Botulinumtoxin in der Schmerztherapie

Univ. Prof. Dr. Rudolf Likar, MSc

Vorstand der Abteilung für Anästhesiologie, allgemeine Intensivmedizin, Notfallmedizin, interdisziplinäre Schmerztherapie und Palliativmedizin
Klinikum Klagenfurt am Wörthersee
LKH Wolfsberg

Lehrabteilung der Medizinischen Universität Graz, Innsbruck, Wien

Lehrstuhl für Palliativmedizin SFU

SFU Fakultät für Medizin

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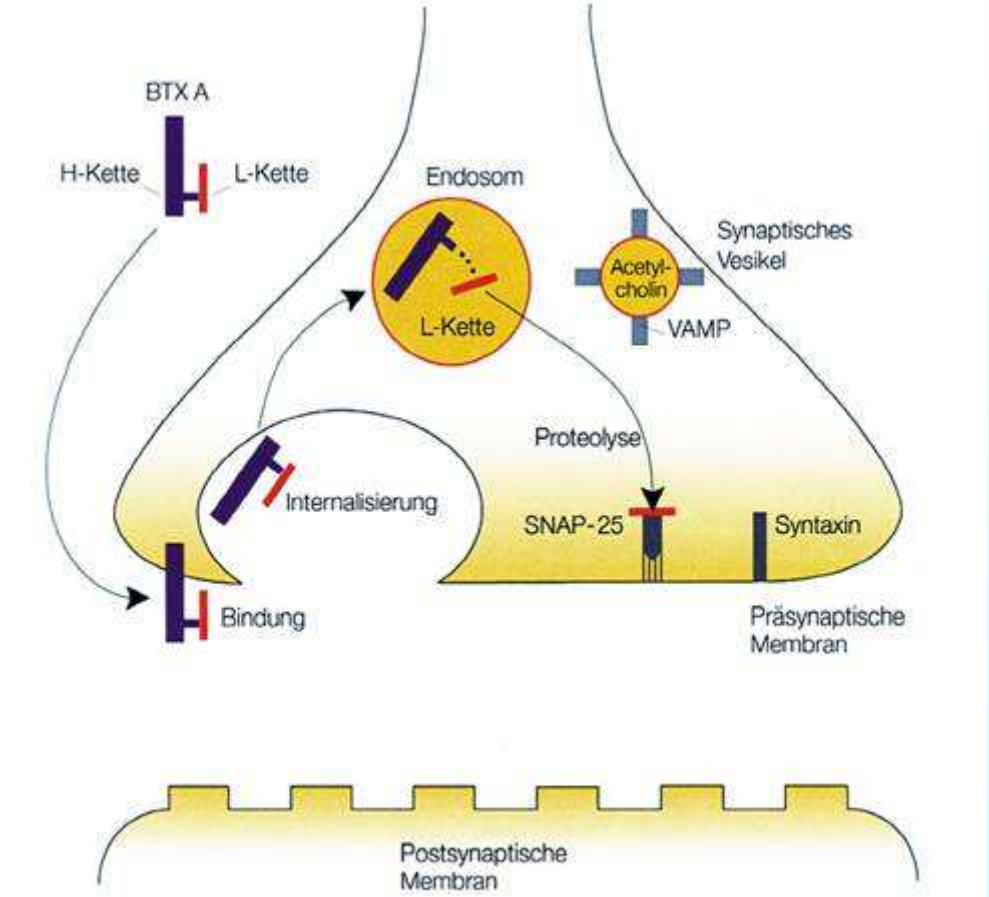
Wirkmechanismus



Btx-A:

schwere H-Kette und leichte L-Kette

H-Kette:

Bindung an Rezeptor

Internalisierung

Aufnahme ins Endosom

Im Endosom:

Trennung der Btx-A Ketten

L-Kette:

Proteolyse von SNAP-25

des Vesikel-Fusionskomplex

Ach-Vesikel bindet nicht komplett

==> Hemmung Ach-Freisetzung

Neuromuskuläre Endplatte

Präsynaptisches Nervenende mit schematischer Darstellung der Wirkungsweise der SNARE-Proteine und ihrer Spaltung durch BoNT

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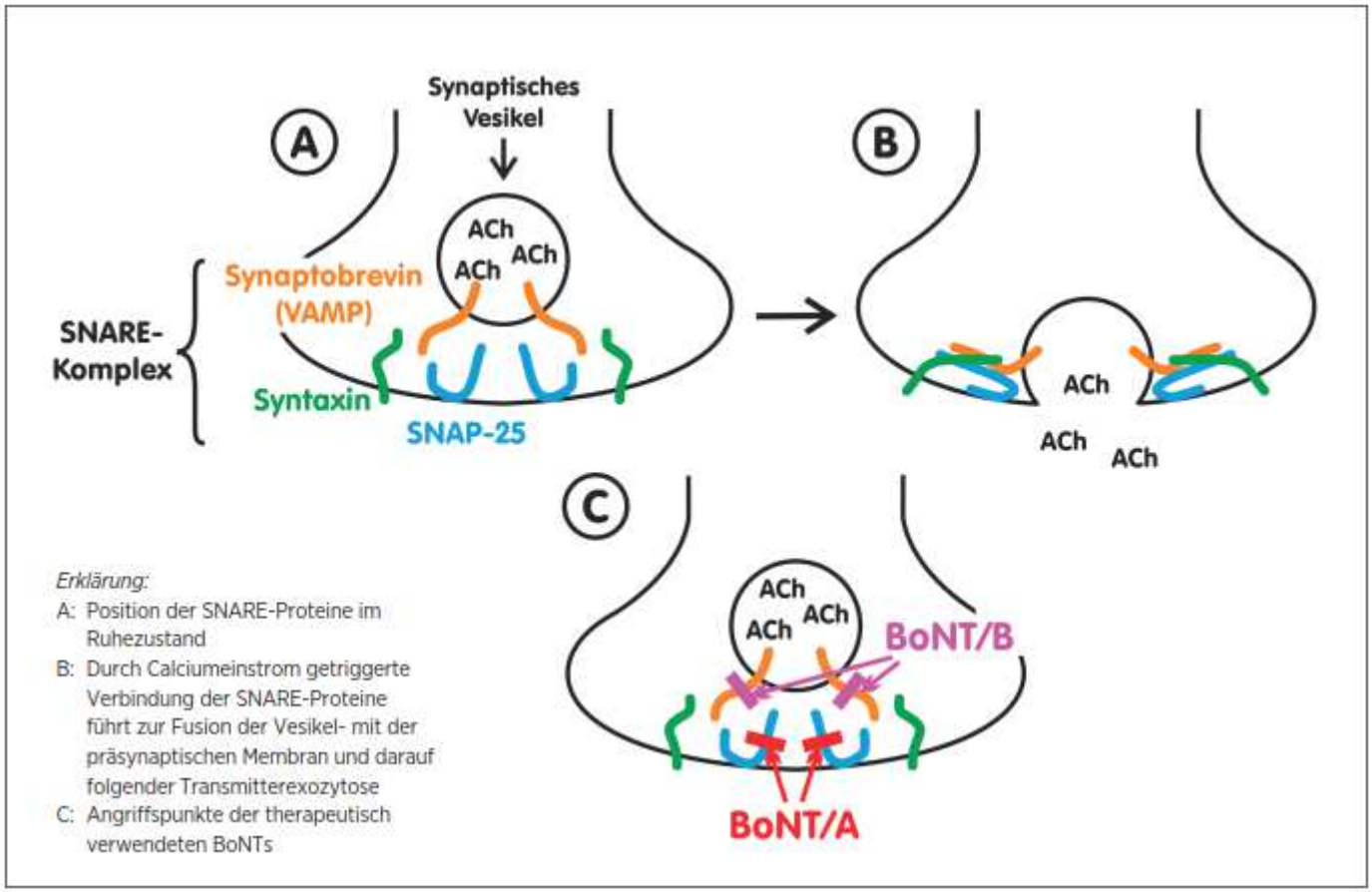

Holzer U, Donnerer J. Botulinum-Neurotoxin in der Schmerztherapie. Schmerznachrichten Nr. 3, Sept. 2021. S. 40-44.

1. Schritt – Bindung und Internalisation

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Nach der Membranbindung werden die BoNTs internalisiert. Starke neurale Aktivität fördert die Internalisierung und die Toxizität der BoNTs.

Dies passt auch zur Wirksamkeit der BoNTs bei der Behandlung von Syndromen aufgrund hyperaktiver Nervenendigungen (Spasmen), denn neuromuskuläre Endplatten mit einer hohen Umsatzrate von Vesikel Exo-Endozytose begünstigen die Toxinaufnahme.

Bindung von BoNT/A1 an den glykosylierten SV2C Rezeptor:
-> erfolgt durch Protein-Protein und Protein-Glykan Interaktionen
-> das Glykosylierungsmuster kann interindividuell unterschiedlich sein;
-> folglich kann auch die Menge des gebundenen Toxins von Patient zu Patient unterschiedlich sein, obwohl die gleiche Dosis injiziert wurde.

Wirkmechanismus

- **Hemmung der Ca^{++} - abhängigen ACH-Freisetzung**
- **Irreversible Hemmung der neuromuskulären Übertragung**
- **Spaltung des Transportproteins Synaptobrevin**
- **Normalisierung gesteigerter Aktivität von Muskelspindeln**
- **Retrograde neuronale Aufnahme ins ZNS**
- **Hemmung vesikel-abhängiger Exocytose von SP**
- **Expression von Enkephalin, Neurotension, Galanin, VIP, Neuropeptid Y**

Wirkeintritt - Wirkdauer

Wirkeintritt: nach 2 - 10 Tagen

Wirkmaximum: ist nach ca. 14 Tagen erreicht

Wirkdauer: 3 - 6 Monate

Indikationen in der Schmerztherapie

- **Myofasziale Schmerzsyndrome**
- **Masseterhypertrophie mit assoziiertem Gesichtsschmerz**
- **Epicondylitis**
- **Kiefergelenks-Dysfunktion**
- **Spannungskopfschmerzen**
- **Migräne**
- **Clusterkopfschmerz**
- **zervikogener Kopfschmerz nach HWS Schleudertrauma**
- **Fibromyalgie ?????**
- **Stumpfschmerz**

Botulinumtoxin in der Schmerzbehandlung

Wirkprofil

Lokal applizierbar
Relaxierung und Atrophie
Andere Wirkmechanismen?
Kaum Interaktionen (Begleit-therapien, Medikamente)
Selten Kontraindikationen
Keine systemischen Neben-wirkungen
Einmalinjektion

Einsatz in der Schmerztherapie

Fokales Schmerzsyndrom
Muskuläre (Mit-)ursache, Trigger
Schmerzfasern?, Substanz P?
Zusatzmedikation problemlos

Jedes Alter
Gute Verträglichkeit
Sehr gute Compliance

Aktuell verfügbare Botulinum Neurotoxin Zubereitungen

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Botox und Dysport: gereinigte Precursor Toxin Komplexe, beinhaltend das BoNT/A1 Molekül als aktiven pharmazeutischen Bestandteil und weitere Proteine;

Xeomin: enthält nur das gereinigte BoNT/A1.

Alle Zubereitungen enthalten humanes Serum Albumin als „Füllsubstanz“, um den Toxinverlust durch die Gefriertrocknung, durch Proteinaggregation und Oberflächenadsorption zu verhindern, und die Lagerungsstabilität zu verbessern.

Die Zubereitungen kommen in Pulverform in den Handel und werden vor Gebrauch mit einer Pufferlösung rekonstituiert.

Table 1 BoNT preparations and FDA-approved indications

BoNT preparation	Brand name (manufacturer)	FDA-approved indications[a]
OnabotulinumtoxinA	Botox (Allergan, Inc., Irvine, CA)	Blepharospasm, CD, upper extremity spasticity, lower extremity spasticity, CM
AbobotulinumtoxinA	Dysport (Ipsen Ltd., Paris, France)	CD, upper extremity spasticity
IncobotulinumtoxinA	Xeomin (Merz Pharmaceuticals, Frankfurt, Germany)	Blepharospasm, CD, upper extremity spasticity
RimabotulinumtoxinB	Myobloc Neurobloc (US WorldMeds/Solstice Neurosciences, Louisville, KY)	CD

Abbreviations: BoNT = botulinum neurotoxin; CD = cervical dystonia; CM = chronic migraine; FDA = Food and Drug Administration.
[a] FDA approvals relevant to this review.

Simpson D. M. et al.; Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: American Academy of Neurology 2016, 1818-1826.

Therapeutische Sicherheit

Dosierung von Botulinumtoxin A*:

500 U (1 Ampulle) : z.B. Torticollis

max. 2.000 U (4 Ampullen) : Spastik

Letale Dosis für einen 70 kg schweren Menschen:

40.000 - 80.000 U (80 - 160 Ampullen!)

==> *Therapeutische Breite* 1 : 40 - 80

Schmerzbehandlung: 50 - 320 U

**** Die Dosierungsangaben beziehen sich auf das Medikament Dysport®***

Kontraindikationen

Neuromuskuläre Erkrankungen

(z. B. Myasthenia gravis, Lambert-Eaton-Syndrom)

Behandlung mit Pharmaka, die die neuromuskuläre Übertragung beeinträchtigen

(z. B. Aminoglykosid- und Makrolidantibiotika)

Blutgerinnungsstörungen oder Einnahme von die Gerinnung beeinflussenden Arzneimitteln

Schwangerschaft und Stillzeit

Lokale Infekte

Einschlusskriterien

Chronische myofasziale Schmerzen (HWS, LWS)

an 15 Tagen pro Monat seit mindestens 6 Monaten

konventionelle Therapie hat versagt

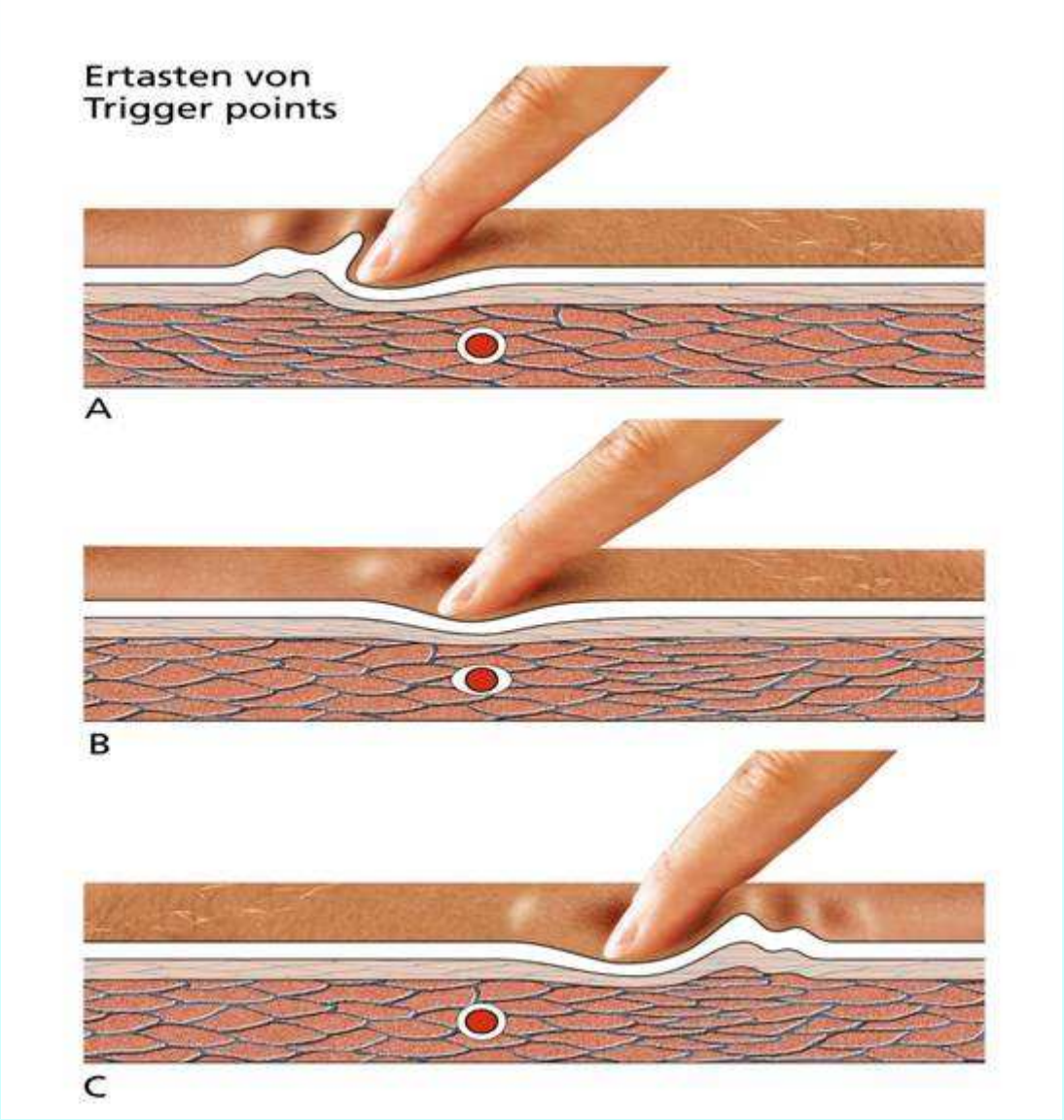
oder ist kontraindiziert

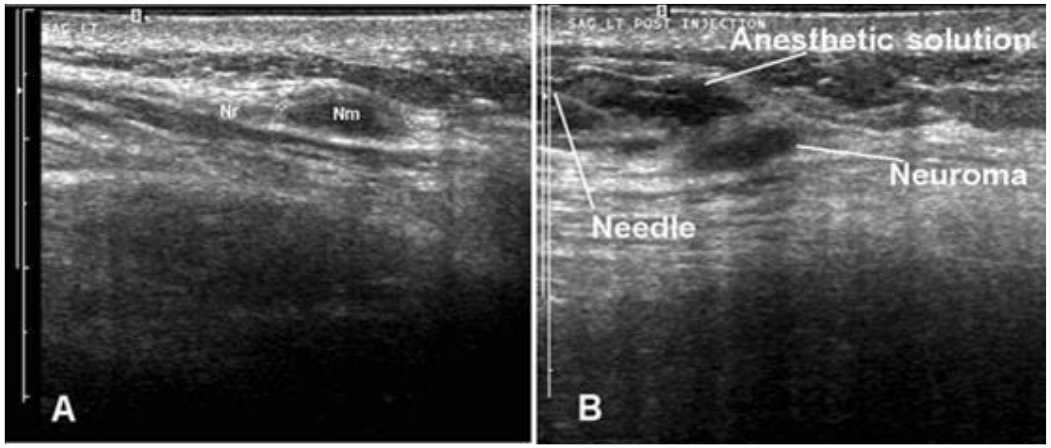
***keine* Hinweise auf andere spezifische Erkrankungen**

im Bereich des Bewegungssystems

Definition von myofaszialen Triggerpunkten

1.)	lokaler Punkt mit hohem Druckschmerz in einem verspannten Muskelband	+++
2.)	Lokale Zuckungsreaktion	++
3.)	Übertragener Schmerz	+++
4.)	Auslösen der primären Schmerzsituation	+++
5.)	Bewegungseinschränkung	+
6.)	Schwäche ohne Atrophie	+
7.)	Autonome Symptome (lokale Rötung)	+


Ertasten von
Trigger points
A
B
C



Hughes RJ, Ali K, Jones H, Kendall S, Connell DA. Treatment of Morton's neuroma with alcohol injection under sonographic guidance: follow-up of 101 cases. AJR Am J Roentgenol. 2007;188:1535–1539

Methods:

Fifteen patients suffering from PHN for more than 1 months were enrolled. Data collected were patients` age, sex and lesion site, the dermatome involved and the duration and severity of pain by visual analog scale (VAS). Botulinum (15 units /every 10 cm^2 of body involved) was injected intradermally. The patients were followed 2, 14 and 30 days after injection.

Conclusions:

It seems that intradermal injection of botulinum toxin decreases pain in PHN patients and this decrease is less prominent by passing time.

Emad Mr, Emad M, Taheri P; The Efficacy of Intradermal Injection of Botolium Toxin in Patients with Post-Herpetic Neuralgia; Iranian Red Crescent Medical Journal, 2011; 13 (5):323-327

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Tab. 1 Charakteristika und Hauptergebnisse der ausgewerteten Fallberichte, -serien und Studien zur Behandlung der Post-Zoster-Neuralgie mit Botulinumtoxin

Autor, Jahr	Studienart	*N*	Applikation	Injektionsort	Serotyp	Dosis	Untersuchungszeitraum	Ergebnis
Klein 2004 [23]	Fallbericht	1	i. d.	Punktuell	A onaA	20 E	4 Monate	Komplette Schmerzreduktion
Liu et al. 2006 [26]	Fallbericht	1	s. c.	Fächerartig im Allodyniareal	A onaA	20 × 5 E	52 Tage	VAS-Reduktion von 10 auf 1
Ruiz Huete u. Bermejo 2008 [42]	Fallbericht	1	i. d.	Flächig	A Nicht spezifiziert	n. a.	2 Monate	Schmerzverbesserung
Ranoux et al. 2008 [41]	RCT, doppelblind (insgesamt $n = 29$)	4	i. d.	Rasterartig im Allodynieareal	A onaA	Bis zu 40 × 5 E	14 Wochen	NNT für 50 % Schmerzreduktion nach 12 Wochen: 3,03
Sotiriou et al. 2009 [48]	Fallserie	3	s. c.	Rasterartig	A onaA	20 × 5 E	12 Wochen	VAS-Reduktion von 8,3 auf 2
Xiao et al. 2010 [55]	RCT, doppelblind	60	s. c.	Rasterartig im Allodynieareal	A onaA	Bis zu 40 × 5 E	3 Monate	Signifikante Schmerzreduktion und Verbesserung des Schlafs, weniger Opiodbedarf
Emad et al. 2011 [15]	Fallserie	15	i. d.	in Schmerz Areal	A aboA	15 U/cm²	30 Tage	Signifikante Schmerzreduktion
Apalla et al. 2013 [2]	RCT, doppelblind	30	s. c.	Rasterartig	A onaA	40 × 5 E	20 Wochen	Signifikante Schmerzreduktion und Schlafverbesserung von Woche 2–16
Ponce et al. 2013 [39]	Fallserie	12	i. d./s. c. (Widerspruch)	Rasterartig	A onaA	8–10 × 2,5 E	3 Monate	Signifikante Schmerzreduktion
Li u. Xiao 2015 [25]	Fallbericht	1	s. c.	Orbita	A Nicht spezifiziert	1oo E	6 Monate	Schmerzreduktion
Attal 2016 [5]	RCT, doppelblind (insgesamt $n = 66$)	5	s. c.	Rasterartig im Allodynieareal	A onaA	Bis 60 × 5 E, Wiederholung nach 12 Wochen	24 Wochen	Signifikante Schmerzreduktion

aboA Abobotulinumtoxin A, *i.d.* intradermal, *NNT* „number needed to treat", onaA Onabotulinumtoxin A, *RCT* randomisierte kontrollierte Studie, *s.c.* subkutan, *VAS* visuelle Analogskala

Halb L. et al.; Einsatz intra- bzw. subkutaner Botulinumtoxine bei Post-Zoster-Neuralgie: Nervenarzt 2017, 88:408-414.

