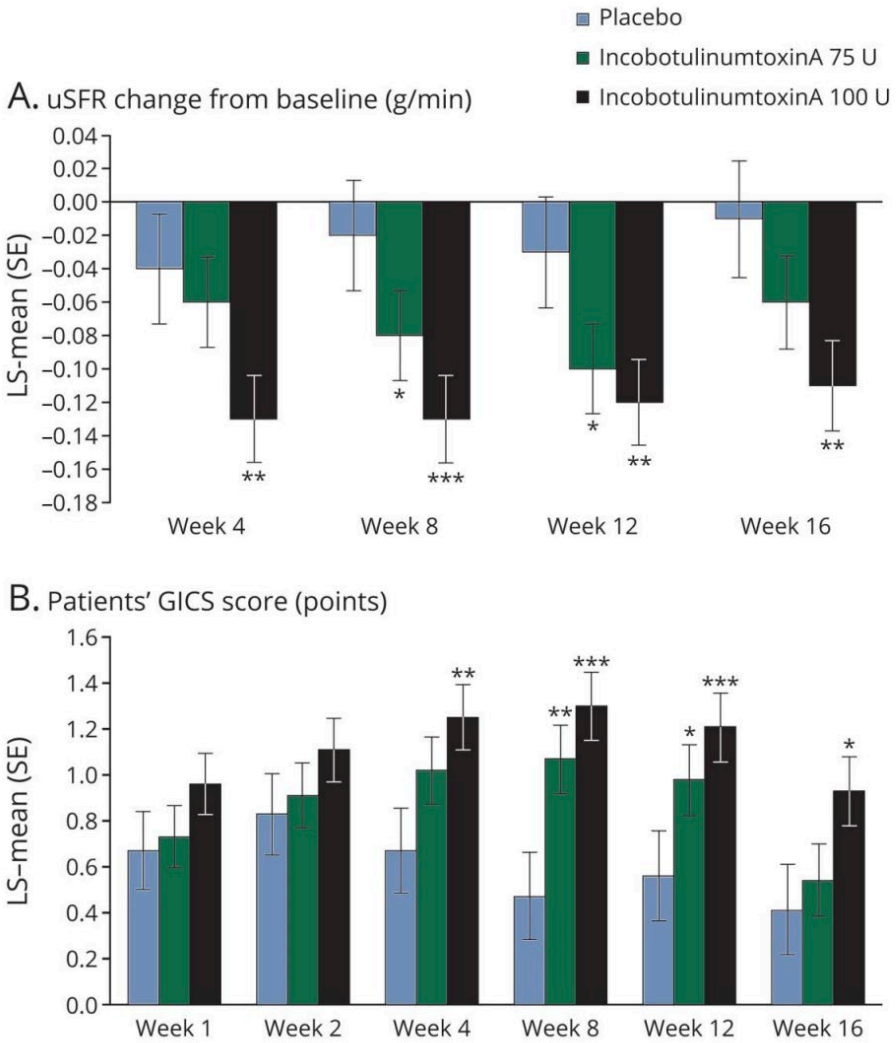
Placebo-controlled, randomized, double-blind study of incobotulinumtoxinA for sialorrhea



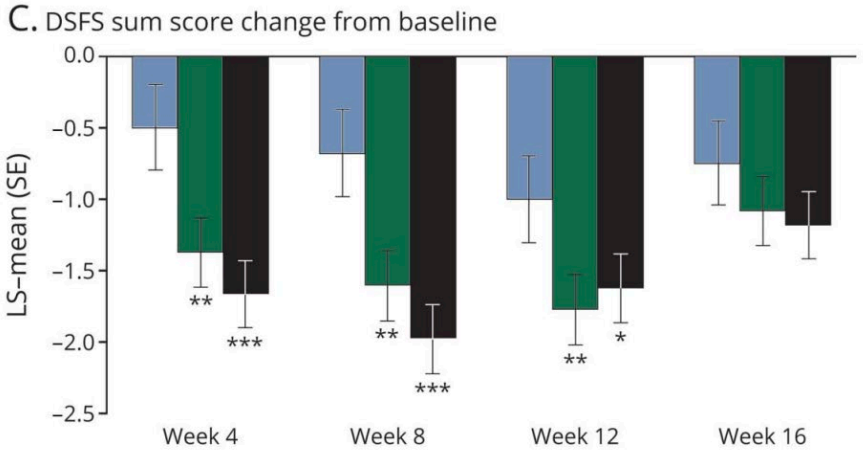
Characteristic	Placebo (n = 36)	IncobotulinumtoxinA 75 U (n = 74)	IncobotulinumtoxinA 100 U (n = 74)	Total (N = 184)
Sex, n (%)				
Male	28 (77.8)	50 (67.6)	52 (70.3)	130 (70.7)
Female	8 (22.2)	24 (32.4)	22 (29.7)	54 (29.3)
Age, y, mean (SD)	63.5 (10.6)	65.2 (11.7)	66.0 (11.6)	65.2 (11.4)
Weight, kg, 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)

Neurology, 2019

Unstimulated salivary flow rate (uSFR)



Drooling Severity and Frequency Scale (DSFS)



AEs
15 (41.7%) - placebo,
32 (43.2%) - incobotulinumtoxinA 75 U,
34 (45.9%) - incobotulinumtoxinA 100 U

The most frequent treatment-related AEs were dry mouth

Neurology, 2019

Botulinum Toxin in Sialorrhea

- Efficacy and safety
- **Doses**
- Selection of salivary glands
- Use of guidance technique (US vs anatonical landmarks)
- Outcome measures
- Long term treatment of chronic scialorrhea

- Incobotulinumtoxin A 75-100U
- Rimabotulinumtoxin B 2500U – 3500U

Doses

for higher doses further recommandation are needed

Botulinum Toxin in Sialorrhea

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- Outcome measures
- Long term treatment of chronic scialorrhea

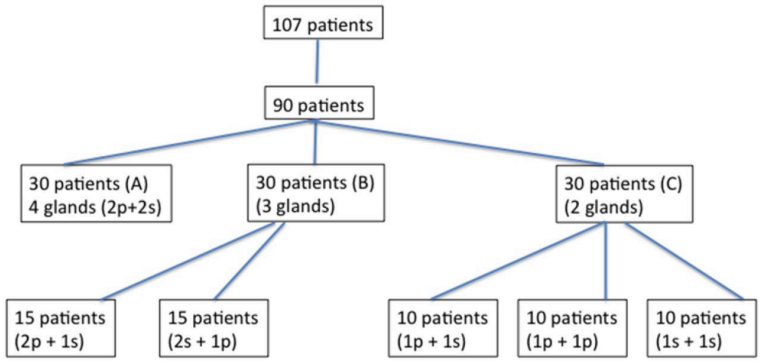
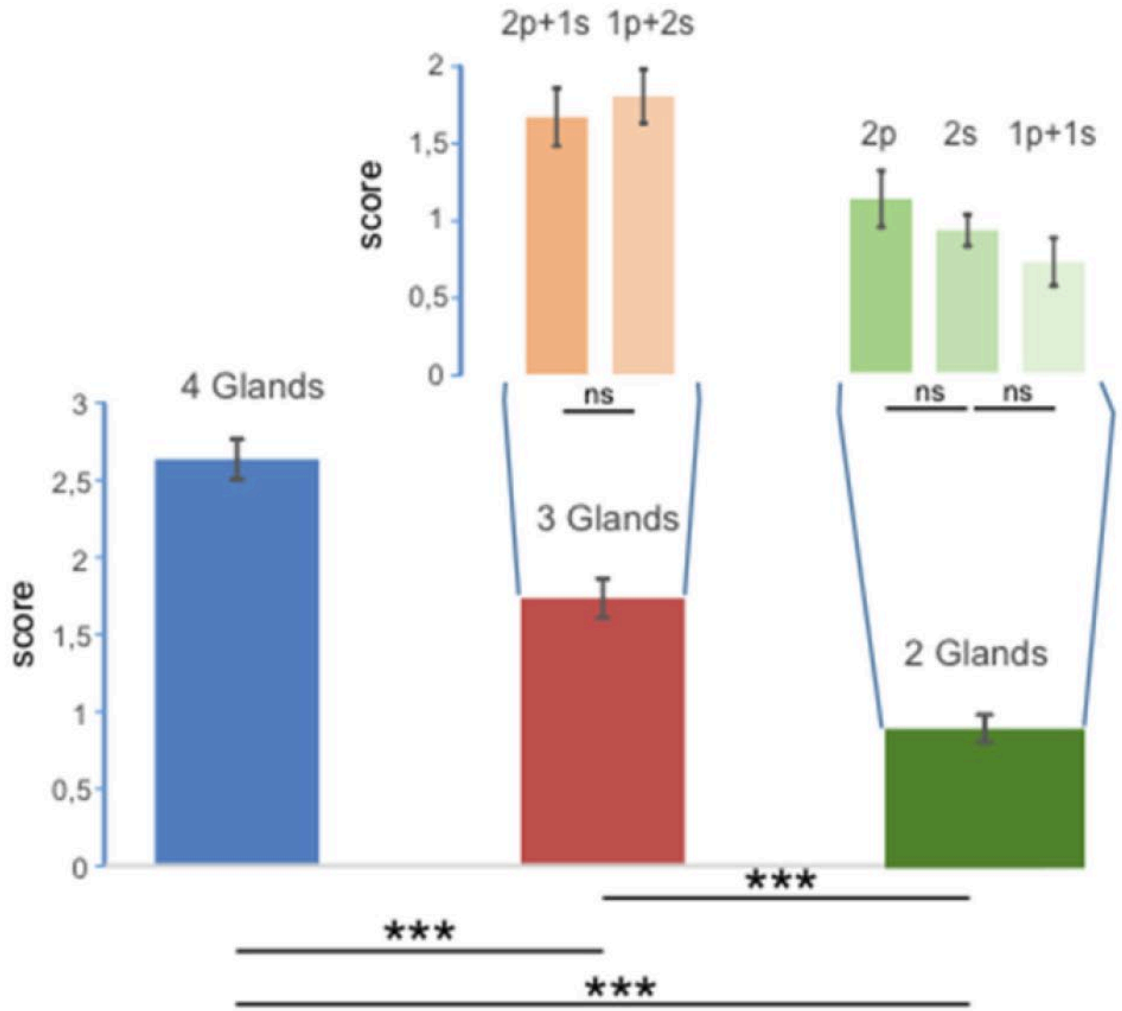


Figure 3. Study profile.