Table 1. Key and reviewed studies on the employment of botulinum toxin type A (BoNT-A) and type B (BoNT-B) therapy in the treatment of piriformis muscle syndrome (PMS).

First author and year of publication	Study design	Number of patients with PMS	Doses (U) and number of injections	Injection guide	Outcome measures	Adjunctive therapy	Clinical results/adverse effects
Fanucci *et al.*, 2001 [4]	Prospective	30	OnabotulinumtoxinA 100 U: 26 received one injections 4 received two injections	CT	Not specific pain score	Not indicated	Reduction of pain intensity after 5–7 days for 26 subjects; other 4 subjects reported a complete pain reduction in the following week/No adverse effects
Fishman *et al.*, 2002 [17]	RCT double-blind, parallel	21	AbobotulinumtoxinA 200 U	EMG	VAS	Twice-weekly physical therapy program	65% of the patients reported a 50% of pain reduction/No adverse effects
Childers *et al.*, 2002 [3]	RCT double-blind, crossover	9	OnabotulinumtoxinA 100 U	FL EMG	VAS	Not indicated	Reduction of pain intensity, distress, spasm and interference with activities respect to baseline/No adverse effects
Fishman *et al.*, 2004 [20]	Prospective	27	BoNT-B 12,500 U	EMG	VAS	Physical therapy twice weekly for 3 months	A total of 24 of 27 study patients had a pain relief of 50%. The most severe adverse effects were dry mouth and dysphagia, approaching 50% of patients at 2 and 4 weeks
Lang *et al.*, 2004 [21]	Prospective	20	BoNT-B 5,000 U	EMG	VAS	Dry mouth was reported in 6 of 20 patients	Reduction of myofascial buttock and hip pain associated with PMS/No adverse effects
Yoon *et al.*, 2006 [6]	Prospective	20	AbobotulinumtoxinA 150 U: One injection	CT	NRS at 4, 8, 12 weeks Korean SF-36	Stretching exercise 20 times/day for 12 week	Pain reduction respect to baseline($p < 0.0001$) Improvement of physical functioning, role physical, bodily pain, general health, vitality and social functioning/Mild and transient adverse events (one case of flu-like syndrome lasting 2 days, five cases of worsening muscular pain lasting 2–3 days, one patient had ecchymosis in the lower limb for 2 days, two patients had atrophy of the piriformis muscle, one case of transient numbness lasting no longer than 72 h
Michel *et al.*, 2013 [16]	Prospective	122	OnabotulinumtoxinA Ranged between 50 and 100 U: 51 received one Injection; 43 received two injections; 18 received three injections; 9 received four injections; 1 received five injections	EMG	VAS	Not indicated	"Very good' or 'Good" in 77% of the cases "Average" in 7.4% of the cases "Poor" in 15.6% of the cases/No adverse effects
Fabregat *et al.*, 2014 [18]	Feasibility study	10	OnabotulinumtoxinA 100 U	US	Not indicated	Not indicated	No adverse effects during the BoNT-A injections
Al-Al-Shaikh *et al.*, 2015 [19]	Retrospective	12	OnabotulinumtoxinA 100 U	US CT	VAS	Not indicated	Buttock and sciatic pain reduction respect to baseline ($p < 0.001$)/No adverse effects

CT: Computed Tomography; RCT: Randomized Clinical Trial; EMG: Electromyography; VAS: Visual Analogue Scale; FL: Fluoroscopy; NRS: Numeric Rating Scale; SF-36: 36-Item Short Form Health Survey; US: Ultrasound.

(a) (b)

Figure 1. Positioning of the probe initially with its lateral side medial to the greater trochanter (**a**) and finally positioned with its medial side lateral to the ischial tuberosity (**b**).

Santamato et al., Ultrasound-Guided Injection of Botulinum Toxin Type A for Piriformis Muscle Syndrome: A Case Report and Review of the Literature. Toxins 2015, 7, 3045-3056

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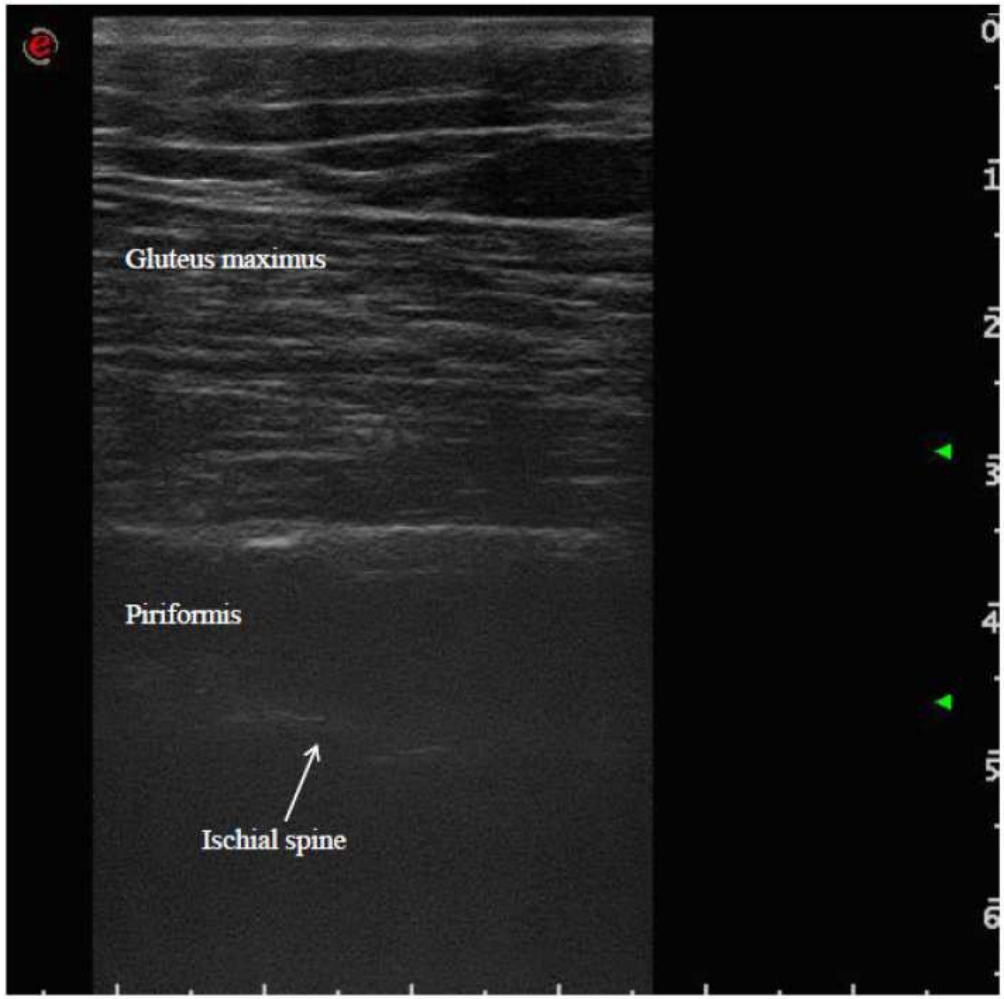

Figure 2. Ultrasound identification of the piriformis muscle between gluteus maximus muscle and ischial spine.

Santamato et al., Ultrasound-Guided Injection of Botulinum Toxin Type A for Piriformis Muscle Syndrome: A Case Report and Review of the Literature. Toxins 2015, 7, 3045-3056

Study design and description of relevant studies which met the inclusion criteria

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First author	Year of study	Study design	Number of patients who received BoNT	BoNT dose(U) per injection into PM	Total number of BoNT per patient	Frequency/ interval between each injection	Modalities to guide injection	Needle size and length	Physical therapy after intervention with botulinum toxin	Outcome measures	Adverse effects
H Najdi et al.	2019	Retrospective case control	7	7 patients each received BoNT A (Botox) ranging from 100 to 300	1	-	CT	Not mentioned	Nil	No specific pain scale mentioned; 7 patients who received BoNT had transient pain relief from one week to one month; no other functional outcomes reported.	No adverse effects reported; no intervention needed
Fishman	2017	RCT comparing botulinum toxin with normal saline	56	A 4-site injection of 3 cc containing 300 units of incobotulinum toxin A	1	-	EMG	22 to 25G 3.5 inch	One physical therapy per week for 12 weeks	Reduction of VAS over a period of 12 weeks; reduction of VAS of 0.36 at week 2, 0.39 at week 4, 0.55 at week 6, 0.65 at week 8, 0.55 at week 10, 0.62 at week 12	Five mild adverse effects: injection site pain, flu-like symptoms, wobbly neck in botulinum toxin group; no intervention needed
Al–Al-Shaikh et al.	2014	Retrospective case control study	12	100 of botulinum toxin A (Botox) each into PM and obturator internus	1 to 4	Minimum of 3 months between each injection with a mean of 2.1 injections	Either US or CT	Not mentioned	Nil	Reduction of VAS buttock pain from 7.5 to 3.2 and sciatic pain from 7.04 to 1.7.	No adverse effects reported
Yoon et al.	2007	Prospective cohort study	20	150 of botulinum toxin A	1	Only once	CT	3.5 inch, 22G	Stretching exercises 20 times each day for 12 weeks after treatment	Drop in baseline mean pain score 0f 7.06 to 4.45 at 4weeks, 3.55 at 8 weeks and 3.48 at 12 weeks; Improvement in all subdomain scores of SF-36 4 weeks after treatment	Mild and transient adverse effects; one case of flu-like symptoms for 2days, transient numbness of less than 72 h in the other, lower limb ecchymosis in two patients; no intervention needed
Fishman	2004	Prospective cohort study	26	5000, 7500, 10,000, 12,500 of BoNT B in 4 groups	Seven patients had 2 injection, 19 had 1 injection	Not mentioned	EMG	23G of 3.5 inch	Physical therapy twice weekly for 3months	Overall mean reduction of VAS of 3.6 in 5000 group, 2.12 in the 7500 group, 2.89 in the 10,000 group and 4.51 in the 12,500 group; improvement in FAIR tests in most groups at 12 weeks	One case: monocular blurred vision.; two cases each: gastroesophageal reflux; lump in throat; One case: constipation; two cases: difficulty in swallowing; none needed medical attention; no intervention needed
Fishman	2002	RCT comparing botulinum toxin versus lidocaine and triamcinolone versus normal saline	21	200 of botulinum toxin A with 2 cc saline dilution	1	Only once	EMG detection of H reflex	Not mentioned	Standard physical therapy protocol twice weekly for 12 weeks	VAS assessment into two groups: 50% improvement or more versus less than 50%; 65% improvement observed in the Botox group	No adverse effects reported
MK Childers et al.	2002	RCT comparing botulinum toxin versus normal saline	10	100 of botulinum toxin A	1	Only once	Fluoroscopic or EMG guidance	5.5 inch, 20G needle	Had concurrent physiotherapy and home stretching but changes in physiotherapy program not permitted	Greater reduction in VAS, distress spasm and pain interference with activities over 10 weeks when compared with saline group	No adverse effects reported

Abbreviations: CT, Computed Tomography; FAIR, Flexion, adduction and internal rotation, MRN; Magnetic Resonance Neurography, MRI; Magnetic Resonance Imaging, mm: millimeters,ms:milliseconds, PM: Piriformis muscle; PE, physical examination; QOL: quality of life, RCT, randomized control trial, US, Ultrasound; VAS:Visual Analogue Scale.

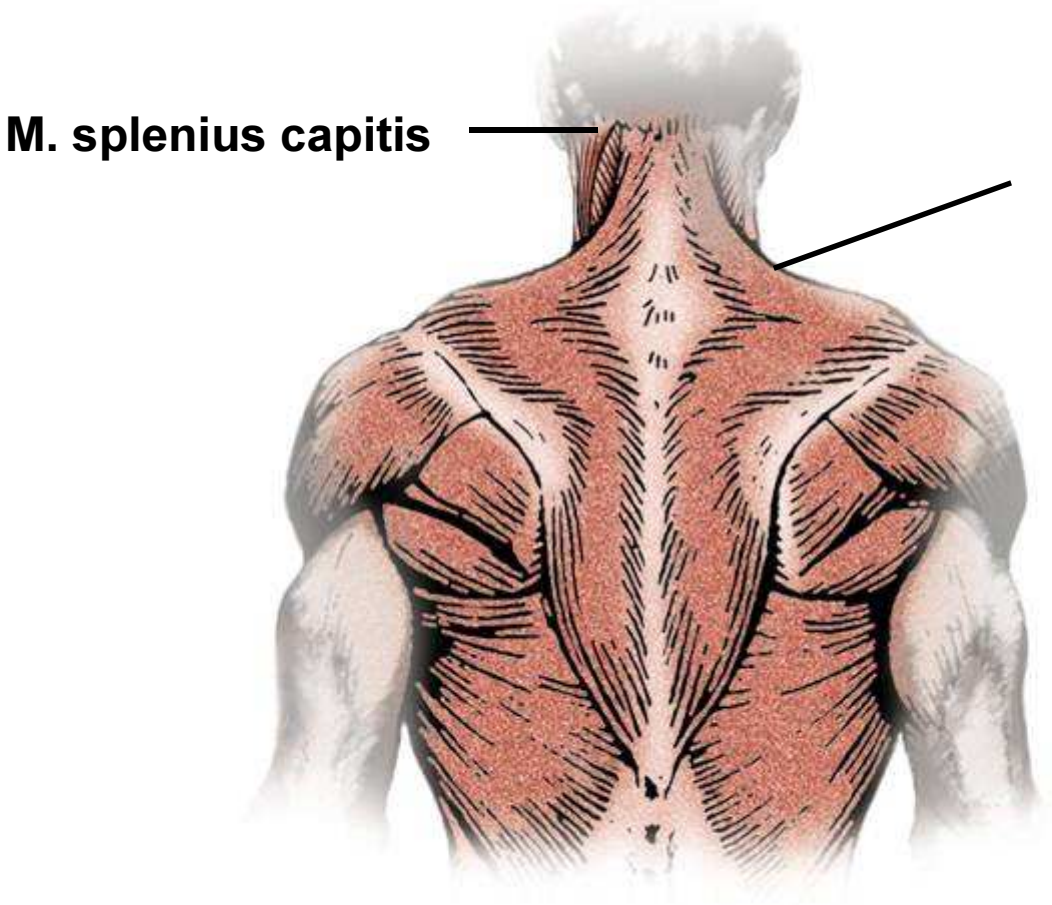
Koh MM, Tan YL. Use of botulinum neurotoxin in the treatment of piriformis syndrome: A systematic review. J Clin Orthop Trauma. 2022 Jul 9;31:101951. doi: 10.1016/j.jcot.2022.101951. PMID: 35865325; PMCID: PMC9294329.

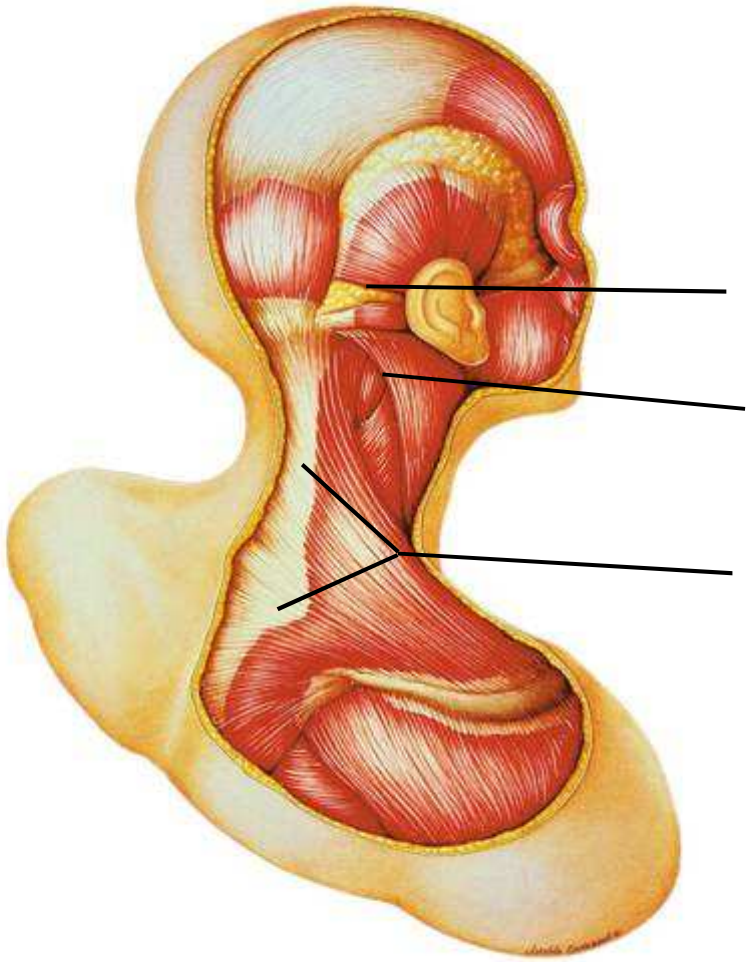
Synthesis:
Seven studies (n ¼ 152 patients) were included consisting of three randomized controlled studies (RCTs), two case control studies and two cohort studies. The qualities of these studies were: Two good and one fair for the RCTs, fair for both the case controls and one good and fair for the cohort studies. Most studies reported some reduction in pain using various modalities to guide injection (CT, EMG, US or fluoroscopy). However, the included studies were heterogeneous, making it difficult to quantify pain reduction. There was minimal description of other functional outcomes. Botulinum toxin A doses range from 100 to 300U. Mild adverse effects were reported with no medical intervention needed.

Conclusions:
There is fair quality of evidence to suggest botulinum toxin is safe to reduce pain in piriformis syndrome. There is insufficient data to quantify pain reduction and to describe other functional outcomes. The optimal dose of botulinum toxin A remains unclear. Modalities to guide botulinum injection into the piriformis muscle remain heterogeneous.

Koh MM, Tan YL. Use of botulinum neurotoxin in the treatment of piriformis syndrome: A systematic review. J Clin Orthop Trauma. 2022 Jul 9;31:101951. doi: 10.1016/j.jcot.2022.101951. PMID: 35865325; PMCID: PMC9294329.

Muskulatur HWS



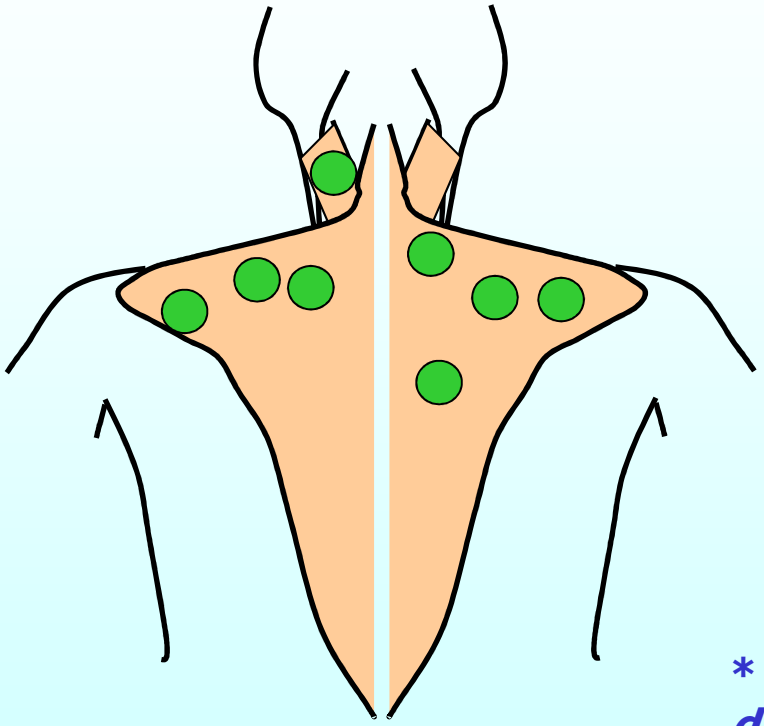


M. semispinalis capitis

M. splenius capitis

M. trapezius

Myofasziale Schmerzen der Schulter-Nacken-Muskulatur



Empfehlung pro Körperseite:

maximal 4 Injektionen

M. splenius : 0 oder 1 Injektionen

M. trapezius : 3 oder 4 Injektionen

Dosis* **pro Punkt: 20 - 40 U**

Gesamtdosis*: bis 320 U

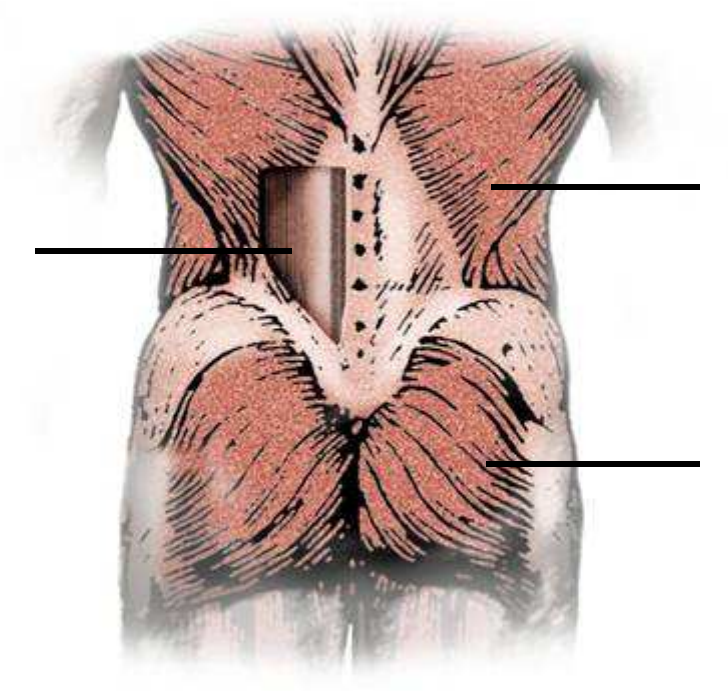
Beispiel für Injektionspunkte

** Die Dosierungsangaben beziehen sich auf das Medikament Dysport®*

Gobel H, Heinze A, Reichel G, Hefter H, Benecke R; Dysport myofascial pain study group. Efficiacy and safety of a single botulinum type A toxin complex treatment (Dysport) for the relief of upper back myofascial pain syndrome: results from a randomized double-blind placebo-controlled multicentre study. Pain 2006;125(1-2):82-8. (+)

Ojala T, Arokoski JP, Partanen J. The effect of small doses of botulinum toxin a on neck-shoulder myofascial pain syndrome: a double-blind, randomized, and controlled crossover trial. Clin J Pain 2006;22(1):90-6. (-)