Restivo, Toxin, 2018

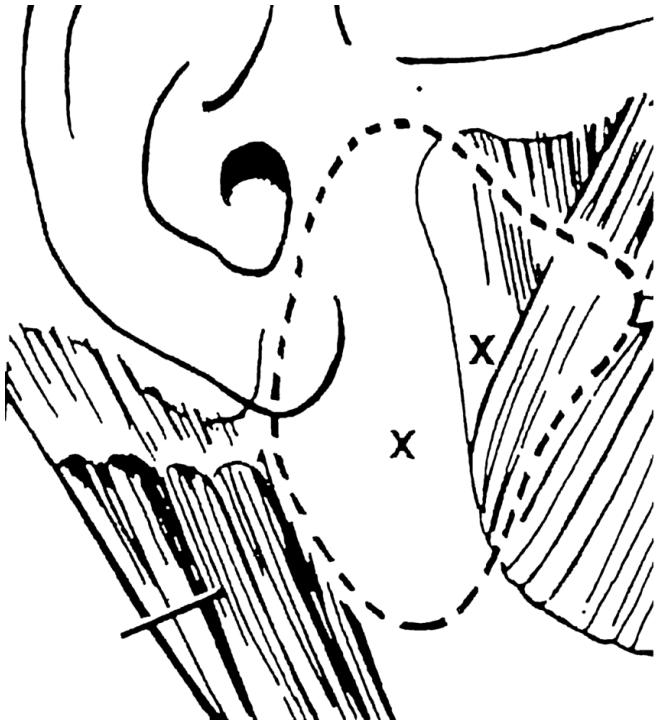
- The parotid gland provides the bulk of salivary secretion during stimulation, but
- ***The basal salivary secretion*** remains debilitating for the patients

70% submandibular
and sublingual

Selection of salivary glands

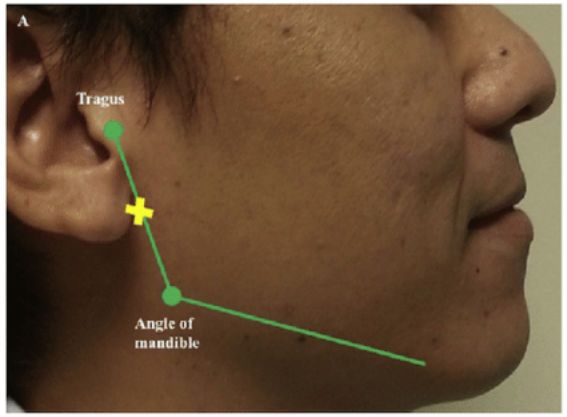
Treatment of 4 SG should be considered for better results

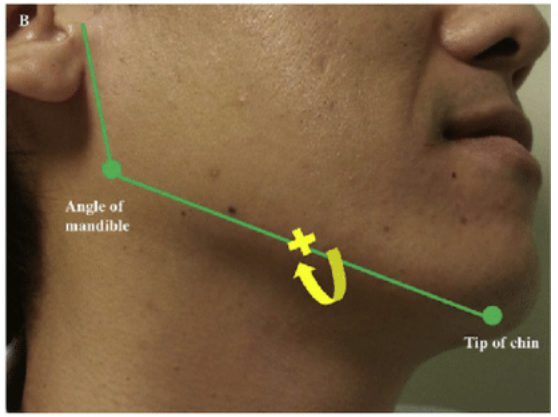
Use of guidance technique (US vs anatonical landmarks)



« the midpoint on the line connecting the **tragus** to the **angle of the mandible**, approximately the site of the ear lobe. Deliver injection 1 cm anterior to this…"

"…the midpoint between the **angle of the mandible and the tip of the chin.** Inject 1 finger breath medial to the inferior surface of the mandible at this point»

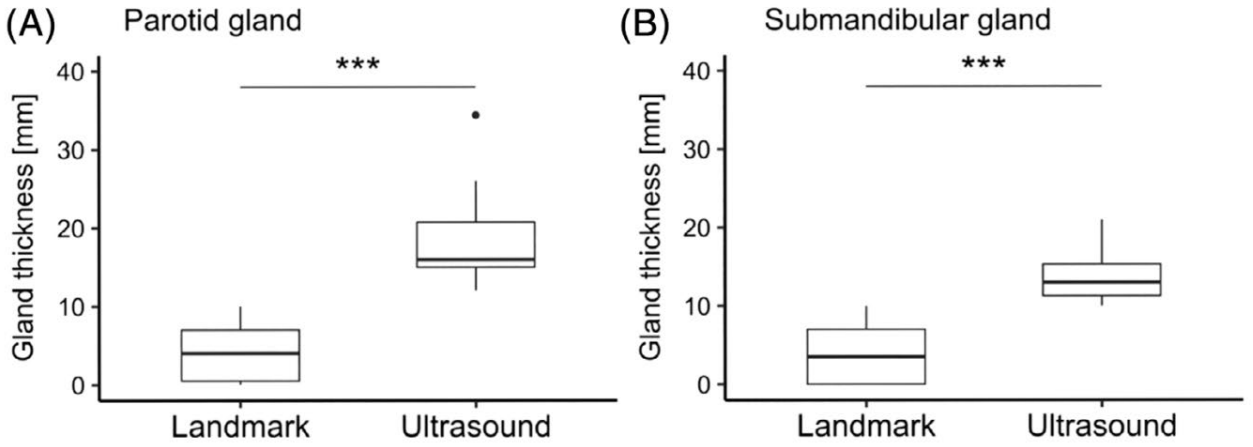


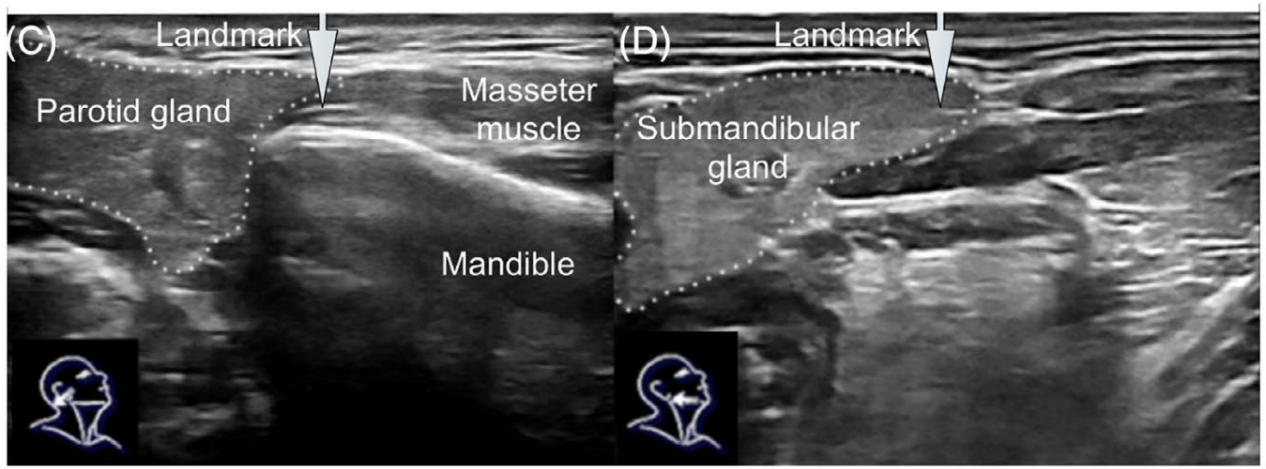


McGeachan

Localization of Salivary Glands for Botulinum Toxin Treatment: Ultrasound Versus Landmark Guidance

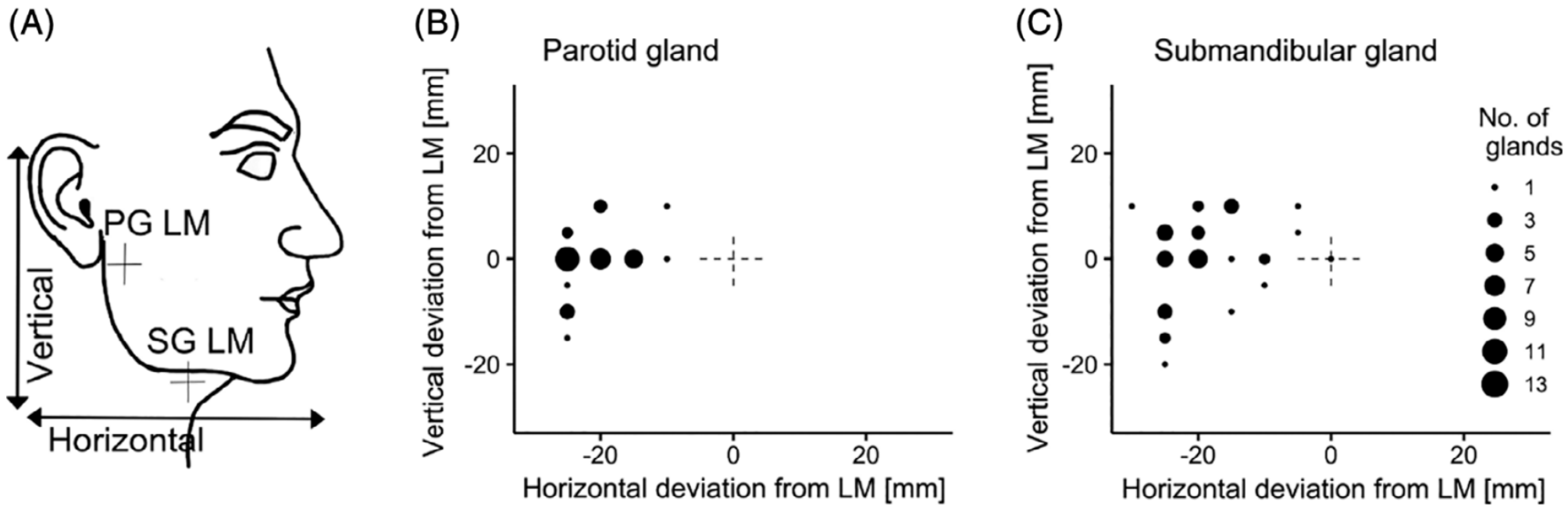
Sebastian Loens, MD,1,* Norbert Brüggemann, MD,1,2 Armin Steffen, MD,3 and Tobias Bäumer, MD1