Muskulatur unterer Rücken

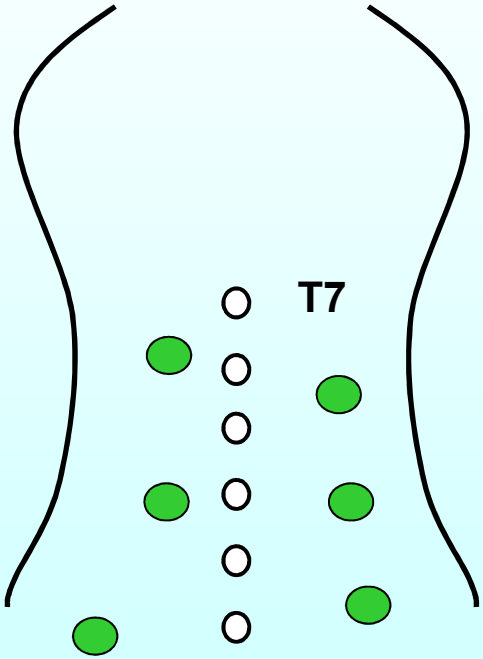


M. erector spinae

M. latissimus dorsi

M. gluteus maximus

Myofasziale Schmerzen der Rückenmuskulatur



Empfehlung pro Körperseite:

maximal 3 Injektionen

mind. 3 cm lateral der Wirbelsäule

Höhe T7 bis Glutealmuskulatur

Dosis* **pro Punkt: 40 - 60 U**

Gesamtdosis*: bis 360 U

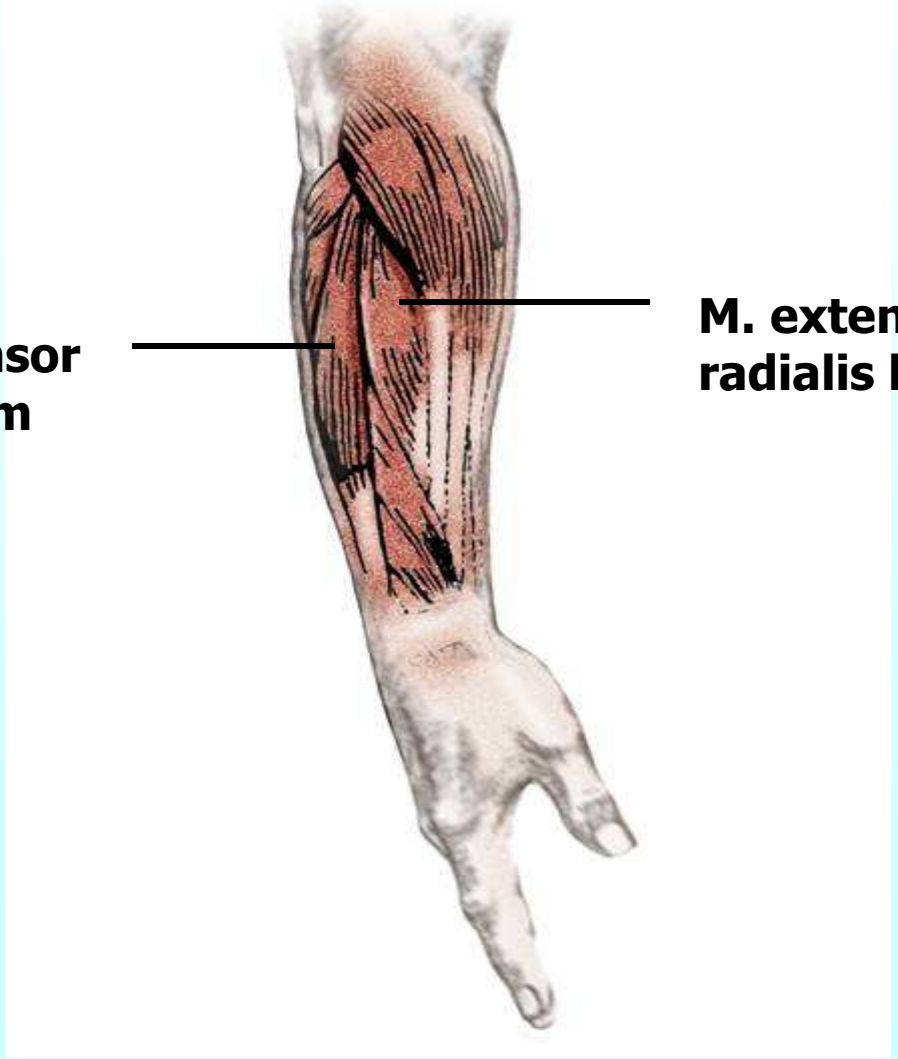
Beispiel für Injektionspunkte

** Die Dosierungsangaben beziehen sich auf das Medikament Dysport® 60 U = Xeomin 20 Units*

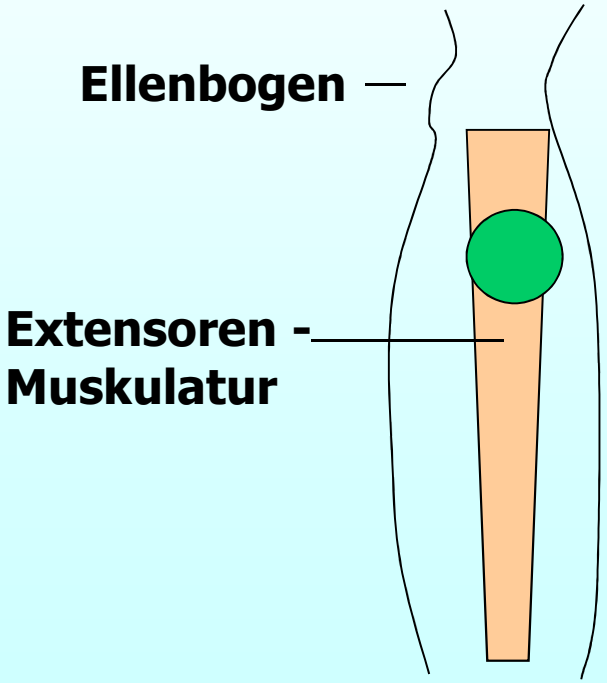
Jabbari B, Ney J, Sichani A, Monacci W, Foster L, Difazio M. Treatment of refractory, chronic low back pain with botulinum neurotoxin A: an open-label, pilot study. Pain Med 2006;7(3):260-4. (+)

Ney JP, Difazio M, Sichani A, Monacci W, Foster L, Jabbari B. Treatment of chronic low back pain with successive injections of botulinum toxin a over 6 months: a prospective trial of 60 patients. Clin J Pain 2006;22(4):363-9. (+)

Unterarmmuskulatur



Epicondylopathie



Injektion:

Nach klinischem Palpationsbefund

- in die Extensoren-Muskulatur

etwas distal des Sehnenansatzes

(M. extensor carpi radialis brevis,

M. extensor digitorum communis)

1 - 2 Injektionspunkte

Gesamtdosis*:

50 - 100 U (je nach Muskelmasse)

** Die Dosierungsangaben beziehen sich auf das Medikament Dysport ®*

Table 1 The treatment of patients with BoNT-A

	Case 1	Case 2	Case 3
Age (years)	54	42	45
Cause	Accident	Accident	Landmine
Mean BoNT-A Dosage (U)	300	500	200
Latency of response (days)	1–3	2–4	1–3
Duration of response (weeks)	9–10	8–11	9–10
VAS before treatment	9–10	7–10	6–8
VAS after treatment	0–2	1–3	1–2
GCI	3	3	3

VAS = visual analog scale (0–10); GCI = Global clinical improvement (0 = no effect; 3 = marked improvement).

Lingjing Jin, MD, Katja Kollewe et al; Treatment of Phantom Limb Pain with Botulinum Toxin Type A; American Academy of Pain Medicine 300-303

Schlussfolgerung

Alle Patienten hatten klinische Verbesserungen. Die Schmerzintensität und Schmerzmedikation wurde signifikant reduziert, keine Nebenwirkungen, die Dauer der Verbesserung war über 11 Wochen. Die Therapie mit Botulinum Toxin A scheint eine effektive und sichere Behandlung zu sein bei Phantomschmerzen und sollte näher untersucht werden.

Es wurden bis zu 500 Unit unter EMG-Kontrollen appliziert.

Studies excluded from analysis

Reference	Reason for exclusion	Authors' conclusion
Ney et al. (2006)	Open-label trial	BTA efficacious
Vasan et al. (2004)	Open-label trial	BTA efficacious
Lang (2004)	Open-label trial	BTA efficacious
De Andres et al. (2003)	Open-label trial	BTA efficacious
Lang (2000)	Open-label trial	BTA efficacious
Wheeler and Goolkasian (1998)	Retrospective cohort study	BTA efficacious
Freund and Schwartz (2000a)	Duplicate report	BTA efficacious
Diaz and Gould (1999)	Case report	BTA efficacious
Acquadro and Borodic (1994)	Case report	BTA efficacious
Childers et al. (2002)	BTA injection for piriformis syndrome	BTA efficacious
Fishman et al. (2002)	BTA injection for piriformis syndrome	BTA efficacious
Porta (2000)	BTA injection into piriformis, scalenus anterior and iliopsoas	BTA efficacious
Graboski et al. (2005)	<10 patients enrolled	BTA comparable to bupivacaine
Kamanli et al. (2005)	<10 patients enrolled	BTA comparable to lidocaine
Cheshire et al. (1994)	<10 patients enrolled	BTA efficacious
Foster et al. (2001)	<10% of patients had TPs	BTA efficacious

BTA, Botulinum toxin A; TP, trigger point.

Kok-Yuen Ho, Kian-Hian Tan; Botulinum toxin A for myofascial trigger point injection: A qualitative systematic review; European Journal of Pain 11 (2007) 519-527

Randomized controlled trials of Botulinum toxin A injection for myofascial pain

Author	Study design	Location of pain	Duration of pain	Dose regimen (BTA/control)	No. of patients	Age (mean ± SD)	Sex (M/F)	Concurrent therapy	Study duration	Outcome Measures	Results	Author's conclusion
Ojala et al. (2006)	Double-blind, randomized, crossover	Neck and shoulder	10.0 ± 8.6 months	(i) 28 ± 6 U BTA (15-35 U); 5 U per TP (ii) Saline	(i) 15 (ii) 16	44.4 ± 7.7	3/28	Paracetamol	4 Weeks	VAS pain score at 4 weeks; VRS (efficacy); PPT	No difference in VAS, PPT and VRS (efficacy) ($P > 0.05$)	Negative
Ferrante et al. (2005)	Double-blind, randomized	Neck and shoulder	>6 months	(i) 10 U BTA (ii) 25 U BTA (iii) 50 U BTA in each TP (Max. 5 TP per patient) (iv) Saline	(i) 32 (ii) 34 (iii) 31 (iv) 35	(i) 43.3 ± 10.9 (ii) 46.6 ± 15.1 (iii) 46.5 ± 12.2 (iv) 45.3 ± 10.1	52/80	Standardized regimen of amitriptyline, ibuprofen and propoxyphene-acetaminophen	12 Weeks	VAS pain score at 24 h and 1, 2, 4, 6, 8 and 12 weeks; rescue medication use; PPT; SF-36	No difference in VAS, PPT and rescue dosing ($P > 0.05$); lower score in BTA group for SF-36 emotional subscale ($P < 0.05$)	Negative
Wheeler et al. (2001)	Double-blind, randomized	Cervico-thoracic	8.6 ± 9.6 years	(i) 231.20 ± 50.1 U BTA (ii) Saline	(i) 25 (4 dropouts) (ii) 25 (1 dropout)	43.6 ± 10.7	12/38 (sex of dropouts NR)	NR	16 Weeks	NPAD; global assessment of improvement; SF-36; BDI	No difference ($P > 0.05$)	Negative
Freund and Schwartz (2000b)	Double-blind, randomized	Cervical	>6 months	(i) 20U BTA (ii) saline	(i) 14 (ii) 12	46	11/15	NR	4 Weeks	VAS headache pain score and ROM of neck at 2 and 4 weeks	Lower VAS in BTA group at 4 weeks ($P < 0.01$)	Positive
Wheeler et al. (1998)	Double-blind, randomized	Cervico-thoracic	(i) 930.2 days (ii) 1038.3 days (iii) 1067.5 days	(i) 50 U BTA (ii) 100 U BTA in each TP (iii) saline	(i) 11 (ii) 11 (iii) 11	(i) 40.7 (ii) 43.4 (iii) 38.1	NR	NR	4 Months	PPT; NPAD at 1, 3, 6, 9, 12 and 16 weeks; subjective assessment of improvement	No difference in PPT, NPAD and subjective assessment ($P > 0.05$)	Negative

K.-Y. Ho, K.-H. Tan / European Journal of Pain 11 (2007) 519–527

Kok-Yuen Ho, Kian-Hian Tan; Botulinum toxin A for myofascial trigger point injection: A qualitative systematic review; European Journal of Pain 11 (2007) 519-527

Zusammenfassung

- **Die aktuelle Evidenz unterstützt nicht die Verwendung von Botulinumtoxin A für die Injektion für Triggerpunkte für myofascialen Schmerz. Die Daten sind limitierend und heterogen. Botulinumtoxin A hat keine größere Effektivität, wenn man sie mit anderen Injektionen mit Kochsalz oder Lokalanästhetika oder trockener Nadelung für superfiziale Triggerpunkte in der zervikothorakalen, cervikalen, thorakalen und low-back Region vergleicht. Die Kosten für Botulinumtoxin A sind hoch und weitere Studien sind notwendig um die Kosten-Effektivität für Botulinumtoxin – Injektionen zu belegen.**

Kok-Yuen Ho, Kian-Hian Tan; Botulinum toxin A for myofascial trigger point injection: A qualitative systematic review; European Journal of Pain 11 (2007) 519-527

Schlussfolgerung

- **Es wurden 3 Studien verifiziert, die das Botulinumtoxin für low-back pain untersuchten. Eine Studie hat das Risiko von Bias,da sie Patienten mit unspezifischen Rückenschmerz evaluierten.**

- **Weitere Untersuchungen sollten standardisiert werden, hinsichtlich der Patientenpopulation, Behandlungsprotokolle und Vergleichsgruppe.**

Waseem Z, Boulias C, Gordon A, Ismail F, Sheean G, Furian AD; Botulinum toxin injections for low-back pain and sciatica; Cochrane Database Syst Rev. 2011 Jan 19;1:CD008257

Botulinumtoxin für Schulterschmerzen

- **Die Ergebnisse sollten mit Vorsicht interpretiert werden, betreffend der wenigen Studien mit geringer Patientenanzahl und hohem Risiko von Bias. Botulinum toxin A Injektionen scheinen die Schmerzintensität zu reduzieren und die Schulterfunktion zu verbessern und auch das Bewegungsausmaß - wenn man Botulinum toxin A Injektionen mit Placebo bei Patienten mit Schulterschmerzen wegen Hemiplegie oder Arthritis vergleicht. Es ist unklar warum der Benefit bei poststroke Schulterschmerzen erst gesehen wird nach 3 bis 6 Monaten aber nicht nach einem 1 Monat. Neue Studien mit Sicherheitsdaten sind notwendig.**

Singh JA, Fitzgerald PM; Botulinum toxin for shoulder pain; Cochrane Databas Syst Rev. 2010 Sept 8;(9):CD008271

Botulinum toxin for myofascial pain syndromes in adults

BACKGROUND:

Myofascial pain syndrome (MPS) is a regional muscular pain syndrome characterised by the presence of trigger points, which are painful points in one or more muscles. The pain can be felt at the site where the trigger point is located or it can be felt away from that place when the muscle is pressed (referred pain). Botulinum toxin is a protein produced by the bacterium Clostridium botulinum and is a potent neurotoxin that eventually inhibits muscle contractions. It is capable of selectively weakening painful muscles and interrupting the pain cycle.

SEARCH METHODS:

The search strategy was composed of terms for myofascial pain and botulinum toxin. We searched the Cochrane Pain, Palliative and Supportive Care (PaPaS) Review Group's Specialised Register until December 2011, CENTRAL (Cochrane Database of Systematic Reviews 2011, Issue 4), PUBMED (from 1966 to 2011), EMBASE (from 1980 to 2011) and LILACS (from 1982 to 2011). There was no language restriction.

Soares A, Andriolo RB, Atallah AN et al; Botulinum toxin for myofascial pain syndromes in adults; Cochrane Database Syst Rev. 2012 Aprl 18

MAIN RESULTS:

Four studies with a total of 233 participants, comparing botulinum toxin A (BTXA) with placebo, met the inclusion criteria.

In one study with 145 participants, a significant improvement rate of pain intensity scores, as shown by the mean difference (MD) of -0.23 (95% confidence interval (CI) -0.26 to -0.20; P value < 0.00001) and duration of daily pain (MD -1.11; 95% CI -1.37 to -0.85; P value < 0.00001), was demonstrated when comparing BTXA with placebo.

The three other studies showed that there was no statistically significant difference between BTXA and placebo in pain intensity.

Soares A, Andriolo RB, Atallah AN et al; Botulinum toxin for myofascial pain syndromes in adults; Cochrane Database Syst Rev. 2012 Aprl 18

AUTHORS' CONCLUSIONS:

There is inconclusive evidence to support the use of botulinum toxin in the treatment of MPS based on data from four studies with a total of 233 participants, which we considered adequate to be included in this review.

Meta-analyses were not possible due to the heterogeniety between studies.

We suggest that in future studies the same methodology to assess pain, a standardised dose of treatment, follow-up of at least four months (to observe the maximum/minimum curve of the drug effect) and appropriate data presentation should be used.

More high-quality RCTs of botulinum toxin for treating MPS need to be conducted before firm conclusions on its effectiveness and safety can be drawn.

Soares A, Andriolo RB, Atallah AN et al; Botulinum toxin for myofascial pain syndromes in adults; Cochrane Database Syst Rev. 2012 Aprl 18

Wieviel wird injiziert?

- **Dosis abhängig**
  - **Größe des Muskels**
  - **Anatomische Verhältnisse**
  - **Schmerzintensität**
  - **Anzahl anderer symptomatischer Muskeln**
  - **Gesamtdosis**
- **Mittlere Dosis pro Stelle**
  - **Nackenbereich: 60 u Dysport®, 20 u Botox,Xeomin®**
  - **Gesichtsbereich: 5 u Dysport ®, 1,5 u Botox,Xeomin®**
- **Mittlere Gesamtdosis für Erstbehandlung**
  - **300 mu Dysport ®**
  - **100 mu Botox,Xeomin®**

MATERIALS AND METHODS:
In this randomized double-blind placebo-controlled clinical trial study, diabetic patients aged <70 years with neuropathic pain in both feet were enrolled. Diabetic neuropathy (DN) in selected patients was diagnosed using DN4 questionnaire and nerve conduction velocity examinations. They randomized in two intervention (BTX-A injection/100 unit, N = 20) and placebo groups (normal saline injection, N = 20). The outcome of injection on diabetic neuropathic pain was assessed using neuropathy pain scale (NPS) and visual analog scale (VAS) score and compared in two studied groups.

RESULTS:
There was no significant difference in DN4, NPS and VAS scales of studied population after intervention in the placebo group. Intradermal injection of BTX-A reduced NPS scores for all items except cold sensation (P = 0.05). It reduced DN4 scores for electric shocks, burning, pins and needles and brushing (P < 0.05). According to VAS scale 30% and 0% of patients in intervention and placebo groups have no pain after intervention (P = 0.01).

CONCLUSION:
Intradermal injection of BTX-A is a well-tolerated agent that has a significant effect on DPN pain.

Ghasemi M, Ansari M, Basiri K. The effects of intradermal botulinum toxin type a injections on pain symptoms of patients with diabetic neuropathy. J Res Med Sci. 2014 Feb; 19 (2):106-11

Conclusion

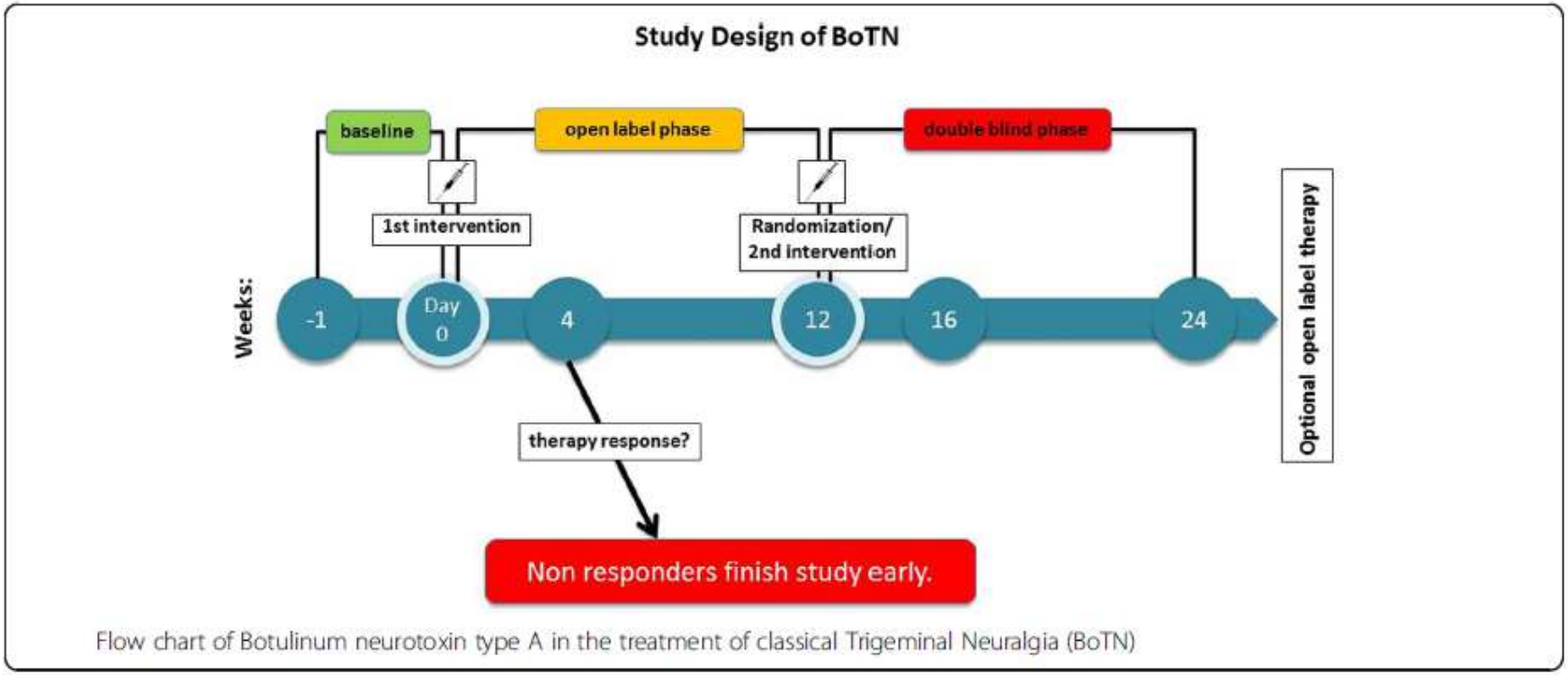
Trigeminal neuralgia is a clinical entity characterized by severe pain. Various conservative medicinal, minor, and major surgical procedures were used in the past with variable success. Unfortunately, few patients failed to respond to these established treatment modalities.

Various new treatment alternatives have been tried to provide permanent cure to the patient with minimal morbidity andmortality. Botulinum toxin type-A is one of the recent treatment alternatives.

Limited number of case reports and open-ended studies reported favorable outcomes in this regard. But these studies lack scientific merits. Based on the review of the scientific literature, it can be concluded that the scientific literature is insufficient to definitely establish the efficacy of botulinum toxin type-A in the management of trigeminal neuralgia.