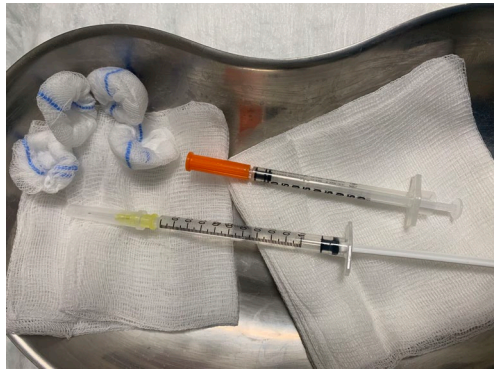
Gland thickness in mm

Loens, MOVEMENT DISORDERS CLINICAL PRACTICE 2020



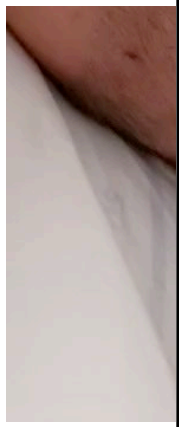
For both glands, the optimal position was located posteriorly with a mean **horizontal deviation of 21 mm** for the PG and **19.6 mm for the SG**, resulting in a significant difference in thickness between the LM and US positions
for both glands.

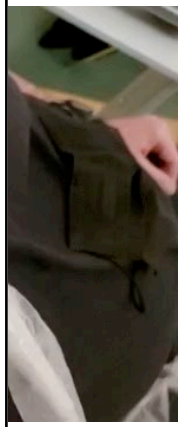
Loens, MOVEMENT DISORDERS CLINICAL PRACTICE 2020

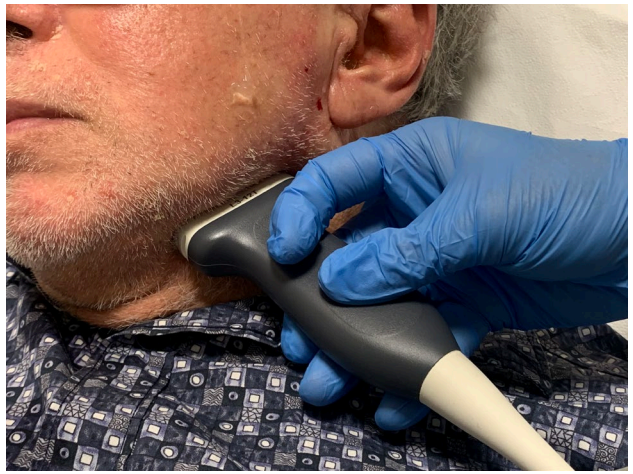


30 - 27

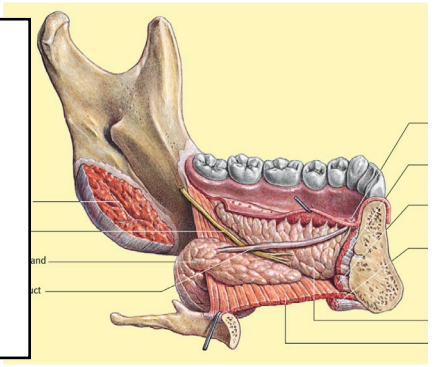
Dilution







Submandubular gland



Parotid gland

Use of guidance technique (US vs anatonical landmarks)

US – guide in particular for first treatment is highly recommended

- Efficacy and safety
- Doses
- Selection of salivary glands
- Use of guidance technique (US vs anatonical landmarks)
- **Outcome measures**
- Long term treatment of chronic scialorrhea

✓Clinical score

- ✓**Drooling Severity and Frequency Scale (DSFS)** (PD, Parkinsonisms, ALS, CP)
- ✓Sialorrhea Scoring Scale (ALS)
- ✓Sialorrhea Clinical Scale for PD (SCS-PD)
- ✓The Radboud Oral Motor Inventory for PD subscale for saliva (ROMP-S)
- ✓Global Impression of Change Scale GICS

The Drooling Score equals the sum of the Severity and Frequency sub-scores.

Drooling Severity Scale

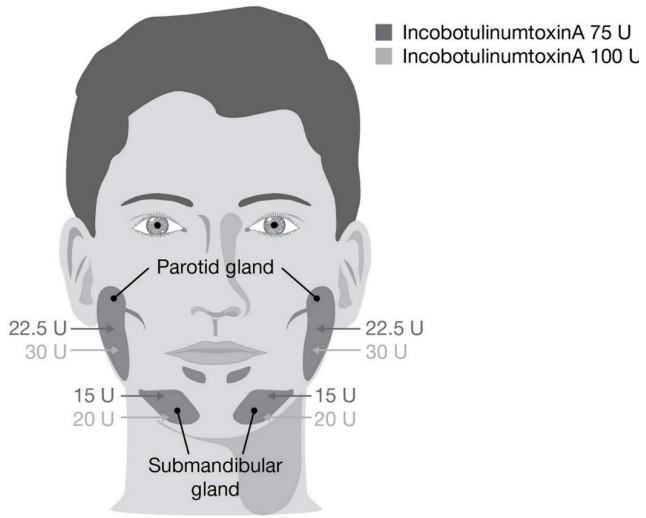
1 = Never drools, dry
2 = Mild-drooling, only lips wet
3 = Moderate- drool reaches the lips and chin
4 = Severe- drool drips off chin & onto clothing
5 = Profuse- drooling off the body and onto objects (furniture, books)

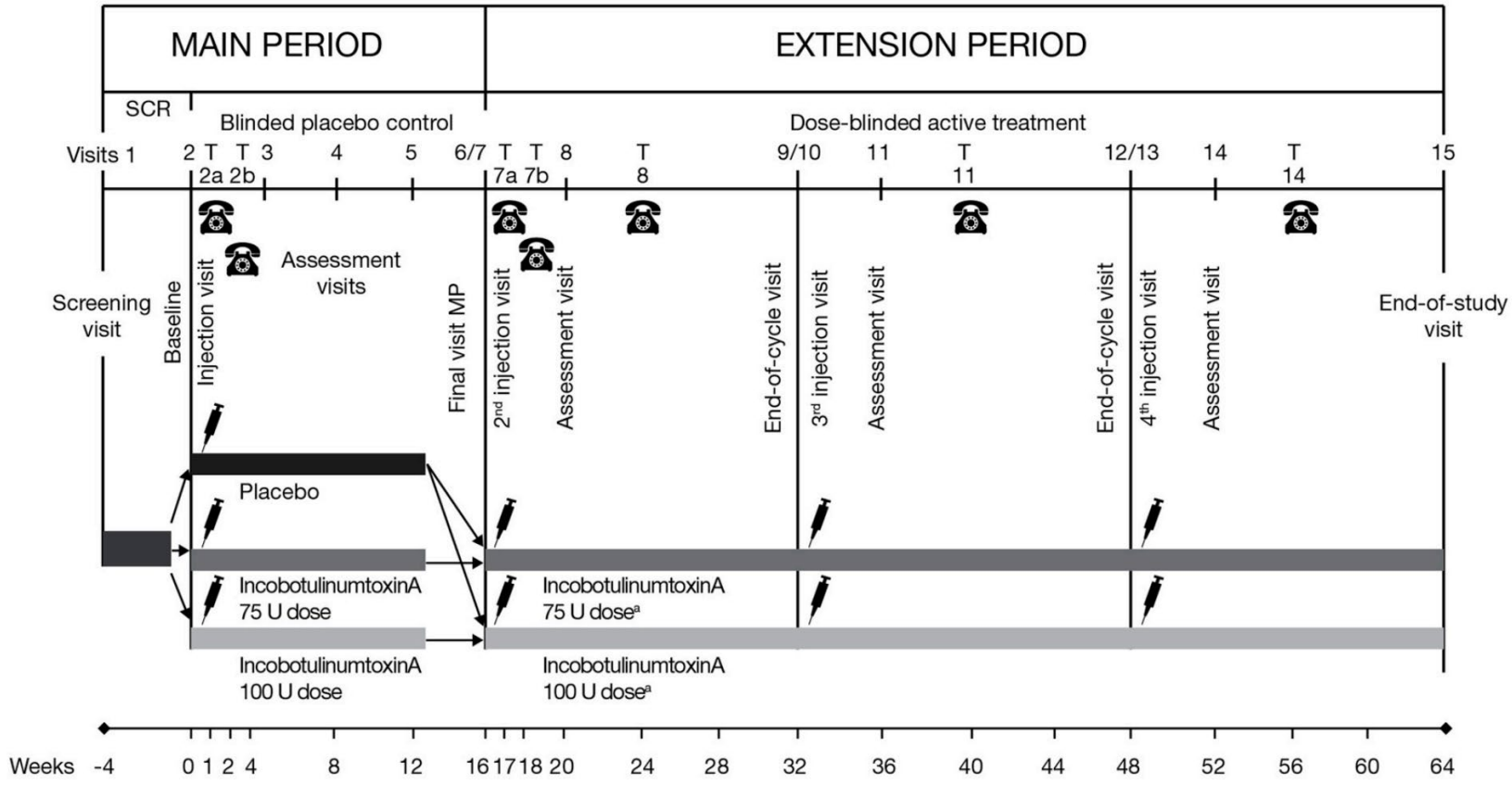
Drooling Frequency Scale

1 = No drooling
2 = Occasionally drools
3 = Frequently drools
4 = Constant drooling

- Efficacy and safety
- Doses
- Selection of salivary glands
- Use of guidance technique (US vs anatonical landmarks)
- Outcome measures
- **Long term treatment of chronic scialorrhea**