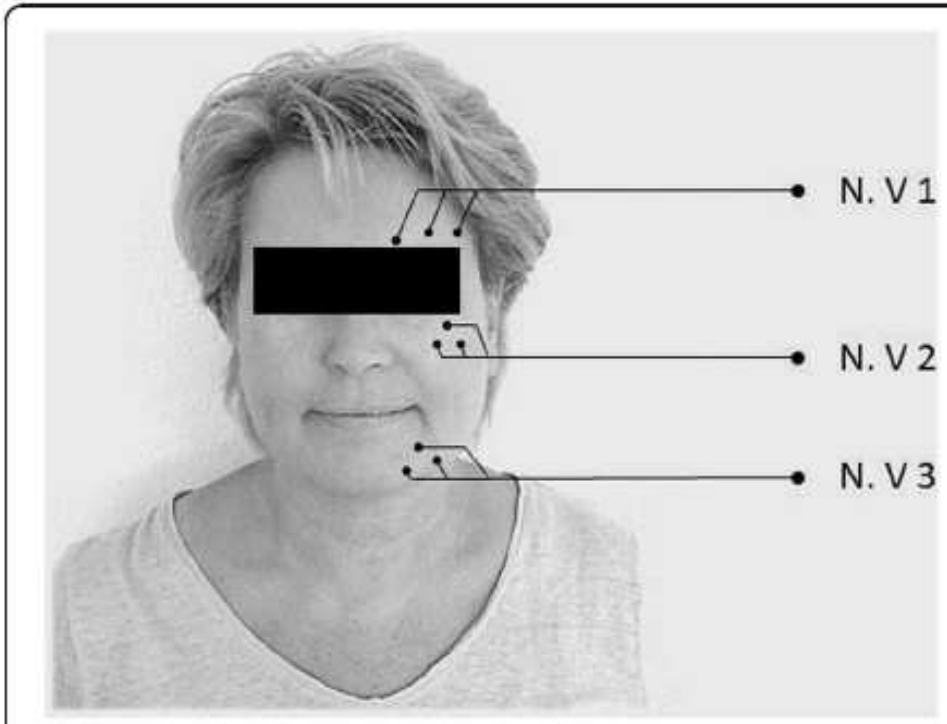
Further studies with larger sample size are required in this regard.

Verma G, Role of Botulinum Toxin Type A (BTX-A) in the Management of Trigeminal Neuralgia. Hindawi Publishing Vol 2013



Flow chart of Botulinum neurotoxin type A in the treatment of classical Trigeminal Neuralgia (BoTN)

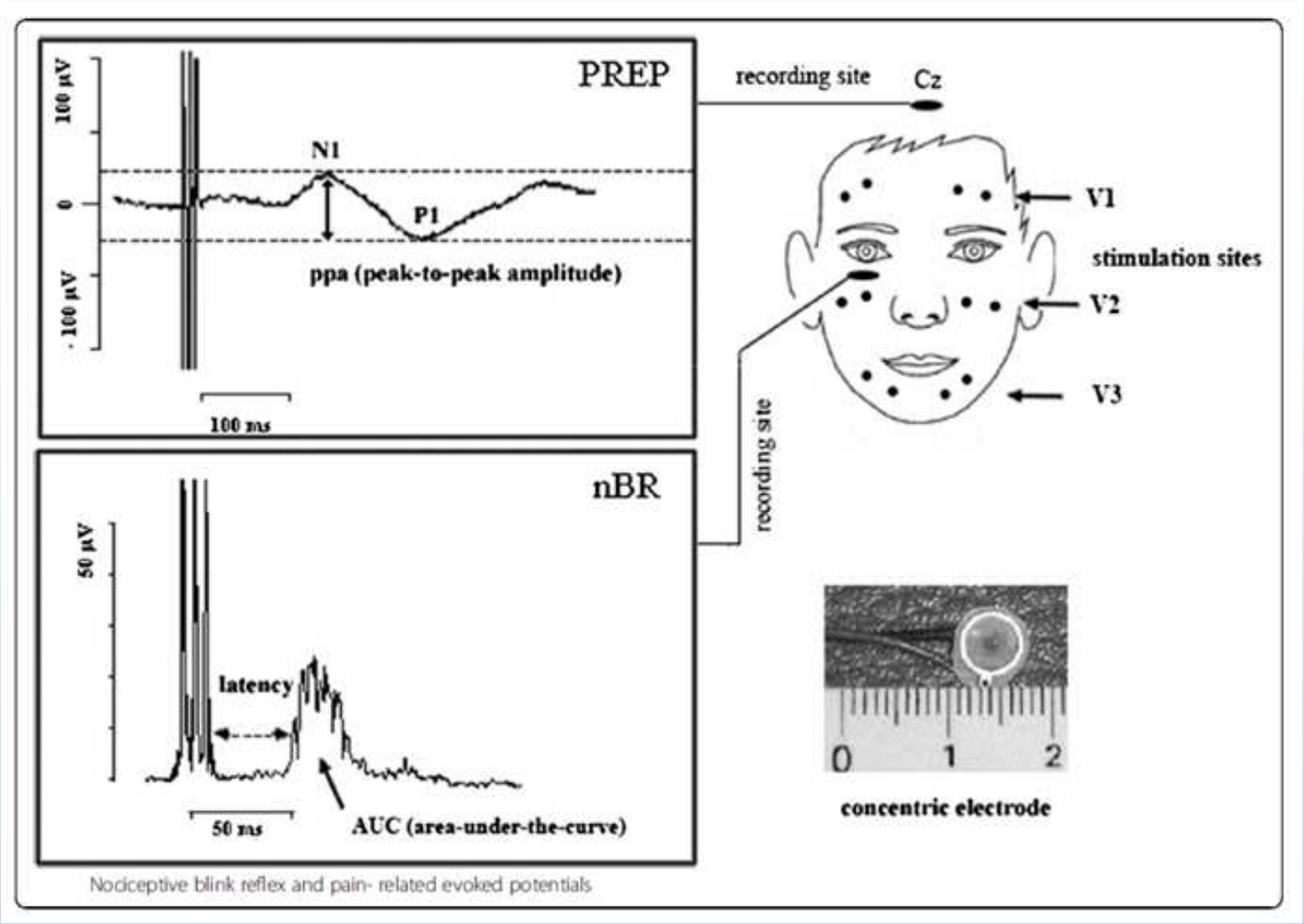
Burmeister et al. Botulinum neurotoxin type A in the treatment of classical Trigeminal Neuralgia (BoTN): study protocol for a randomized controlled trial. Trials (2015) 16:550



Injection scheme of Botulinum neurotoxin type A in the treatment of classical Trigeminal Neuralgia (BoTN). Nerve exits of the affected trigeminal branches will be palpated and identified. Five units of BT-A are injected at three sites per branch 1.5 cm apart. Injection sites of the first trigeminal branch are kept 1.5 cm above the eyebrows in order to prevent ptosis

Burmeister et al. Botulinum neurotoxin type A in the treatment of classical Trigeminal Neuralgia (BoTN): study protocol for a randomized controlled trial. Trials (2015) 16:550

KABEG
KLINIKUM KLAGENFURT
AM WÖRTHERSEE



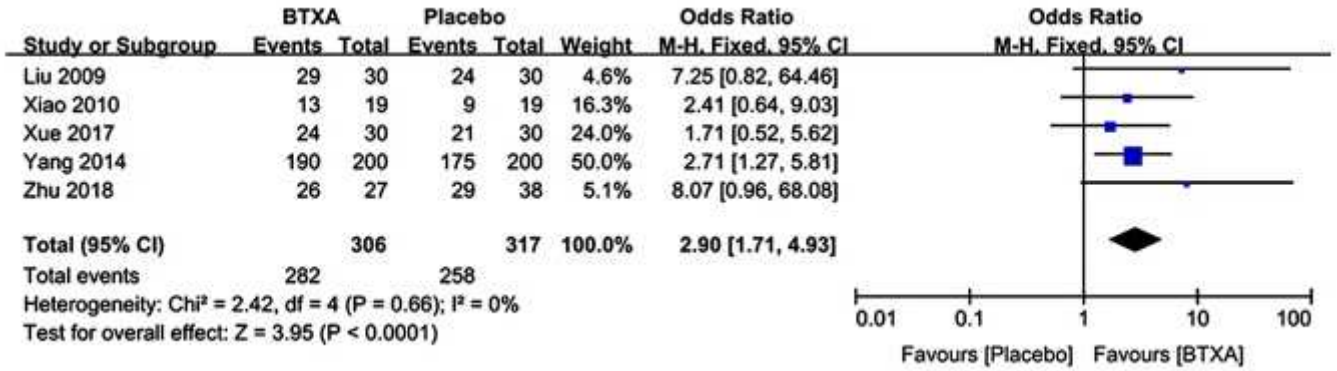
Burmeister et al. Botulinum neurotoxin type A in the treatment of classical Trigeminal Neuralgia (BoTN): study protocol for a randomized controlled trial. Trials (2015) 16:550

Table I.

Characteristics of trials included.

		Age (years)		Sex (male/female)				
First author (year)	Patients, total (study completion)	BTX-A group	Lidocain group	BTX-A group	Lidocain group	Interventions	Outcome measures	(Refs.)
Dai (2018)	71 (71)	64.5±8.9	66.2±8.4	18/14	21/18	BTX-A+gabapentin vs. Lidocain+gabapentin	VAS score, adverse events	(20)
Yang (2014)	400 (400)	56.32±5.69	56.34±4.88	120/80	115/85	BTX-A vs. Lidocain+carbamazepine	VAS score, effective rate	(21)
Xiao (2009) (2010)	40 (38)	70±15.41	65±14.20	11/9	8/12	BTX-A+gabapentin vs. Lidocain+gabapentin	VAS score, effective rate, adverse events	(22,23)
Zhu (2018)	65 (65)	/	/	/	/	BTX-A+Pregabalin+vitamin B1 vs. Lidocain+Pregabalin+vitamin B1	VAS score, effective rate	(24)
Xue (2017)	60 (60)	53.37±6.28	53.78±6.34	16/14	15/15	BTX-A+Pregabalin vs. Lidocain+Pregabalin	VAS score, effective rate	(25)
Yuan (2015)	[redacted]	58±3.5	57±4.3	16/12	11/17	BTX-A vs. Lidocain	Mcgill pain questionaire	(26)
Liu (2009)	60 (60)	56.36±0.9	56.8±0.9	13/17	14/16	BTX-A vs. Lidocain+carbamazepine	VAS score, effective rate, Mcgill pain questionaire	(27)

VAS, Visual Analogue Scale; BTX-A, botulinum toxin A.



BTX-A vs. lidocaine for post-herpetic neuralgia: Effective rate. BTX-A, botulinum toxin A; df, degrees of freedom; M-H, Mantel-Haenszel.

Xin-Long Li, Zeng X., Zeng S., et al. Botulinum toxin A treatment for post-herpetic neuralgia: A systematic review and meta-analysis. Experimental and therapeutic medicine 19: 1058-1064. 2020.

Drugs or drug classes with strong or weak recommendations for use based on the GRADE classification

	Total daily dose and dose regimen	Recommendations
Strong recommendations for use		
Gapabentin	1200–3600 mg, in three divided doses	First line
Gabapentin extended release or enacarbil	1200–3600 mg, in two divided doses	First line
Pregabalin	300–600 mg, in two divided doses	First line
Serotonin-noradrenaline reuptake inhibitors duloxetine or venlafaxine*	60–120 mg, once a day (duloxetine); 150–225 mg, once a day (venlafaxine extended release)	First line
Tricyclic antidepressants	25–150 mg, once a day or in two divided doses	First line†
Weak recommendations for use		
Capsaicin 8% patches	One to four patches to the painful area for 30-60 min every 3 months	Second line (peripheral neuropathic pain)‡
Lidocaine patches	One to three patches to the region of pain once a day for up to 12 h	Second line (peripheral neuropathic pain)
Tramadol	200–400 mg, in two (tramadol extended release) or three divided doses	Second line
Botulinum toxin A (subcutaneously)	50–200 units to the painful area every 3 months	Third line; specialist use (peripheral neuropathic pain)
Strong opioids	Individual titration	Third line§

GRADE=Grading of Recommendations Assessment, Development, and Evaluation (see appendix for details about the GRADE classification). *Duloxetine is the most studied, and therefore recommended, of the serotonin-noradrenaline reuptake inhibitors. †Tricyclic antidepressants generally have similar efficacy (appendix); tertiary amine tricyclic antidepressants (amitriptyline, imipramine, and clomipramine) are not recommended at doses greater than 75 mg/day in adults aged 65 years and older because of major anticholinergic and sedative side-effects and potential risk of falls,[33] an increased risk of sudden cardiac death has been reported with tricyclic antidepressants at doses greater than 100 mg daily.[34] ‡The long-term safety of repeated applications of high-concentration capsaicin patches in patients has not been clearly established, particularly with respect to degeneration of epidermal nerve fibres, which might be a cause for concern in progressive neuropathy. §Sustained release oxycodone and morphine have been the most studied opioids (maximum doses of 120 mg/day and 240 mg/day, respectively, in clinical trials; appendix); long-term opioid use might be associated with abuse, particularly at high doses, cognitive impairment, and endocrine and immunological changes.[35-37]

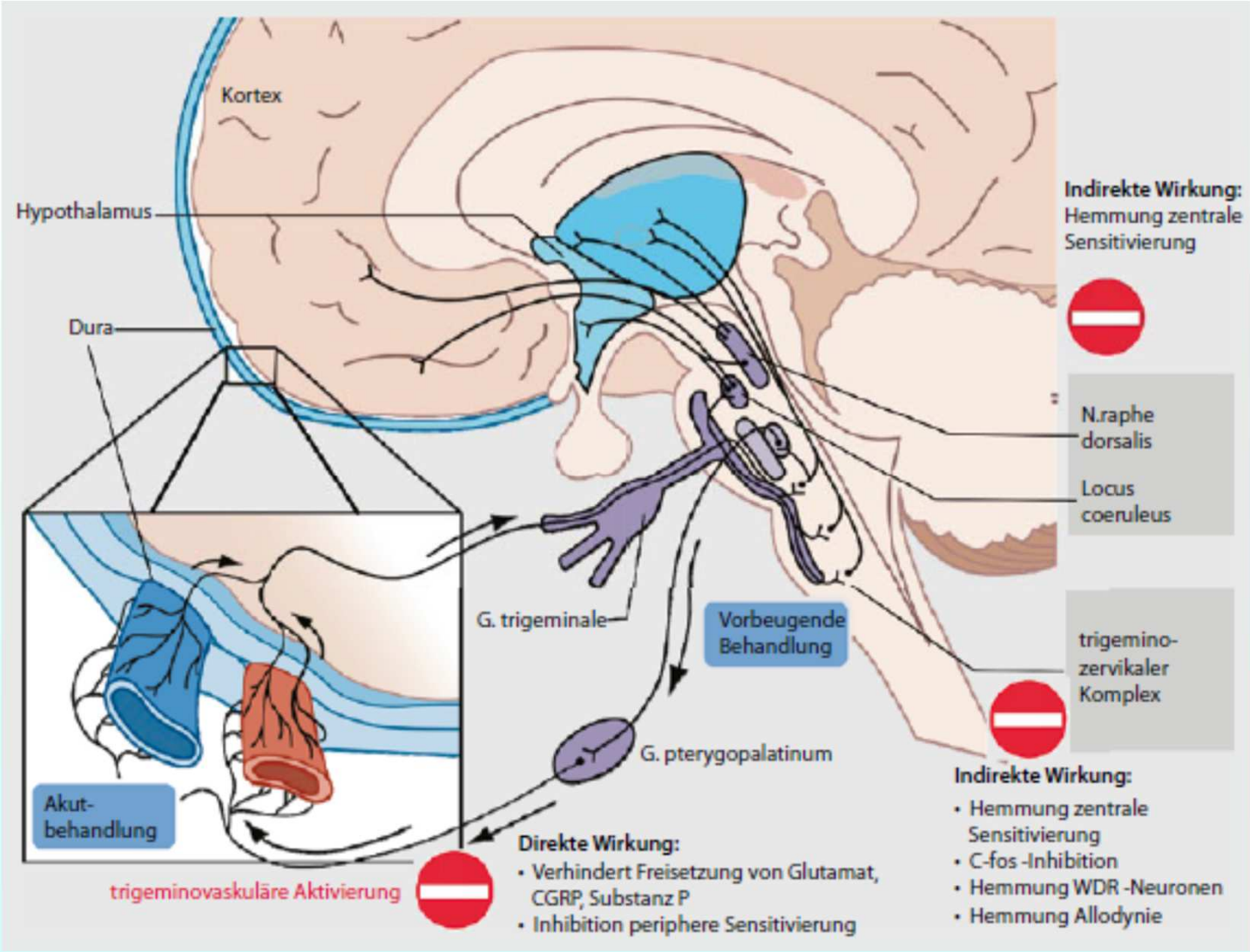
Finnerup NB, Attal N, Haroutounian S et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015; 162–73

Intramuscular onabotulinumtoxinA: clinical considerations in CM prevention
Only therapy specifically approved for the prevention of headaches in adults with CM in the EU
Therapy involves regular (3-monthly) injections
Efficacy and tolerability in large clinical trials confirmed in large real-world studies
Beneficial in patients regardless of whether or not they are acute medication overusers
Neck pain, (facial-) muscle weakness and eyelid ptosis are the most common treatment-related adverse events

Frampton J. E. et al.; OnabotulinumtoxinA: A Review in the Prevention of Chronic Migraine: CrossMark (2018) 78:589-600.

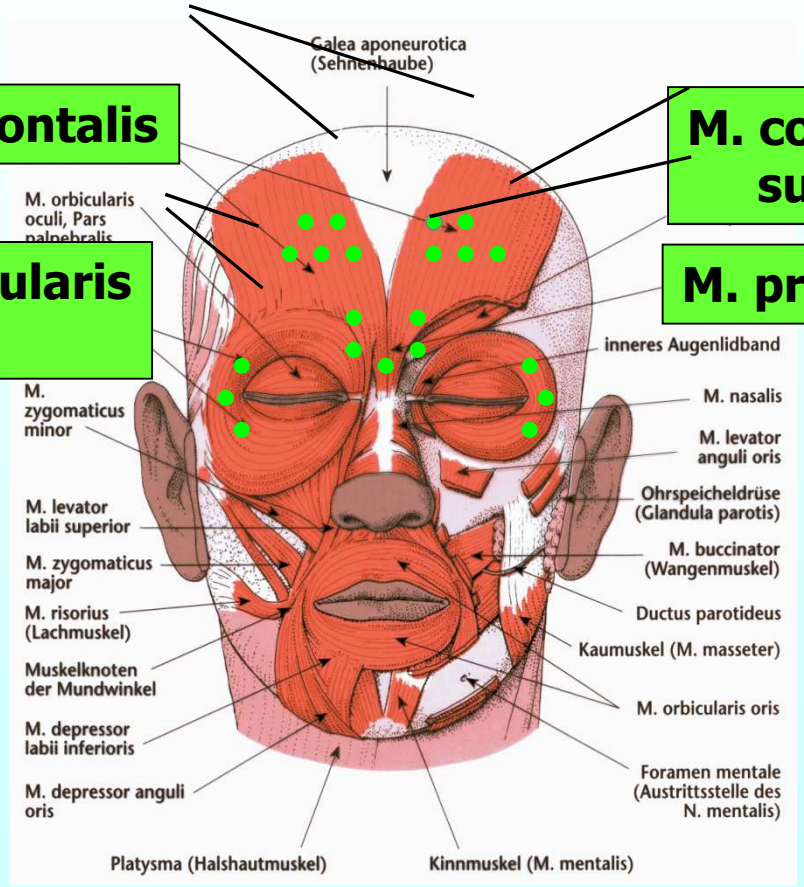
BTX in der Migräne - Probleme

- **Nur standardisierte Injektionen**
- **Injektionen im Stirn und Schläfenbereich**
- **Keine Nackeninjektionen**
- **Kopfschmerzdiagnose laut IHS**
- **Keine Berücksichtigung muskulärer Faktoren**
  - **Verspannungen als muskuläre Trigger**
  - **Initialschmerz**
  - **Lokalisation der Schmerzen**
  - **Ausschluss von Patienten mit anderen Triggern**



H Göbel, A Heinze; Prophylaxe der chronischen Migräne mit Botulinumtoxin Typ A; Der Schmerz 5/2011:563-571

Mimische Gesichtsfalten



Dosis pro Injektionspunkt

Glabella: 10 - 20U

Stirn: 10U

Krähenfüße:5 - 10U

500 U BTX-A* in
4 ml NaCl rekonstituieren
==> 125 U / ml

12,5 U / 0,1 ml

6,75 U / 0,05 ml

** Die Dosierungsangaben beziehen sich auf das Medikament Dysport®*

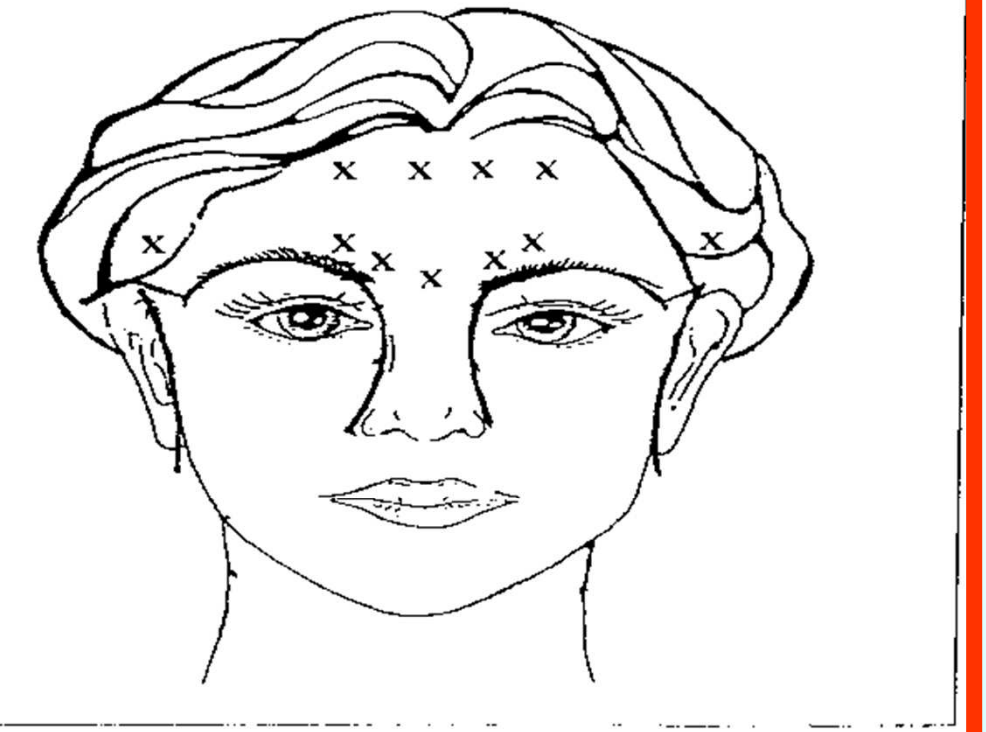


Fig 1.—Injection sites. Subjects received injections (10 U or 30 U) into four frontalis sites, two temporalis sites (6 U or 18 U), and five glabellar sites (corrugator: four sites, 6 U or 18 U; procerus: one site, 3 U or 9 U). The lower doses were administered to the subjects receiving a total dose of 25 U BTX-A and the higher doses were administered to the subjects receiving a total dose of 75 U BTX-A.