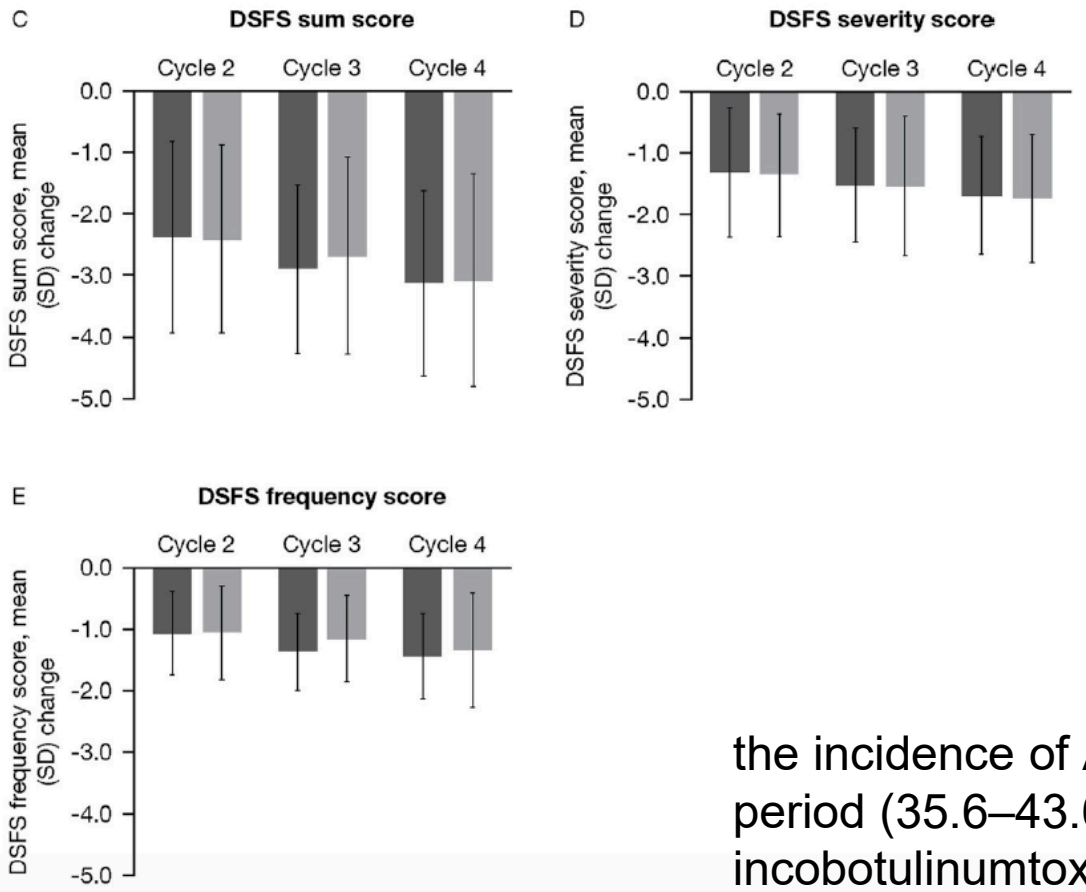
SIAXI
173 pts
64-week observation period
Open
Each cycle: 16 weeks



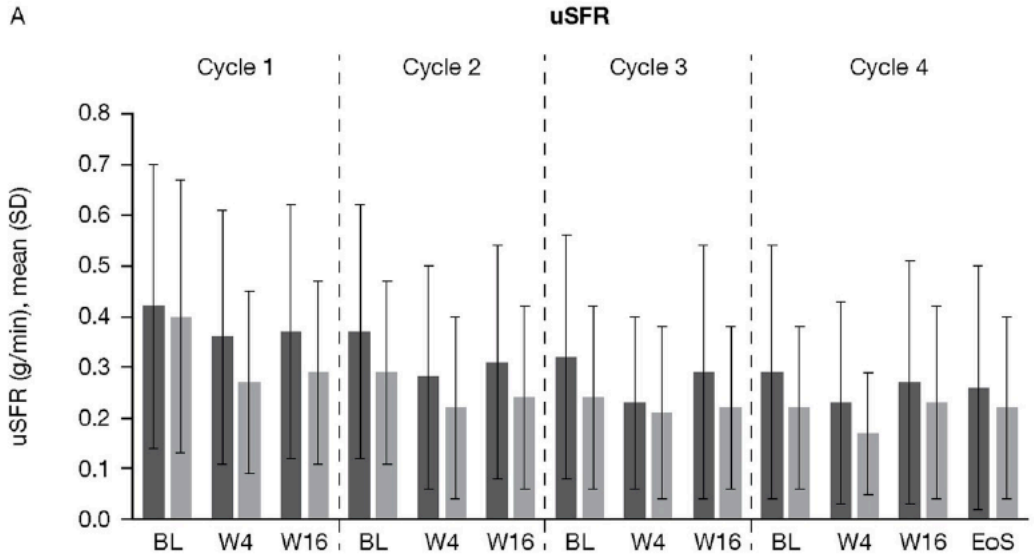


Jost, Parkinsonism and Related Disorders, 2020

Long-term incobotulinumtoxinA treatment for sialorrhea



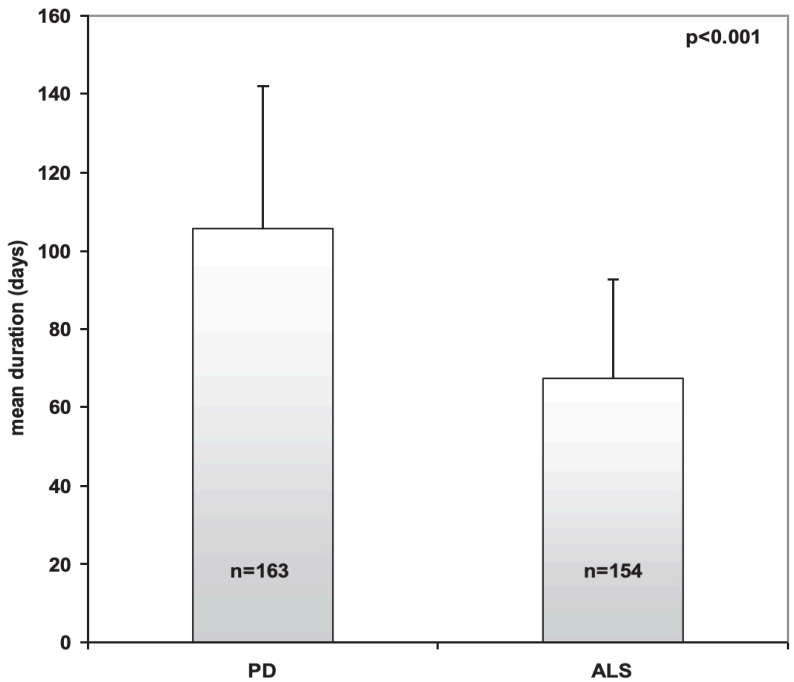
Unstimulated salivary flow rate (uSFR)