Gupta VK. Botulinum toxin – a treatment for migraine? A systematic review. Pain Med 2006;7(5):386-94. (+/-)

Headache
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Research Submission

OnabotulinumtoxinA for Treatment of Chronic Migraine: Pooled Results From the Double-Blind, Randomized, Placebo-Controlled Phases of the PREEMPT Clinical Program

David W. Dodick, MD; Catherine C. Turkel, PharmD, PhD; Ronald E. DeGryse, MS; Sheena K. Aurora, MD; Stephen D. Silberstein, MD; Richard B. Lipton, MD; Hans-Christoph Diener, MD; Mitchell F. Brin, MD, on behalf of the PREEMPT Chronic Migraine Study Group

Objective.—To assess the efficacy, safety, and tolerability of onabotulinumtoxinA (BOTOX®) as headache prophylaxis in adults with chronic migraine.

Background.—Chronic migraine is a prevalent, disabling, and undertreated neurological disorder. Few preventive treatments have been investigated and none is specifically indicated for chronic migraine.

From the Mayo Clinic Arizona, Phoenix, AZ, USA (D.W. Dodick); Allergan, Inc., Irvine, CA, USA (C.C. Turkel, R.E. DeGryse, and M.F. Brin); Swedish Neuroscience Institute, Seattle, WA, USA (S.K. Aurora); Thomas Jefferson University, Philadelphia, PA, USA (S.D. Silberstein); Albert Einstein College of Medicine, Bronx, NY, USA (R.B. Lipton); Department of Neurology, University of Essen, Germany (H.-C. Diener); Department of Neurology, University of California, Irvine, CA, USA (M.F. Brin).

Funding: Allergan, Inc.

ClinicalTrials.gov identifiers: NCT00156910, NCT00168428.

Address all correspondence to D.W. Dodick, Mayo Clinic, Scottsdale – Neurology, Department of Neurology, 13400 East Shea Blvd, Scottsdale, AZ 85259, USA.

Accepted for publication March 22, 2010.

Tab. 1 Definition einer chronischen Migräne im PREEMPT-Studienprogramm. (Nach [4, 7, 8])
Ausgewählte Ein- und Ausschlusskritierien
Mindestens 15 Kopfschmerztage im Monat mit jeweils mindestens 4 Kopfschmerzstunden am Tag
An mindestens 50% der Kopfschmerztage sind die ICHD-II-Kriterien einer Migräne ohne Aura, einer Migräne mit typischer Aura oder einer wahrscheinlichen Migräne erfüllt.
Kein Vorliegen einer Migränekomplikation (mit Ausnahme der chronischen Migräne), einer Migräne vom Basilaristyp, einer hemiplegischen oder ophthalmoplegischen Migräne
Kein Vorliegen eines pausenlosen Dauerkopfschmerzes
Ausschluss eines chronischen Kopfschmerzes vom Spannungstyp, einer Hemicrania continua oder eines neu aufgetretenen täglichen Kopfschmerzes („new daily persistent headache") bzw. eines sekundären Kopfschmerzes
Ein eventueller Medikamentenübergebrauch, definiert über eine Einnahme von Kopfschmerzakutmedikation an mindestens 10 Tagen/Monat, war zugelassen.
ICHD Internationale Kopfschmerzklassifikation.

H Göbel, A Heinze; Prophylaxe der chronischen Migräne mit Botulinumtoxin Typ A; Der Schmerz 5/2011:563-571

Tab. 2 Therapieoptionen bei chronischer Migräne

Option	Empfehlungsstärke/Evidenz	Dosierungen
Botulinumtoxin A	A ↑	155–195 Einheiten Botox®/3 Monate
Topiramat	B ↑	50–100 mg/Tag
Valproinsäure	B ↔	500–1000 mg/Tag
Amitriptylin	B ↔	25–75 mg/Tag
β-Blocker (Metoprolol, Propranolol)	B ↔	50–150 mg/Tag
Flunarizin	B ↔	5–10 mg/Tag
Periphere Nervenstimulation, N. occipitalis	In klinischen Studien	

H Göbel, A Heinze; Prophylaxe der chronischen Migräne mit Botulinumtoxin Typ A; Der Schmerz 5/2011:563-571

Injektionsorte mit Dosierung

an 31 klar definierten Stellen in 7 Muskel werden

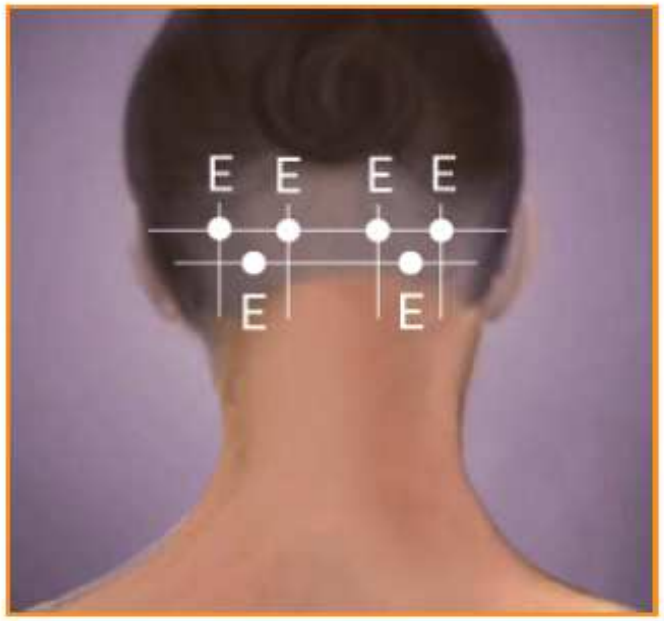
155 U Botulinum Toxin Typ A oder Plazebo appliziert

+ ggf 40 U zusätzlich in 3 weiteren Muskelgruppen

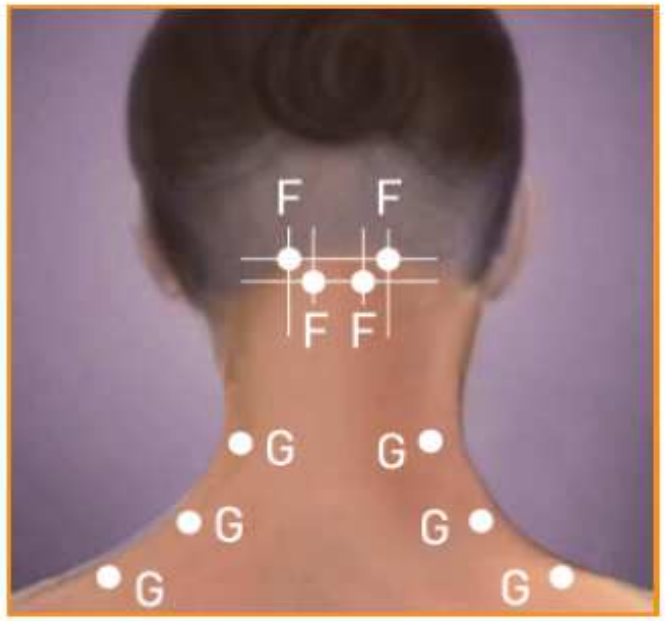
Maximale Dosis 195 U

Verdünnung: 100 U in NaCl (2 ml)

Sitting



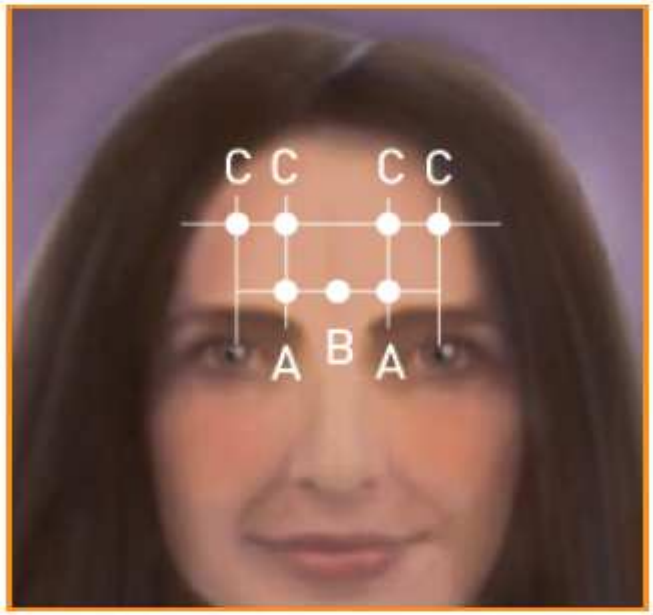
E. Occipitalis
FSFD: 30 U (in 6 sites)
FTP: 5 U/site (in ≤2 additional sites)

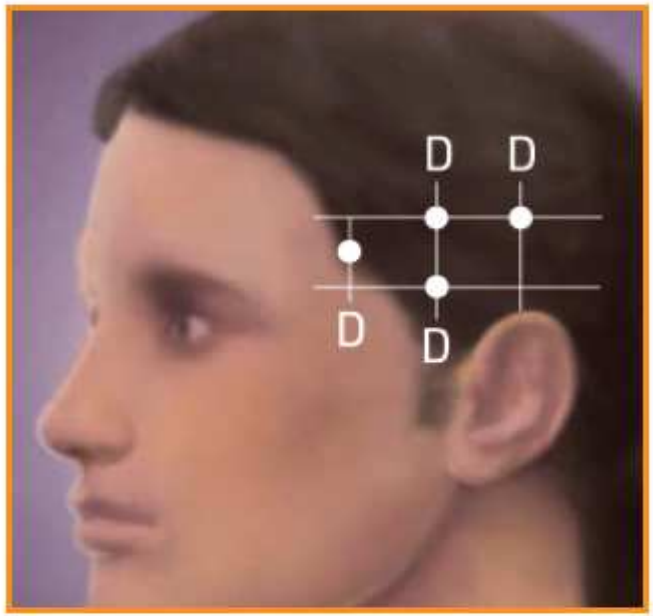


F. Cervical paraspinal
FSFD: 20 U (in 4 sites)

G. Trapezius
FSFD: 30 U (in 6 sites)
FTP: 5 U/site (in ≤4 additional sites)

Supine





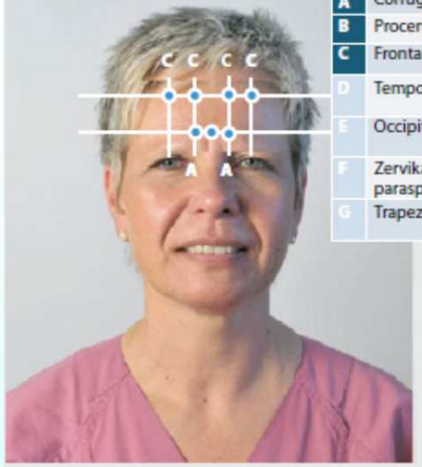
A. Corrugator
FSFD: 10 U (in 2 sites)

B. Procerus
FSFD: 5 U (in 1 site)

C. Frontalis
FSFD: 20 U (in 4 sites)

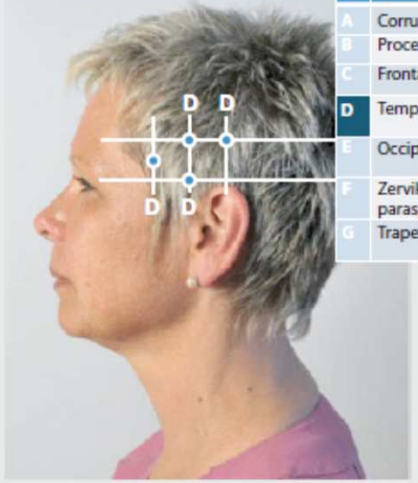
D. Temporalis
FSFD: 20 U (in 4 sites)
FTP: 5 U/site (in ≤2 additional sites)

a



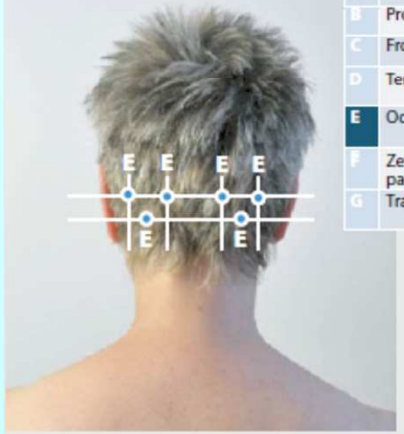
	Muskel	Einheiten (Orte je Seite)	Optionale Einheiten (Orte)
A	Corrugator	10 (1)	–
B	Procerus	5	–
C	Frontalis	20 (2)	–
D	Temporalis	40 (3)	10 (bis zu 2)
E	Occipitalis	30 (3)	10 (bis zu 2)
F	Zervikal paraspinal	20 (2)	–
G	Trapezius	30 (3)	20 (bis zu 4)

b



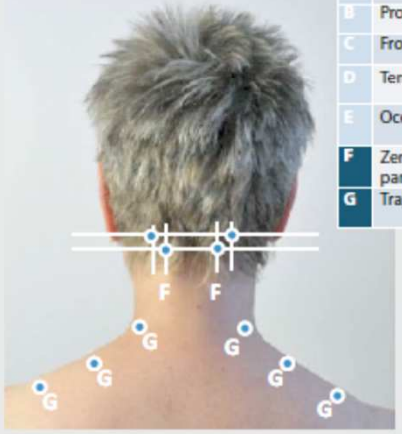
	Muskel	Einheiten (Orte je Seite)	Optionale Einheiten (Orte)
A	Corrugator	10 (1)	–
B	Procerus	5	–
C	Frontalis	20 (2)	–
D	Temporalis	40 (3)	10 (bis zu 2)
E	Occipitalis	30 (3)	10 (bis zu 2)
F	Zervikal paraspinal	20 (2)	–
G	Trapezius	30 (3)	20 (bis zu 4)

c



	Muskel	Einheiten (Orte je Seite)	Optionale Einheiten (Orte)
A	Corrugator	10 (1)	–
B	Procerus	5	–
C	Frontalis	20 (2)	–
D	Temporalis	40 (3)	10 (bis zu 2)
E	Occipitalis	30 (3)	10 (bis zu 2)
F	Zervikal paraspinal	20 (2)	–
G	Trapezius	30 (3)	20 (bis zu 4)

d



	Muskel	Einheiten (Orte je Seite)	Optionale Einheiten (Orte)
A	Corrugator	10 (1)	–
B	Procerus	5	–
C	Frontalis	20 (2)	–
D	Temporalis	40 (3)	10 (bis zu 2)
E	Occipitalis	30 (3)	10 (bis zu 2)
F	Zervikal paraspinal	20 (2)	–
G	Trapezius	30 (3)	20 (bis zu 4)

H Göbel, A Heinze; Prophylaxe der chronischen Migräne mit Botulinumtoxin Typ A; Der Schmerz 5/2011:563-571

PREEEMPT 1 & 2 pooled data Analyse

Migränetage

Tage mit mittelstarken /starken KS

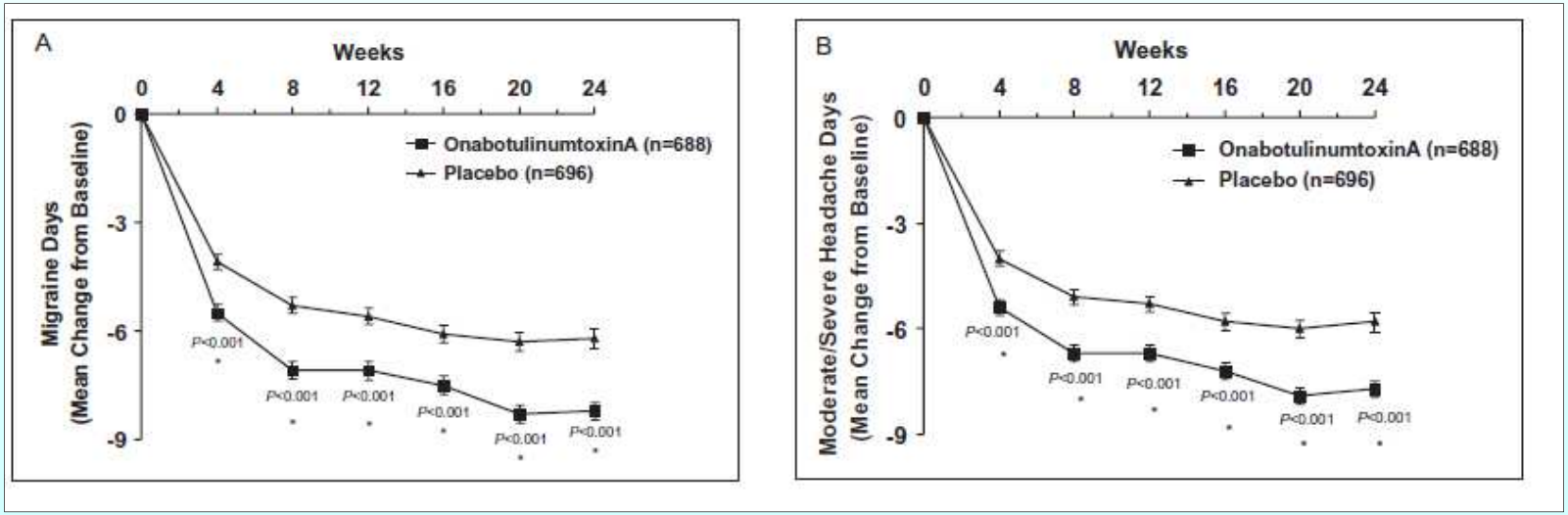
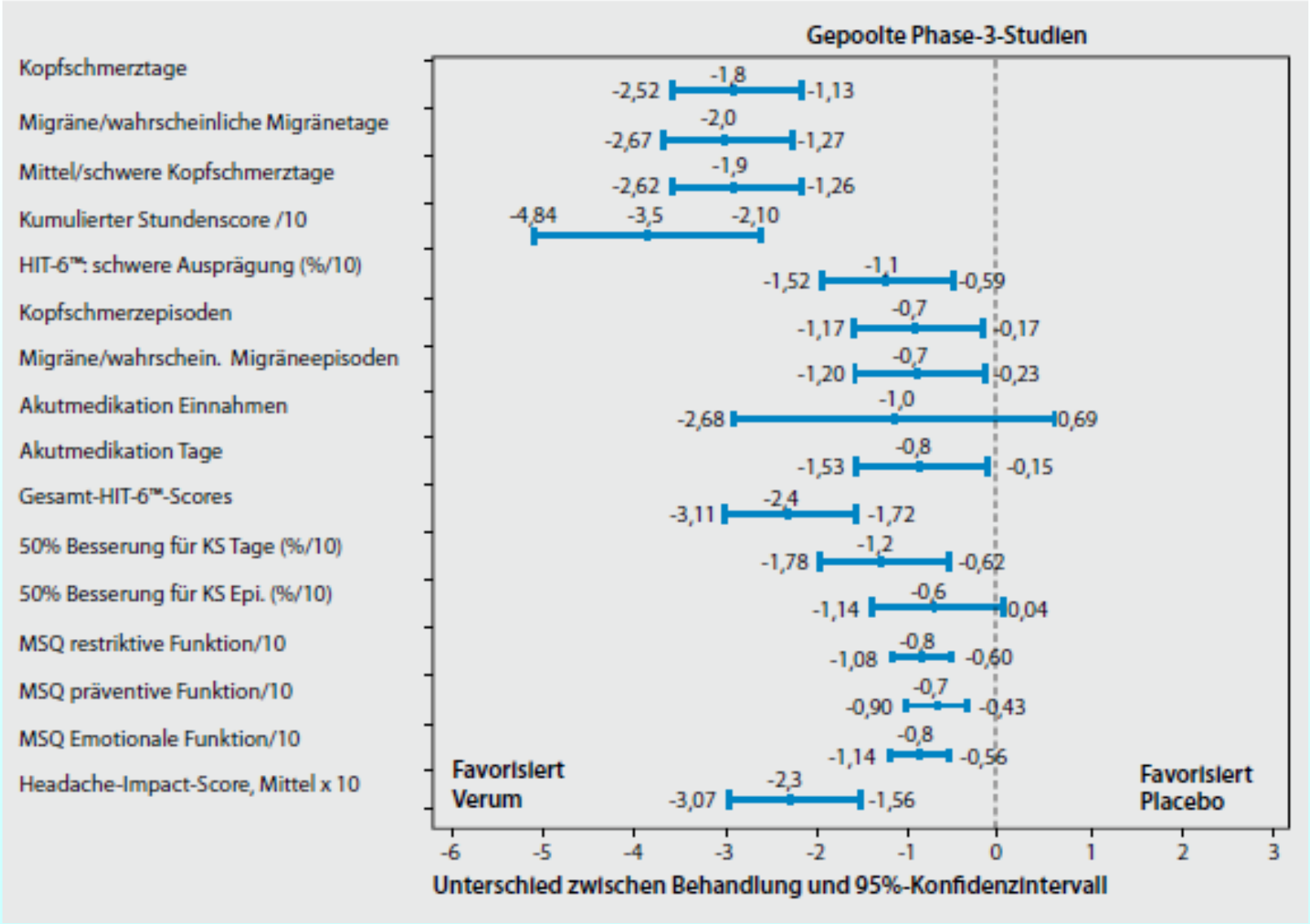


Fig 3.—Secondary efficacy variables per 28 days. (A) Mean change from baseline in frequency of migraine days. Migraine days at baseline: 19.1 0.2 onabotulinumtoxinA group versus 18.9 0.2 placebo group, *P = .328.* (B) Mean change from baseline in frequency of moderate/severe headache days. Moderate/severe headache days at baseline: 18.1 0.2 onabotulinumtoxinA group versus 18.0 0.2 placebo group, *P = .705.*



H Göbel, A Heinze; Prophylaxe der chronischen Migräne mit Botulinumtoxin Typ A; Der Schmerz 5/2011:563-571

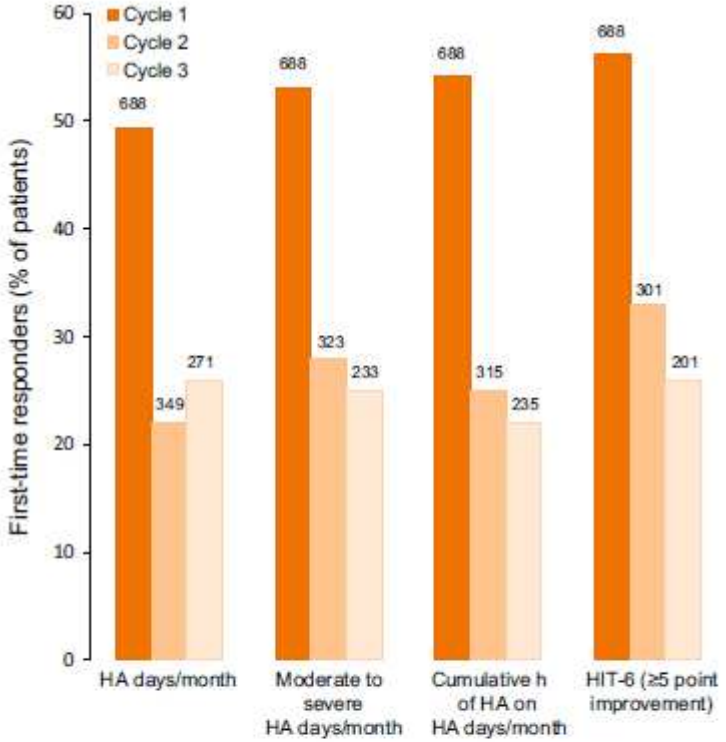


Fig. 1 Proportion of onabotulinumtoxinA-treated patients who responded (with a ≥ 50% improvement from baseline in the headache symptom or impact assessment indicated) for the first time after treatment cycles 1, 2 and 3 in the pooled PREEMPT trials [52]. For each assessment, the maximum possible number of first-time responders in the cycle indicated is shown above the bar. *HA* headache, *HIT*-6 Headache Impact Test-6

Frampton J. E. et al.; OnabotulinumtoxinA: A Review in the Prevention of Chronic Migraine: CrossMark (2018) 78:589-600.

Onabotulinumtoxin A

- **In einer randozmisierten Untersuchung wurde Onabotulinumtoxin A 155-195 Units oder Plazebo-Injektionen alle 12 Wochen durchgeführt. Die gepoolten PREEMPT-Ergebnisse zeigten, dass Onabotulinumtoxin A eine effektive prophylaktische Behandlung ist für chronische Migräne. Onabotulinumtoxin A bewirkt eine signifikante Verbesserung verglichen mit Plazebo bei verschiedenen Kopfschmerzsymptomen und reduziert signifikant kopfschmerzbezogene Disability und verbessert die Funktion der Vitalität und die gesundheitsbezogene Lebensqualität. Wiederholte Behandlungen mit Onabotulinumtoxin A sind sicher und werden gut toleriert.**

Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, Lipton RB, Diener HC, Brin MF; PREEMPT Chronic Migraine Study Group; OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program; Headache 2010 Jun;50(6):921-36. Epub 2010 May 7

Zusammenfassung

- **nach 24 Wochen zeigten die Patienten der Verum Gruppe signifikant stärkere Reduktion der KS- und Migräne tage (-8,4 versus -6,6)**
- **HIT-6-Score nahm in der Verum Gruppe ab (- 5 versus - 2 Punkte)**
- **Abnahme der kumulativen KS Stunden pro Monat (-120 versus -80 h)**
- **Unerwünschte Nebenwirkungen traten unter Verum bei 62% gegenüber 52% bei Placebo auf.**

Table 2. Information for selected studies.

Author (Year)	Sample Size	Botulinum Toxin	Total Dose Per Session	Injection Place	Main Outcome
De Ru et al. (2011) [11]	10	BTX-A (Botox, Allergan)	25 U	corrugator supercilii muscle	90% of patients had a drastically lowered pain score post-operatively
De Ru et al. (2008) [12]	10	BTX-A	25 U	corrugator supercilii muscle	All patients had less pain for approximately two months
Erdemoglu et al. (2007) [13]	28	BTX-A (Botox, Allergan)	45–75 U	frontalis, splenius capitis, trapezius, occipitalis, temporalis muscle	Headache frequency was found to be significantly reduced
Pihut et al. (2016) [14]	42	BTX-A (Botox, Allergan)	42 U	masseter muscle	A decrease in the number of referred pain episodes and a decrease in pain in the temporal region
Straube et al. (2008) [15]	125	BTX-A (Dysport, Ipsen Beaufour)	210–420 U	trapezius, splenius, temporalis, frontalis, corrugator muscles	Decreased headache episode number in a group receiving 420 U of BTX-A
Mathew et al. (2007) [16]	82	BTX-A (Botox, Allergan)	100 U	procerus, corrugator, frontalis, temporalis, occipitalis, suboccipitalis muscles	A greater percentage of patients with chronic migraine responded to botox than patients with CTTH
Dowson et al. (2008) [17]	24	BTX-A (Botox, Allergan)	30–100 U	bilaterally at the site of the first trigeminal nerve and the rest of the dose to follow the pain in the cervical area	Significant improvements in headache-related disability, pain and emotional function, headache frequency and medication use
Hamdy et al. (2008) [18]	28	BTX-A (Botox, Allergan)	100 U	frontalis, temporalis, sternocleidomastoideus, trapezius, splenius capitis, semispinalis muscles	Significant improvement after 1 month of BTX-A injection regarding headache days/month
Venancio et al. (2009) [19]	45	BTX-A	25 or 50 U	trigger points	Significant improvement after injection regarding headache days/month
Schroeder et al. (2012) [20]	5 (children)	BTX-A (Botox, Allergan)	20–90 U	splenius, trapezius, semispinalis, scalenius muscles	In the long-term follow up, headache did not exist in any of patients
Harden et al. (2008) [21]	32	BTX-A	25–100 U	trapezius, sternocleidomastoid, splenius capitis muscles	Reduction of headache intensity over time did not differ significantly when compared to the control group

BTX beim Spannungskopfschmerz

- **Individuelle Muskelauswahl erfolgreicher**
- **Höhere Dosierungen im Vergleich zur Migräne erforderlich (100 u Botox,Xeomin 300 u Dysport)**
- **Untersuchung von Subgruppen (mit perikranieller Verspannung, Mischkopfschmerz)**
- **Bislang therapieresistente Patienten**

Gupta VK. Botulinum toxin – a treatment for migraine? A systematic review. Pain Med 2006;7(5):386-94. (+/-)

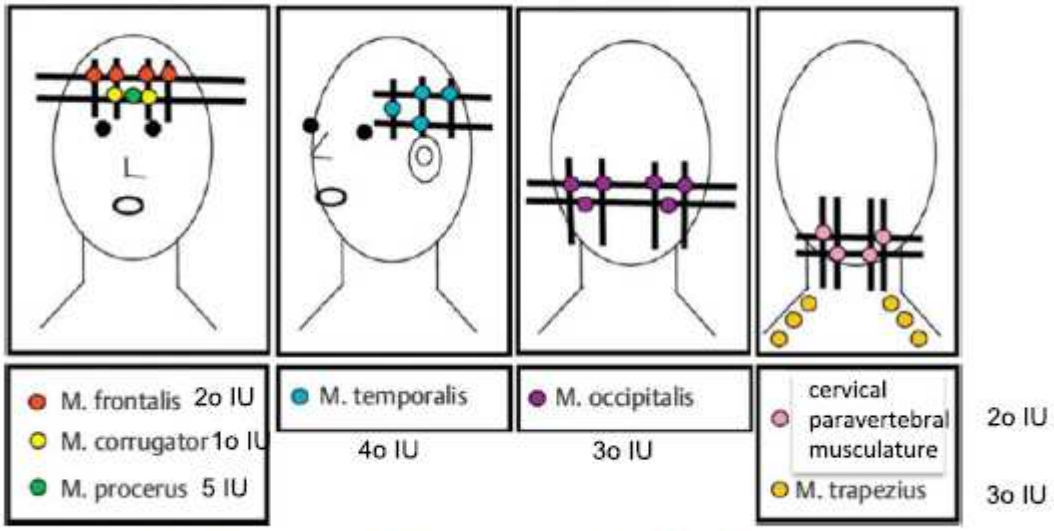


Fig. 1 Injection procedure of OnabotulinumtoxinA according to the PREEMPT study protocol

Lampl C. et al.; OnabotulinumtoxinA in the treatment of refractory chronic cluster headache: The Journal of Headache and Pain (2018) 19:45.

Table 1 Demographic details, medication used to manage CCH before enrolment in the study

patients ID	triptans	oxygen	mid analgesics	Verapamil (mg)		Lithium (mg)*		Propranolol (mg)*		Amitriptyline (mg)*		Topiramate (mg)*		Corticosteroids (mg)**
				hd	ld	hd	ld	hd	ld	hd	ld	hd	ld	
1	✓	12 l	✓	480	480	X	X	120	80	X	X	200	200	25
2	✓	15 l	✓	480	480	450	X	120	80	?	10	100	100	X
3	✓	15 l	✓	600	480	450	X	120	X	X	X	200	200	X
4	✓	15 l	✓	600	240	X	X	120	X	75	75	100	X	X
5	✓	12 l	✓	720	480	X	X	80	40	X	X	100	X	75
6	✓	12 l	✓	240	240	900	450	240	X	25	25	X	X	10
7	✓	12 l	✓	840	480	X	240	X	X	10	X	100	100	50
8	✓	10 l	✓	480	480	X	X	40	X	X	X	100	100	X
9	✓	12 l	✓	600	X	450	X	80	X	?	X	100	X	50
10	✓	15 l	✓	240	240	450	X	120	X	25	X	X	X	50
11	✓	15 l	✓	480	240	450	450	X	X	X	X	100	100	X
12	✓	15 l	✓	480	480	X	X	120	X	X	X	100	100	50
13	✓	15 l	✓	600	600	X	X	40	X	X	X	200	200	25
14	✓	15 l	✓	600	X	450	X	X	X	?	X	150	X	X
15	✓	12 l	✓	600	480	450	X	X	X	X	X	200	200	X
16	✓	15 l	✓	240	240	450	450	X	X	X	X	100	100	25
17	✓	10 l	✓	720	X	450	X	?	X	X	X	200	200	X

l = litre; hd = highest dosage used; ld = last dosage used before enrolled in the study; mg = milligram; ✓□ = used; X = not used; ? = not known; ** no longer than 1 month

Lampl C. et al.; OnabotulinumtoxinA in the treatment of refractory chronic cluster headache: The Journal of Headache and Pain (2018) 19:45.

Table 2 Demographic details, headache scores pre- and post- treatment with OnabotulinumtoxinA

patients ID	duration/y	baseline		treatment phase					patient subjective estimate of response %[b]
		frequency d/mo	duration min	week 12		week 24		improvement %[b]	
				frequency d/mo[a]	sum of min/ bout[a]	frequency d/mo[a]	sum of min bout[a]		
1	7	30	2.250	17	1.755	14	1.320	41.3	50
2	4	25	1.632	8	337	0	0	100	90–100
3	3	28	1.328	11	472	7	221	83.3	60–70
4	5	29	2.598	0	0	0	0	100	100
5	5	30	3.148	12	1.065	8	531	83.1	75
6	5	30	1.912	8	867	5	312	83,6	70
7	9	28	2.491	12	1.289	7	1.333	46.4	50
8	7	30	1.870	8	473	6	328	82.4	70–80
9	7	25	1.140	13	833	11	618	45.8	50
10	4	27	3.456	14	2.855	12	1.565	54.7	50
11	3	30	1.080	30	1.418	30	1.377	0	0
12	3	30	3.020	16	1.844	14	813	73	50
13	3	30	2.280	29	2.065	30	2.555	0	0
14	6	28	1.680	0	0	0	0	100	100
15	4	27	2.479	18	1.349	22	1.662	32,9	20–30
16	2	30	3.040	17	1.364	14	839	72.4	50–70
17	5	23	1.855	21	989	20	1.200	35,3	20
Mean	5	28.2	2.192	13.8	1.117	11.8	863	62	
median	5	29	2.250	13.5	1.065	11	813	62	
(range)	(2–9)	(23–30)	(1.080–3.148)	(0–30)	(0–2.855)	(0–30)	(0–2.555)	(0–100)	

pre = before treatment (=baseline), *y* = year; *mo* = month, *w* = week, *d* = day, *min* = minutes; [a] = mean of every 4 weeks over past 12 weeks;
[b] = baseline vs week 24

Table 3 Headache-associated disability scores pre- and post- treatment with OnabotulinumtoxinA

	HIT- 6 (36–76)			HADS - A (0–21)			HADS - D (0–21)		
patients ID	pre	w 24	change in score	pre	w 24	change in score	pre	w 24	change in score
1	70	50	20	18	15	3	8	6	2
2	58	36	22	15	9	6	12	8	4
3	67	47	20	17	15	2	15	12	3
4	76	42	34	15	6	9	6	3	3
5	78	58	20	15	12	3	9	4	5
6	58	52	6	11	8	3	10	3	7
7	63	58	5	13	11	2	10	7	3
8	63	42	21	13	12	1	8	2	6
9	57	42	13	12	11	1	12	11	1
10	78	68	10	11	12	-1	11	9	2
11	65	68	−3	13	15	−2	14	15	−1
12	68	57	11	11	12	−1	11	5	6
13	65	65	0	18	21	−3	16	16	0
14	56	36	20	12	6	6	4	0	4
15	53	57	−4	14	12	2	15	12	3
16	68	54	14	14	9	5	12	9	3
17	76	72	4	12	11	1	14	11	3
Mean (95% CI)	65.8	53.1	−12.7 (−21.3; −1.8)	13.8	11.6	−2.2 (−6.1; −0.1)	11.0	7.8	−3.2 (−8.2; −0.1)
median (range)	65 (53–78)	54 (36–72)	13 (− 3–34)	13 (11–18)	12 (6–21)	2 (− 2–9)	11 (6–16)	8 (0–16)	3 (− 1–7)

pre = before treatment (=baseline), *w* = week; *HIT-6* = Headache Impact Test, *HADS*=Hospital Anxiety and Depression Scale, *A* = anxiety, *D* = depression

Lampl C. et al.; OnabotulinumtoxinA in the treatment of refractory chronic cluster headache: The Journal of Headache and Pain (2018) 19:45.

- **Für chronische tägliche Kopfschmerzen gibt es konsistenten Ergebnisse durch plazebo-kontrollierte randomisierte Studien für die Verwendung von Botulinumtoxin. Es scheint wenn man Sub-Gruppen analysiert, dass Patienten identifiziert werden können, die einen Benefit haben von Botulinumtoxin und in diesem Kontext scheint eine Subgruppe von Patienten mit explosiven Kopfschmerzenqualität und Allodynie ein wichtiger Prädiktor für die Effektivität von Botulinumtoxin zu sein.**

Stefan Evers; Review of botulinum toxin type a for the prophylactic treatment of chronic daily headache; Neuropsychiatric Disease and Treatment 2007:3(6) 761-764

Schlussfolgerung

- **Topiramat und Onabotulinumtoxin A zeigt signifikante Effektivität in der Behandlung von Patienten mit chronischer Migräne.**
- **Ergebnisse zeigen, dass Onabotulinumtoxin A eine nutzvolle Therapie für Patienten mit frequenter Migräne ist.**

Cady R MD, Schreiber C MD, Porter J MD, Blumenfeld A MD, Farmer K; A Multi-Center Double-Blind Pilot Comparison of OnabotulinumtoxinA and Topiramate for the Prophylactic Treatment of Chronic Migraine; Headache 2011;51:21-32

Botulinumtoxin in der Kopfschmerzbehandlung Muskelauswahl

Anamnese

- Wo beginnt der Schmerz?
- Wo ist der Schmerz lokalisiert?
- Wie haben Sie auf Muskelrelaxantien angesprochen?
- Wie haben Sie auf PT/physikal. Maßnahmen reagiert?
- Wurden Sie bereits mit Lokalanästhetika infiltriert?
- Welche Faktoren können zu Nackenverspannungen führen (Stress, Bildschirm, Auto)?

Botulinumtoxin in der Kopfschmerzbehandlung Muskelauswahl

➢ Inspektion und Palpation

- **Besteht eine schmerzbedingte Schonhaltung?**
- **Besteht eine unwillkürliche Bewegungsstörung?**
- **Finden sich verdickte, verquollene Muskeln?**
- **Besteht eine eingeschränkte Kopfbeweglichkeit und welche Muskeln sind verkürzt?**
- **Wo finden sich lokale Schmerz- oder Triggerpunkte?**

Nebenwirkungen

Muskelparesen bei Überdosierung

Schwächung benachbarter Muskeln

Indikationsabhängig können vereinzelt auftreten:

- **Doppelbilder (Blepharospasmus)**
- **Schluckstörungen (Torticollis)**
- **Blasenstörungen (Beinspastik)**

Lokale allergische Reaktionen

Grippeähnliche Symptome

Unerwünschte Wirkungen bei Schmerzbehandlungen

Übliche Nebenwirkungen einer intramuskulären Injektion (Hämatome)

Myofasziale Schmerzen (HWS)

Schwächung der Kopfhaltemuskulatur

Epicondylitis

Schwächung der Hand-, Fingermuskulatur

selten, bei sorgfältiger Auswahl der Muskeln und Dosierungen

kurzzeitig und reversibel

Therapiekontrolle

Wirkung der Therapie nach 2 - 4 Wochen kontrollieren

Nachinjektion frühestens nach 12 Wochen

da die Wirkung sonst schwer steuerbar ist

da kurze Injektionsintervalle zu Sekundärresistenzen

durch Bildung von Antikörpern führen können

Benötigte Materialien

Einmalhandschuhe

Hautdesinfektionsmittel (z. B. Octenisept®, Cutasept®-farblos)

Isotone Kochsalzlösung (0,9% NaCl)

Spritzen:

5 ml

1 ml (Tuberkulin-Spritzen)

Einmalkanülen:

20 Gauge (Sterican)

27 Gauge (1 1/2“, Ø 0,4 x 40 mm)

(Sterican Einmal-Dentalkanülen)

Immunität

Neutralisierende Antikörper gegen Btx-A

können zu einem Verlust der Wirkung führen

(Sekundärresistenz)

kurze Injektionsintervalle und höhere Dosen

bei Cervikaler Dystonie > 150 U

(bei Verwendung von Xeomin®)

fördern die Bildung von Antikörpern

deshalb:

so hoch wie nötig, so niedrig wie möglich dosieren

Injektionsintervall von 3 Monaten einhalten

Dosierung Dysport-500 U/Xeomin-Botox 100 U

Verdünnung mit 4 ml

12,5 U pro 0,1 ml/ 2,5 U pro 0,1ml

Verdünnung mit 2 ml

25 U pro 0,1 ml/ 5 U pro 0,1ml

Indikationen

- **Schmerztherapie**
  - **Myofasziale Verspannungen**
  - **Triggerpunktbehandlung**
  - **Kopfschmerz (Spannungskopfschmerz, Migräne)**
  - **cervikogener Kopfschmerz**
  - **Epikondylitis**
  - **Piriformissyndrom**
  - **Hüftadduktion**
  - **Tibialis posterior Syndrom**
  - **Scalenus-anterior**
  - **Stumpfschmerz**
  - **Fibromyalgie ?**

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TABLE 5
Therapeutic uses for botulinum neurotoxin

Ophtalmology
- Strabismus[a,b,c]
- Nistagmus

Neurology
- Focal Dystonias
  - Blepharospasm[a,b,c]
  - Cervical dystonia[a,b,c] (Torticollis, anterocollis, laterocollis)
  - Occupational dystonias (writer's cramp[b], musician's cramps)
  - Laryngeal Dysphonia[c]
  - Oromandibular dystonia
  - Lingual dystonia
- Nondystonic disorders
  - Hemifacial spasm[a,b,c]
  - Tremor (essential, parkinsonism)
  - Tics
  - Bruxism
- Spasticity (poststroke, multiple sclerosis, brain or spinal cord injury)
  - Focal spasticity[a,b,c]: Upper and lower limb spasticity
  - Nonfocal: hemispasticity, paraspasticity, tetraspasticity
  - Cerebral palsy[a,b]
- Hyperhidrosis[a,b,c]
  - Focal: axillary, palmar, plantar
  - Diffuse
- Hypersalivation
  - Sialorrhea[b] (motoneuron diseases/amyotrophic lateral sclerosis)
  - Drooling[b] (Parkinsonian syndromes)
  - Frey's syndrome/gustatory sweating
- Aesthetic (muscle)
  - Glabellar rythides[a,b,c]

Pain
- Muscular
  - Dystonia
  - Spasticity
  - Chronic myofascial pain
  - Temporomandibular disorders
  - Low back pain
- Nonmuscular
  - Migraine (chronic[a] and tension type migraine)
  - Neuropathic pain
  - Trigeminal pain
  - Pelvic pain

Urology
- Detrusor sphincter dyssynergia
- Overactive bladder[a,b,c] (Idiopathic or neurogenic detrusor overactivity)
- Urinary retention
- Bladder pain syndrome
- Pelvic floor spasms
- Benign prostate hyperplasia

Gastroenterology
- Achalasia
- Chronic anal fissures

Psychiatry
- Depression[d]

[a]USA approved indication.
[b]EU approved indication.
[c]Evidence-based therapeutic indication.
[d]To be evaluated.

Pirazzini M. et al.; Botulinum Neurotoxins: Biology, Pharmacology, and Toxicology: Pharmacological Reviews (2017), 69:200-235.

Therapeutische Anwendungen von BoNT (Auswahl)[2]

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Spasmen der Skelettmuskulatur
Fokale Dystonien
Blepharospasmus*
Hemifaziale Spasmen*
Zervikale und **oromandibulare Dystonien*** (**Torticollis** u. Ä.)
Laryngeale Dysphonie (Stimmbandkrampf)
Bewegungsabhängige Krämpfe (Schreibkrampf)
Skelettmuskelspasmen aufgrund von neurologischen Erkrankungen*
Kosmetische Indikation: **unerwünschte Falten im oberen Gesichtsbereich***
Strabismus*
Spasmen glatter Muskulatur, hyperaktive cholinerge autonome Innervation
Neurogene Detrusor-Hyperaktivität, überaktive Blase*
Achalasie, diffuser Ösophagusspasmus
Hyperhidrosis axillaris*, chronische Sialorrhoe*
Schmerzsyndrome
Chronische Migräne*
Spannungskopfschmerz, kraniomandibuläre Dysfunktion
Osteoarthritis großer Gelenke
Interstitielle Zystitis, Vestibulodynie
Post-Zoster-Neuralgie, spinale Radikulopathie
Myofasziale Schmerzen

Erklärungen: fett: in Ö zugelassene Indikationen, * von FDA zugelassen[17]

Holzer U, Donnerer J. Botulinum-Neurotoxin in der Schmerztherapie. Schmerznachrichten Nr. 3, Sept. 2021. S. 40-44.

2 Pirazzini M, Rossetto O, Eleopra R, Montecucco C. Botulinum Neurotoxins: Biology, Pharmacology, and Toxicology. Pharmacol Rev. 2017; 69:200-235
17 Kedlaya D. Botulinum Toxin. MEDSCAPE. 2019, https://emedicine.medscape.com/article/325451 (abgerufen am 3. 2. 2021)

Welche Antwort trifft zu?

- **Botulinumtoxin ist indiziert bei Migräne**
- **Botulinumtoxin ist indiziert bei Spannungs-kopfschmerz**
- **Botulinumtoxin ist indiziert bei myofascialem Schmerz**
- **Botulinumtoxin ist indiziert bei Fibromyalgie**

Welche Antwort trifft zu?