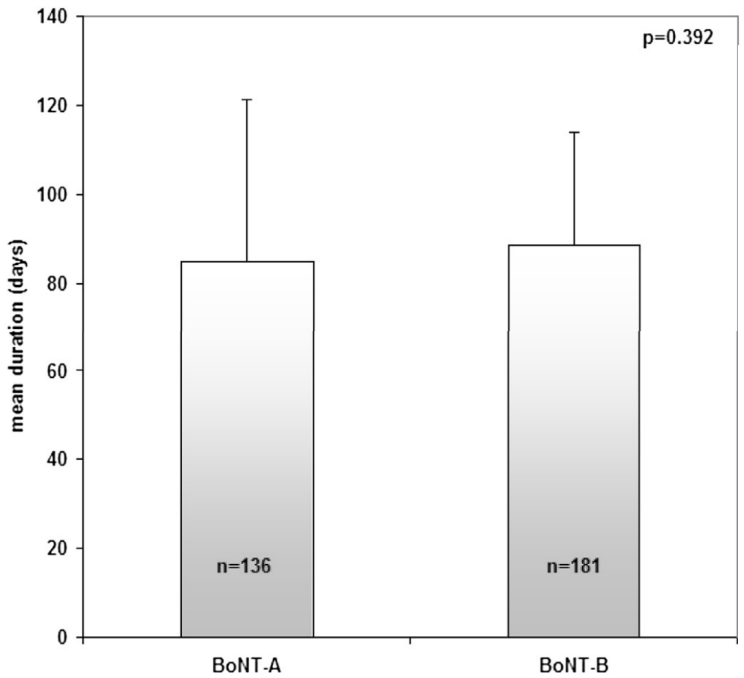


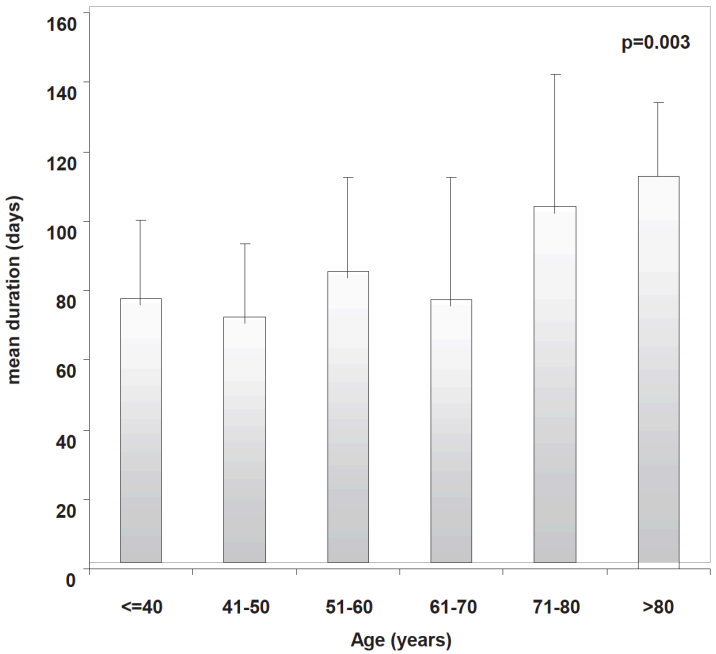
the incidence of AEs per treatment cycle during the extension period (35.6–43.6%) was **similar** to that reported for incobotulinumtoxinA recipients **in Cycle 1** in the main period (44.6%)

Jost, Parkinsonism and Related Disorders, 2020

8 year of follow-up
Failure in 11% of treatments.
AboBoNT 250U
RimaBoNT 2500U







Petracca, 2015

Long term treatment of chronic scialorrhea

Long term treatment showed convincing rate of safety and efficacy

Article

Safety of High-Dose Botulinum Toxin Injections for Parotid and Submandibular Gland Radioprotection

Joerg Mueller [1,*], Thomas Langbein [2], Aditi Mishra [3] and Richard P. Baum [3]

Table 1. Botulinum Toxin (IncoA) treatment details and adverse events.

Patient	PG Right IncoA (Units)	SMG Left IncoA (Units)	Total Dose IncoA (Units)	Adverse Event	AE Severity
1	100	50	150	Painful swallowing	Mild
2	100	50	150	-	-
3	120	70	190	Dry mouth	Mild
4	120	70	190	-	-
5	130	70	200	Dry mouth	Mild
6	170	80	250	Dry mouth *	Moderate *
7	170	80	250	Dry mouth	Mild
8	170	80	250	Dry mouth *	Moderate *
9	170	80	250	Dry mouth	Mild
10	170	80	250	Dry mouth	Mild

PG = Parotid gland, SMG = Submandibular gland, * moderate pre-existing xerostomia.

Mueller, Toxins, 2022

Grazie per l'attenzione