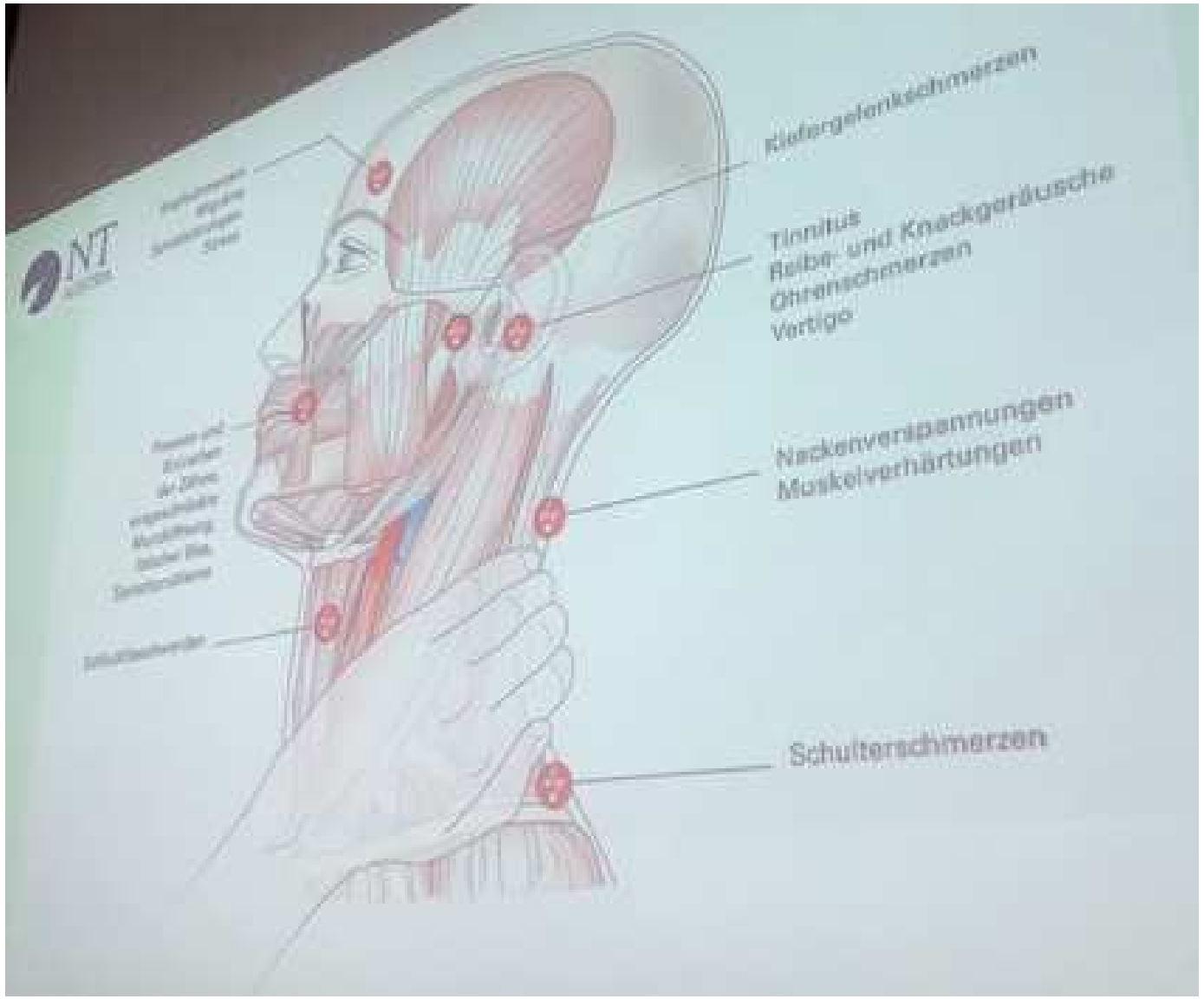
- **Botulinumtoxin wirkt sofort**
- **Wirkdauer 3 – 6 Monate**
- **in der Anwendung im Niedrigdosisbereich bei Migräne ist es toxisch**
- **Botulinumtoxin ist kontraindiziert bei Myasthenia gravis**

Welche Antwort trifft zu?

- **Triggerpunkte und Tenderpoints sind ident**
- **Triggerpunkt löst primär Schmerzsituation aus**
- **Triggerpunkt löst übertragenen Schmerz aus**
- **Triggerpunkt ist gekennzeichnet durch hohen Druckschmerz im verspanntem Muskelbereich**

Welche Antwort trifft zu?

- **Nachinjektion von Botulinumtoxin kann man nach einer Woche durchführen**
- **Nachinjektion von Botulinumtoxin frühestens nach 12 Wochen**
- **Kurze Intervalle führen nicht zu Sekundär-resistenzen**
- **Kurze Intervalle führen zu Sekundärresistenzen**


Kiefergelenkschmerzen
Tinnitus
Reibe- und Knackgeräusche
Ohrenschmerzen
Vertigo
Nackenverspannungen
Muskelverhärtungen
Schulterschmerzen

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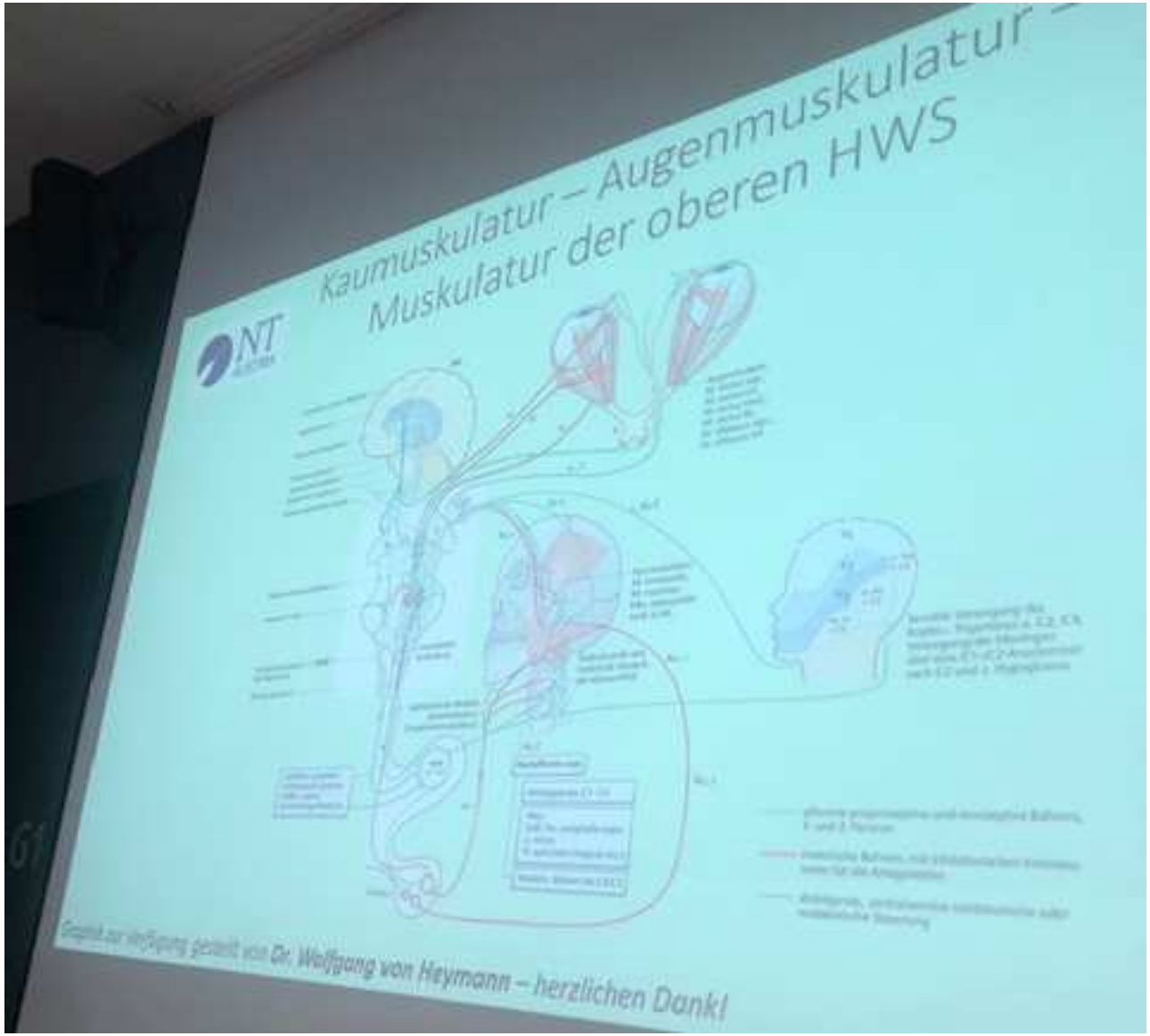

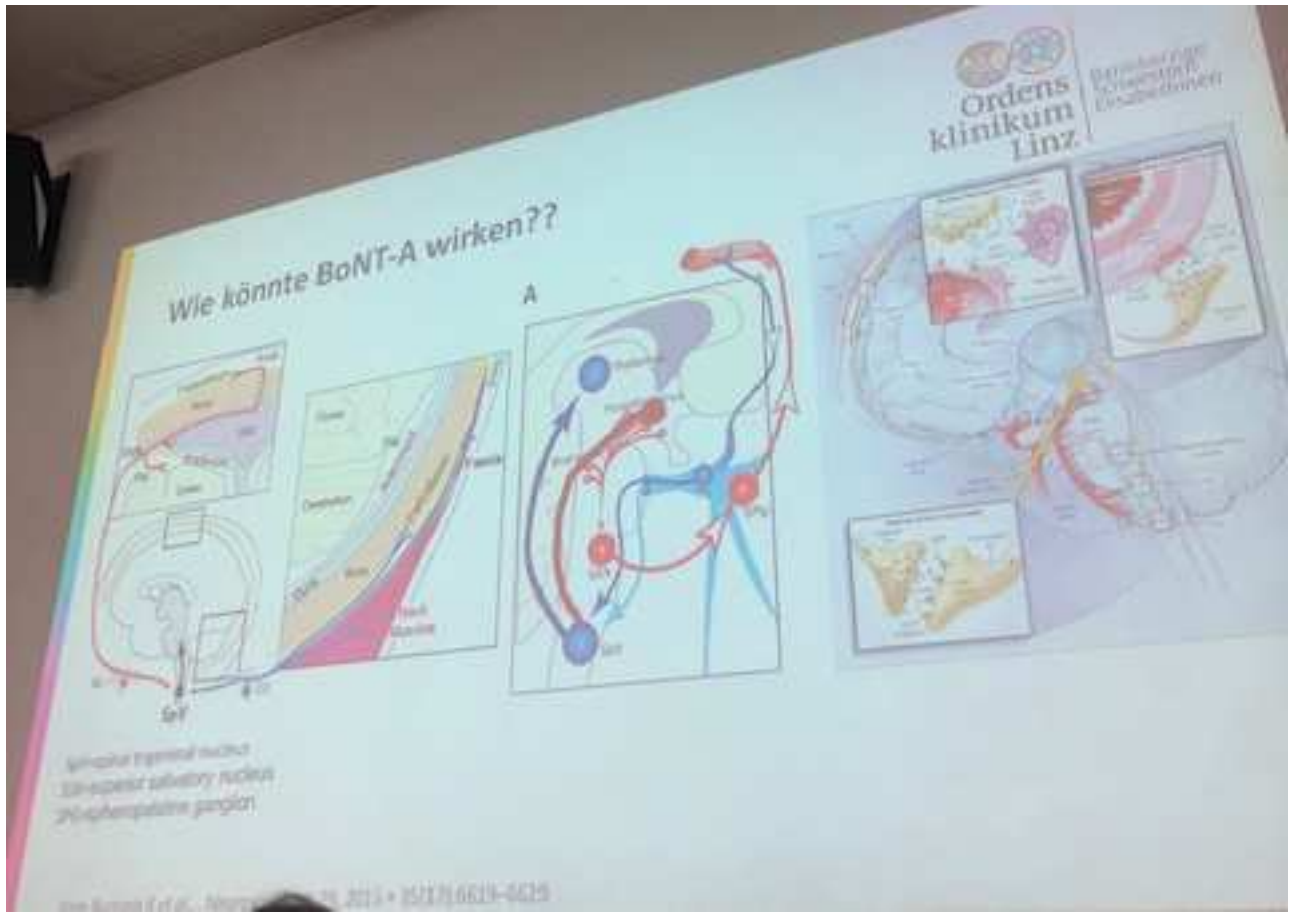
Wie könnte BoNT-A wirken??
A
Ordens klinikum Linz

Table 1 Efficacy of intramuscular onabotulinumtoxinA (Botox®) for prevention of headaches in adults with chronic migraine. Intent-to-treat results from the multicentre PREEMPT 1 [38] and 2 [39] studies and pooled analyses [40, 41, 49] of these trials

	Week 24[a]						Week 56[a]	
	PREEMPT 1 [38]		PREEMPT 2 [39]		Pooled analysis [40, 41, 49]		Pooled analysis [41]	
	OnabotA (n = 341)	PL (n = 338)	OnabotA (n = 347)	PL (n = 358)	OnabotA[b] (n = 688)	PL[b] (n = 696)	OnabotA → onabotA[b] (n = 688)	PL → onabotA[b] (n = 696)
HA days/month[c]	− 7.8**	− 6.4	− 9.0***[d]	− 6.7[d]	− 8.4***[d]	− 6.6[d]	− 11.7*[d]	− 10.8[d]
Moderate to severe HA days/month[c]	− 7.2**	− 5.8	− 8.3***	− 5.8	− 7.7***	− 5.8	− 10.7*	− 9.9
Cumulative h of HA on HA days/month[c]	− 106.7**	− 70.4	− 132.4***	− 90.0	− 119.7***	− 80.5	− 169.1*	− 145.7
HA episodes/month[c]	− 5.2[d]	− 5.3[d]	− 5.3**	− 4.6	− 5.2**	− 4.9	− 7.4	− 7.5
Migraine days/month[c,e]	− 7.6**	− 6.1	− 8.7***	− 6.3	− 8.2***	− 6.2	− 11.2*	− 10.3
Migraine episodes/month[c]	− 4.8	− 4.9	− 4.9**[f]	− 4.2[f]	− 4.9**	− 4.5	− 6.8	− 7.0
Acute HA pain medication intakes/month[c]	− 10.3	− 10.4	− 9.9	− 8.4	− 10.1	− 9.4	− 15.4	− 15.7
Acute HA pain medication intake days/month[c]	− 5.7[f]	− 5.8[f]	− 6.4***[f]	− 4.8[f]	− 6.1*	− 5.3	− 8.4	− 8.5
Triptan medication intakes/month[c]	− 3.3*	− 2.5	− 3.0***	− 1.7	− 3.2***	− 2.1	− 4.2	− 3.8
HIT-6 score[c,g]	− 4.7***	− 2.4	− 4.9***	− 2.4	− 4.8***	− 2.4	− 7.7	− 7.0
Pts with severe HIT-6 score[g] (%)	68.9***	79.9	66.3**	76.5	67.6***	78.2	50.6	51.9
MSQ RR subscale score[c,h]	16.8***[f]	8.8[f]	17.2***[f]	8.4[f]	17.0***	8.6	25.2*	21.8
MSQ RP subscale score[c,h]	12.6**[f]	7.6[f]	13.5***[f]	5.4[f]	13.1***	6.4	19.0	17.3
MSQ EF subscale score[c,h]	16.9***[f]	10.0[f]	19.0***[f]	9.1[f]	17.9***	9.5	25.0	22.1

EF emotional functioning, *HA* headache, *HIT-6* Headache Impact Test-6, *MID* minimal important difference, *MSQ* Migraine-Specific Quality-of-Life Questionnaire (v2.1), *OnabotA* onabotulinumtoxinA, *PL* placebo, *pts* patients, *RP* role preventive, *RR* role restrictive

*$p < 0.05$, **$p < 0.01$, ***$p \leq 0.001$ vs (corresponding) PL

[a]Results at week 24 (end of the double-blind phase) and week 56 (end of the open-label phase) were assessed over a 4-week period ending at week 24 and week 56, respectively

[b]Of the 688 pts originally randomized to onabotA in the double-blind phase, 607 entered the open-label phase (and continued to receive onabotA). Of the 696 pts originally randomized to PL in the double-blind phase, 629 entered the open-label phase (and crossed over to receive onabotA)

[c]Mean change from baseline (week 0) (values at baseline were assessed over the prior 4-week period)

[d]Primary efficacy endpoint

[e]Definite or probable migraine days or episodes

[f]Data derived from the Medicines and Healthcare Products Regulatory Agency UK public assessment report [37]

[g]Score of ≥ 60 indicates a severe impact. The established clinically meaningful MID (between-group) is 2.3; the established clinically meaningful MID from baseline (within-group) is − 5

[h]On a 0–100 scale, with higher scores indicating better health-related quality of life. The established clinically meaningful MIDs (between-group) are 3.2, 4.6 and 7.5 for the RR, RP and EF subscales, respectively; the established clinically meaningful MIDs from baseline (within-group) are 10.9, 8.3 and 12.2 for the RR, RP and EF subscales, respectively

Frampton J. E. et al.; OnabotulinumtoxinA: A Review in the Prevention of Chronic Migraine: CrossMark (2018) 78:589-600.

(Fig. 1). Furthermore, 71 (26%) of the 271 onabotA-treated patients who did not demonstrate a $\geq$ 50% decrease in the monthly frequency of headache days after the first and second cycles did reach this endpoint after the third cycle (Fig. 1). Similar results were seen for other key outcomes (Fig. 1) [52].

Frampton J. E. et al.; OnabotulinumtoxinA: A Review in the Prevention of Chronic Migraine: CrossMark (2018) 78:589-600.

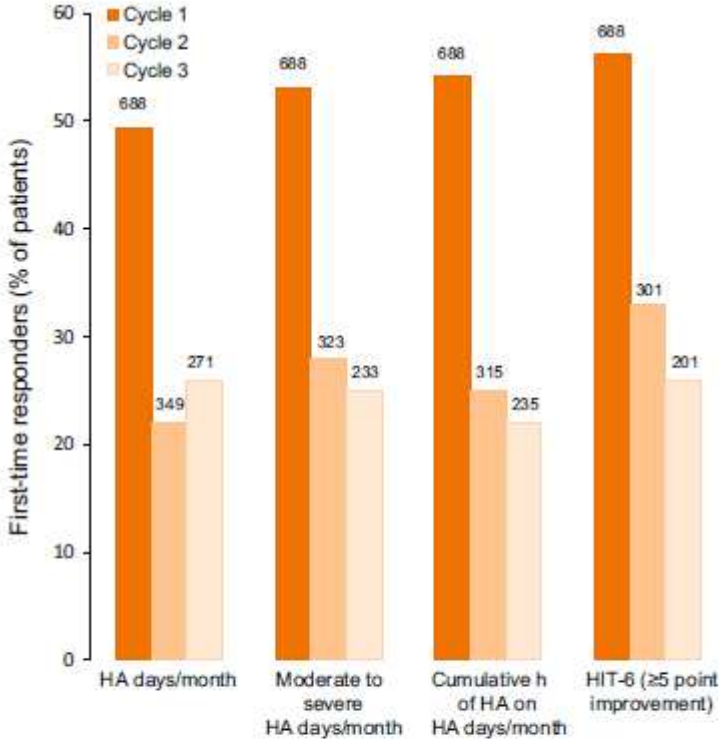

Fig. 1 Proportion of onabotulinumtoxinA-treated patients who responded (with a ≥ 50% improvement from baseline in the headache symptom or impact assessment indicated) for the first time after treatment cycles 1, 2 and 3 in the pooled PREEMPT trials [52]. For each assessment, the maximum possible number of first-time responders in the cycle indicated is shown above the bar. *HA* headache, *HIT*-6 Headache Impact Test-6

Frampton J. E. et al.; OnabotulinumtoxinA: A Review in the Prevention of Chronic Migraine: CrossMark (2018) 78:589-600.

Table 1 BoNT preparations and FDA-approved indications

BoNT preparation	Brand name (manufacturer)	FDA-approved indications[a]
OnabotulinumtoxinA	Botox (Allergan, Inc., Irvine, CA)	Blepharospasm, CD, upper extremity spasticity, lower extremity spasticity, CM
AbobotulinumtoxinA	Dysport (Ipsen Ltd., Paris, France)	CD, upper extremity spasticity
IncobotulinumtoxinA	Xeomin (Merz Pharmaceuticals, Frankfurt, Germany)	Blepharospasm, CD, upper extremity spasticity
RimabotulinumtoxinB	Myobloc Neurobloc (US WorldMeds/Solstice Neurosciences, Louisville, KY)	CD

Abbreviations: BoNT = botulinum neurotoxin; CD = cervical dystonia; CM = chronic migraine; FDA = Food and Drug Administration.
[a] FDA approvals relevant to this review.

Simpson D. M. et al.; Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: American Academy of Neurology 2016, 1818-1826.

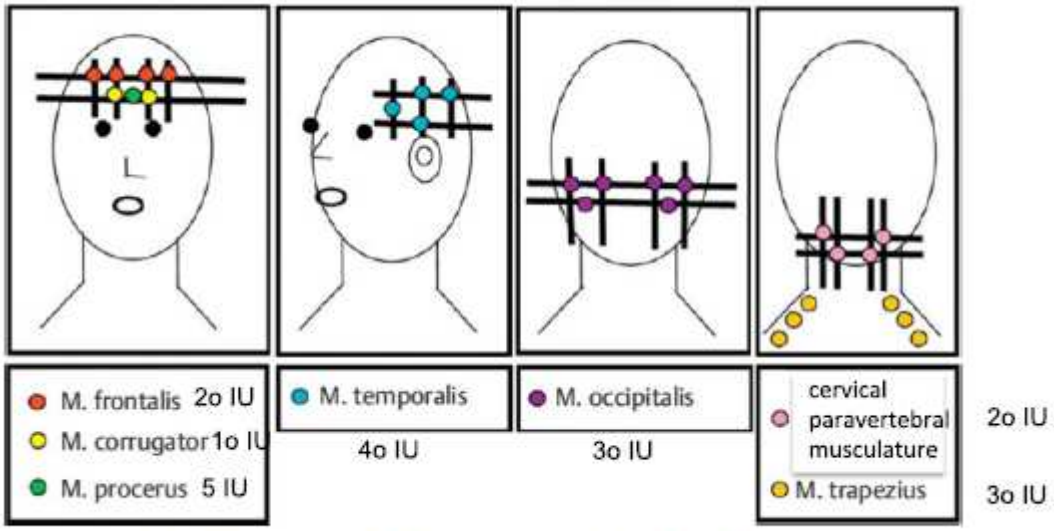

Fig. 1 Injection procedure of OnabotulinumtoxinA according to the PREEMPT study protocol

Lampl C. et al.; OnabotulinumtoxinA in the treatment of refractory chronic cluster headache: The Journal of Headache and Pain (2018) 19:45.

Table 1 Demographic details, medication used to manage CCH before enrolment in the study

patients ID	triptans	oxygen	mid analgesics	Verapamil (mg)		Lithium (mg)*		Propranolol (mg)*		Amitriptyline (mg)*		Topiramate (mg)*		Corticosteroids (mg)**
				hd	ld	hd	ld	hd	ld	hd	ld	hd	ld	
1	✓	12 l	✓	480	480	X	X	120	80	X	X	200	200	25
2	✓	15 l	✓	480	480	450	X	120	80	?	10	100	100	X
3	✓	15 l	✓	600	480	450	X	120	X	X	X	200	200	X
4	✓	15 l	✓	600	240	X	X	120	X	75	75	100	X	X
5	✓	12 l	✓	720	480	X	X	80	40	X	X	100	X	75
6	✓	12 l	✓	240	240	900	450	240	X	25	25	X	X	10
7	✓	12 l	✓	840	480	X	240	X	X	10	X	100	100	50
8	✓	10 l	✓	480	480	X	X	40	X	X	X	100	100	X
9	✓	12 l	✓	600	X	450	X	80	X	?	X	100	X	50
10	✓	15 l	✓	240	240	450	X	120	X	25	X	X	X	50
11	✓	15 l	✓	480	240	450	450	X	X	X	X	100	100	X
12	✓	15 l	✓	480	480	X	X	120	X	X	X	100	100	50
13	✓	15 l	✓	600	600	X	X	40	X	X	X	200	200	25
14	✓	15 l	✓	600	X	450	X	X	X	?	X	150	X	X
15	✓	12 l	✓	600	480	450	X	X	X	X	X	200	200	X
16	✓	15 l	✓	240	240	450	450	X	X	X	X	100	100	25
17	✓	10 l	✓	720	X	450	X	?	X	X	X	200	200	X

l = litre; hd = highest dosage used; ld = last dosage used before enrolled in the study; mg = milligram; ✓□ = used; X = not used; ? = not known; ** no longer than 1 month

Lampl C. et al.; OnabotulinumtoxinA in the treatment of refractory chronic cluster headache: The Journal of Headache and Pain (2018) 19:45.

Table 2 Demographic details, headache scores pre- and post- treatment with OnabotulinumtoxinA

patients ID	duration/y	baseline		treatment phase					patient subjective estimate of response %[b]
		frequency d/mo	duration min	week 12		week 24		improvement %[b]	
				frequency d/mo[a]	sum of min/ bout[a]	frequency d/mo[a]	sum of min bout[a]		
1	7	30	2.250	17	1.755	14	1.320	41.3	50
2	4	25	1.632	8	337	0	0	100	90–100
3	3	28	1.328	11	472	7	221	83.3	60–70
4	5	29	2.598	0	0	0	0	100	100
5	5	30	3.148	12	1.065	8	531	83.1	75
6	5	30	1.912	8	867	5	312	83,6	70
7	9	28	2.491	12	1.289	7	1.333	46.4	50
8	7	30	1.870	8	473	6	328	82.4	70–80
9	7	25	1.140	13	833	11	618	45.8	50
10	4	27	3.456	14	2.855	12	1.565	54.7	50
11	3	30	1.080	30	1.418	30	1.377	0	0
12	3	30	3.020	16	1.844	14	813	73	50
13	3	30	2.280	29	2.065	30	2.555	0	0
14	6	28	1.680	0	0	0	0	100	100
15	4	27	2.479	18	1.349	22	1.662	32,9	20–30
16	2	30	3.040	17	1.364	14	839	72.4	50–70
17	5	23	1.855	21	989	20	1.200	35,3	20
Mean	5	28.2	2.192	13.8	1.117	11.8	863	62	
median	5	29	2.250	13.5	1.065	11	813	62	
(range)	(2–9)	(23–30)	(1.080–3.148)	(0–30)	(0–2.855)	(0–30)	(0–2.555)	(0–100)	

pre = before treatment (=baseline), *y* = year; *mo* = month, *w* = week, *d* = day, *min* = minutes; [a] = mean of every 4 weeks over past 12 weeks;
[b] = baseline vs week 24

Table 3 Headache-associated disability scores pre- and post- treatment with OnabotulinumtoxinA

	HIT- 6 (36–76)			HADS - A (0–21)			HADS - D (0–21)		
patients ID	pre	w 24	change in score	pre	w 24	change in score	pre	w 24	change in score
1	70	50	20	18	15	3	8	6	2
2	58	36	22	15	9	6	12	8	4
3	67	47	20	17	15	2	15	12	3
4	76	42	34	15	6	9	6	3	3
5	78	58	20	15	12	3	9	4	5
6	58	52	6	11	8	3	10	3	7
7	63	58	5	13	11	2	10	7	3
8	63	42	21	13	12	1	8	2	6
9	57	42	13	12	11	1	12	11	1
10	78	68	10	11	12	-1	11	9	2
11	65	68	−3	13	15	−2	14	15	−1
12	68	57	11	11	12	−1	11	5	6
13	65	65	0	18	21	−3	16	16	0
14	56	36	20	12	6	6	4	0	4
15	53	57	−4	14	12	2	15	12	3
16	68	54	14	14	9	5	12	9	3
17	76	72	4	12	11	1	14	11	3
Mean (95% CI)	65.8	53.1	−12.7 (−21.3; −1.8)	13.8	11.6	−2.2 (−6.1; −0.1)	11.0	7.8	−3.2 (−8.2; −0.1)
median (range)	65 (53–78)	54 (36–72)	13 (− 3–34)	13 (11–18)	12 (6–21)	2 (− 2–9)	11 (6–16)	8 (0–16)	3 (− 1–7)

pre = before treatment (=baseline), *w* = week; *HIT-6* = Headache Impact Test, *HADS*=Hospital Anxiety and Depression Scale, *A* = anxiety, *D* = depression

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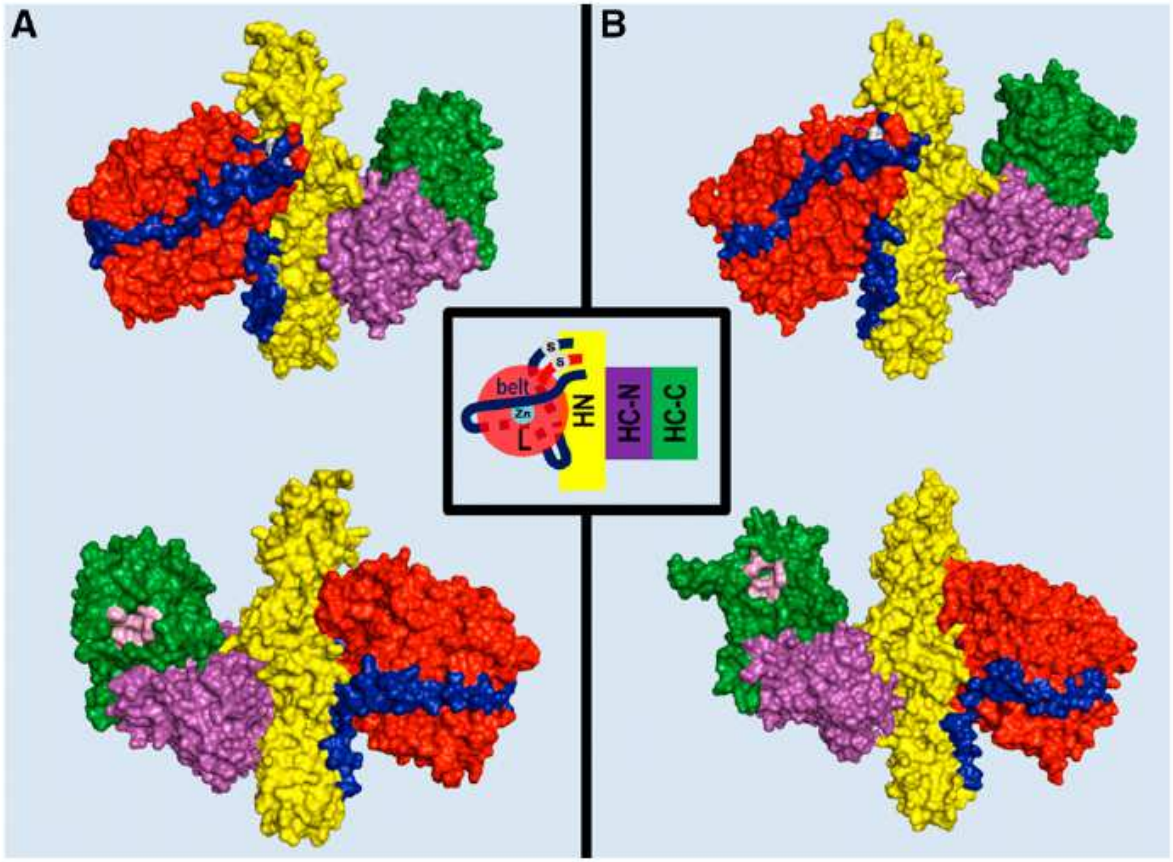

Fig. 1. Structure of BoNT/A1 and BoNT/B1 molecules. Crystal structures of BoNT/A1 (PDB ID: 3BTA) (Lacy et al., 1998) (A) and BoNT/B1 (PDB ID: 1EPW) (Swaminathan and Eswaramoorthy, 2000) (B) represented as space-filling models of the two opposite surfaces of each toxin molecule showing the organization of the three toxin domains: the neurospecific binding HC-C subdomain (green), the lectin-like HC-N subdomain (purple), the translocation HN domain (yellow), and the metalloprotease L domain (red). The pink cavity in the HC-C subdomains shown in the lower panels is the polysialoganglioside binding site. A peptide belt (shown in blue) surrounding the L domain and the interchain disulfide bond (white in the upper panels) linking the L and HN domain, which stabilize the structure, is also shown.

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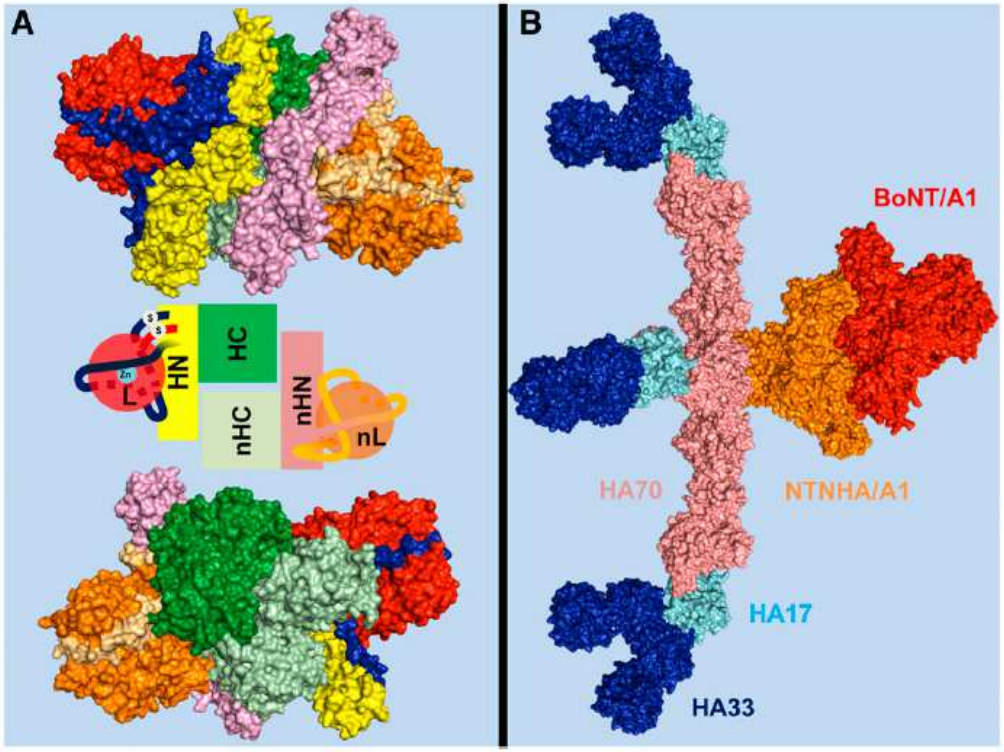

Fig. 2. Structure of BoNTA1-NTNHA1 heterodimer and of the progenitor toxin complex (PTC). (A) Crystal structure of BoNT/A1 in complex with the NTNHA/A1 protein (PDB ID: 3V0B) (Gu et al., 2012) represented as space-filling models of the two opposite surfaces. For BoNT/A1, the L chain is in red, the HN domain is in yellow, and in green the HC domain. The BoNT/A1 protein binds "hand in hand" the NTNHA/A1 protein whose domain structure and organization are very similar to that of the toxin (see central inset for a simplified scheme). For NTNHA/A1 nL is in orange, nHN in pink, and nHC in light green. In blue and in light orange are the belts of toxin and NTNHA, respectively. Notice that NTNHA/A1 shields a large part of the BoNT surface. A similar structure has been determined for BoNT/E1 (PDB ID: 4ZKT) (Eswaramoorthy et al., 2015). (B) Space-filling representation of the large precursor toxin complex (PTC), which has a triskelion-like structure (Amatsu et al., 2013; Lee et al., 2013). BoNT/A1 (red) interacts with NTNHA/A1 (orange) but has no contacts with HA proteins. There are six HA33 proteins (blue), three HA17 proteins (light blue), and three HA70 proteins (pink) in each NTNHA/A1-BoNT/A1 complex. Because the HA proteins do not contact the BoNT/A1 molecule, they are unlikely to play any protective role on BoNT/A1, as previously proposed. Rather, the structure suggests a role as adhesin molecule (see text). Similar structures have been determined for BoNT/D and BoNT/B1 using single particle electron microscopy (Benefield et al., 2013; Hasegawa et al., 2007). The structure of (B) was assembled by joining the structure of the BoNT/A1-NTNHA/A1 heterodimer (PDB ID: 3V0B) and the structure of the triskelion (PDB ID: 3WIN).

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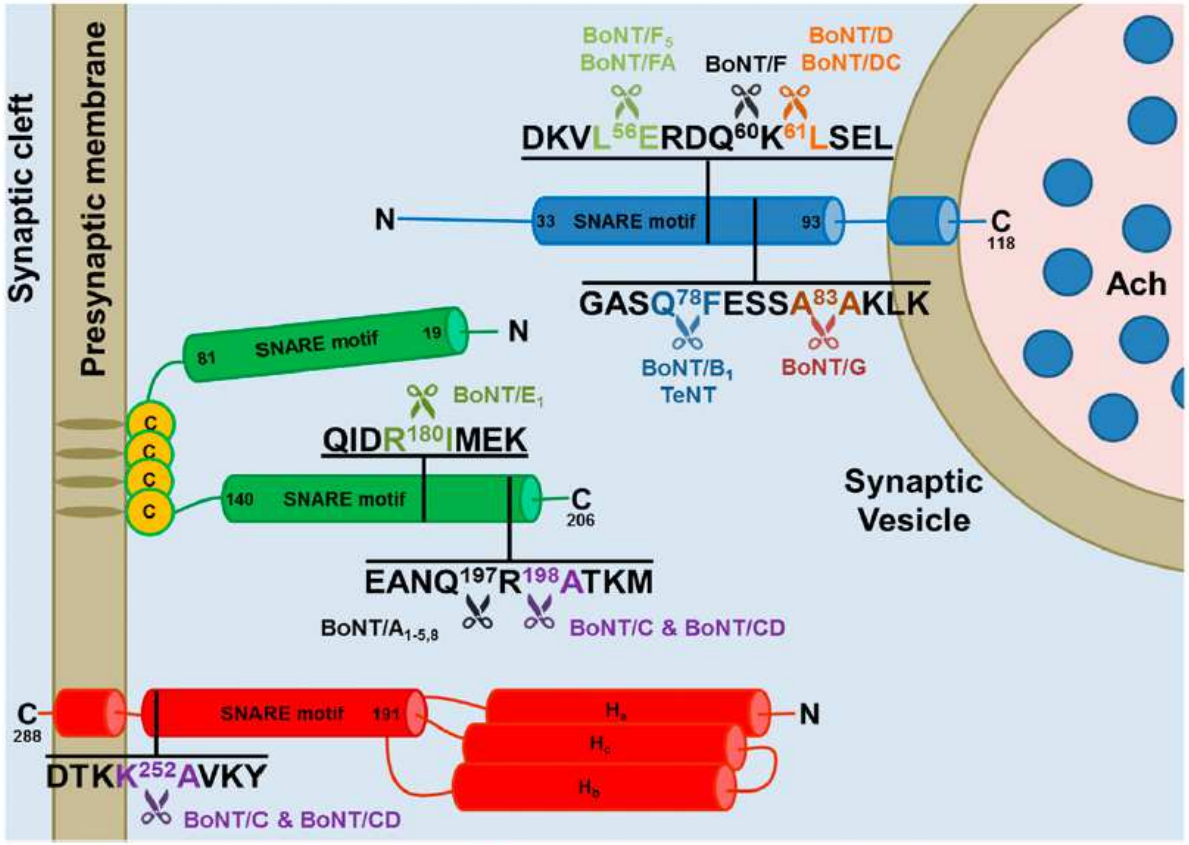

Fig. 3. Cleavage sites of the neuronal SNARE proteins by the different BoNT types and subtypes. The BoNT proteolytic activity is highly specific and directed toward unique peptide bonds within the sequence of their respective SNARE protein targets. VAMP of the synaptic vesicle (in blue, isoform 1 is shown here) or SNAP-25 (in green) or syntaxin (in red, isoform 1B is shown here) mainly localized on the cytosolic side of the presynaptic membrane. Available evidence indicate that all the toxin subtypes and chimeric toxins cleave the same SNARE substrate, although different subtypes may cleave different peptide bonds. For example BoNT/F5 and BoNT/FA, a chimeric toxin derived from a genetic recombination between BoNT/F2, /F5, and A1 neurotoxin genes, cleave VAMP at a peptide bond different from the one cleaved by BoNT/F1. Notice that tetanus neurotoxin and botulinum B1 neurotoxin cleave the same target at the same site proving that the different symptoms of tetanus and botulism are not due to a different target molecule, but to different neuronal targets: the Renshaw cells of the spinal cord for tetanus neurotoxin and peripheral nerve terminals for BoNT/B1.

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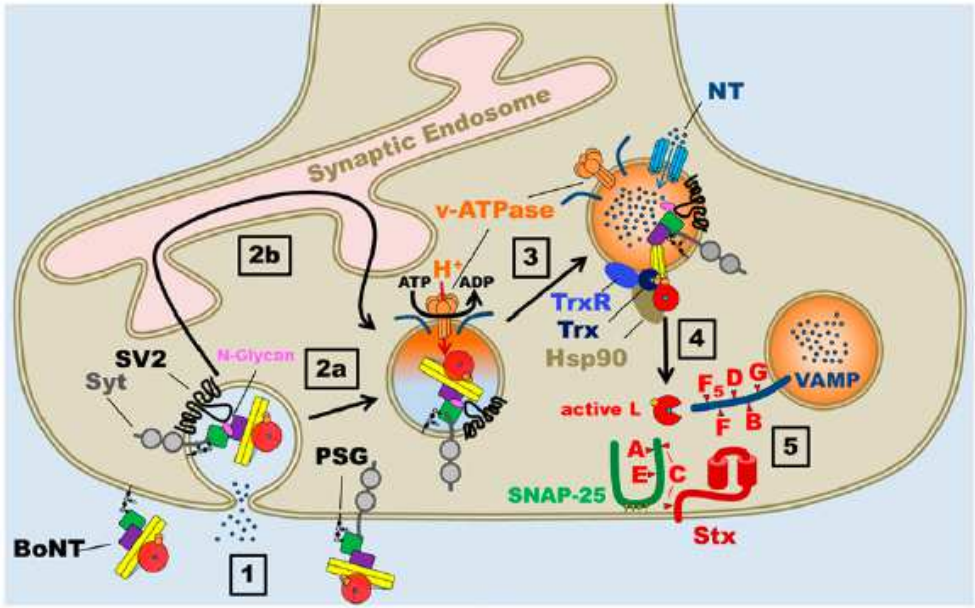

Fig. 4. The nerve terminal intoxication by botulinum neurotoxins is a multi-step process. The first step (1) is the binding of the HC domain (green) to a polysialoganglioside (PSG) receptor of the presynaptic membrane (gray and black), followed by binding to a protein receptor. The currently known protein receptors are *i*) synaptotagmin (Syt, gray) for BoNT/B1, /DC, and /G; *ii*) glycosylated SV2 (black with its attached N-glycan in pink) for BoNT/A1 and /E1. Syt may be located either within the exocytosed synaptic vesicle or on the presynaptic membrane. The BoNT is then internalized inside SVs, which are directly recycled (2a) or inside SVs that fuse with the synaptic endosome and re-enter SV cycle by budding from this intermediate compartment (2b). The acidification (orange) of the vesicle, operated by the v-ATPase (orange), drives the accumulation of neurotransmitter (blue dots) via the vescicular neurotransmitter transporter (light blue). The protonation of BoNT leads to the membrane translocation of the L chain into the cytosol (3), which is assisted by the HN domain (yellow). The L chain (red) is released from the HN domain by the action of the thioredoxin reductase-thioredoxin system (TrxR-Trx, blue and dark blue) and Hsp90 (mud color), which reduce the interchain disulfide bond (orange) and avoid the aggregation of the protease (4). In the cytosol, the L chain displays its metalloprotease activity: BoNT/B, /D, /F, /G cleave VAMP (blue); BoNT/A and BoNT/E cleave SNAP-25 (green); and BoNT/C cleaves both SNAP-25 and syntaxin (Stx, dark red) (5). Each of these proteolytic events is sufficient to cause a prolonged inhibition of neurotransmitter release with consequent neuroparalysis.

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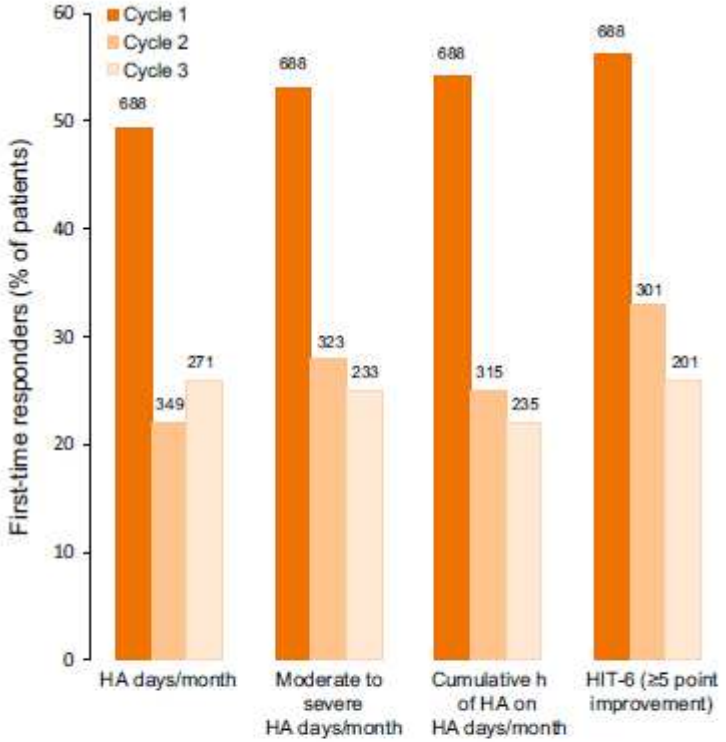

Fig. 1 Proportion of onabotulinumtoxinA-treated patients who responded (with a ≥ 50% improvement from baseline in the headache symptom or impact assessment indicated) for the first time after treatment cycles 1, 2 and 3 in the pooled PREEMPT trials [52]. For each assessment, the maximum possible number of first-time responders in the cycle indicated is shown above the bar. *HA* headache, *HIT*-6 Headache Impact Test-6

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