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TOXINS 2019

International Neurotoxin Association

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PEER-REVIEWED CONFERENCE REPORT

ASPIRE: High Patient and Clinician Satisfaction

Onabotulinum toxin A treatment helps manage spasticity: According to the 1-year interim data from the ASPIRE study, most patients were "extremely satisfied" or "satisfied" with onabotulinum toxin A therapy.

read more on PAGE 8

Investigational Product Gives Hope

Daxibotulinum toxin A injections may provide long-lasting improvement in patients suffering from cervical dystonia as indicated by data from an open-label, dose-escalating phase 2 study.

read more on PAGE 11

SIAXI Data Led to FDA Approval

Sialorrhea can be effectively reduced by incobotulinum toxin A injections without impairing speech or swallowing abilities.

read more on PAGE 12

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Editor Prof. Nadine Attal, INSERM U-987 and University Versailles Saint Quentin, France

Contents

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Letter from the Editor

Prof. Nadine Attal

Dear Reader,

The 2019 edition of the International Neurotoxin Association Conference (Toxins 2019) was recently held in Copenhagen, Denmark and was extremely well attended and received with more than 1,400 participants from 61 countries. The scientific programme featured top speakers, stimulating discussions, and scientific breakthroughs. The articles presented in this conference report provide a very good overview of the plenaries and workshops and cover major innovative developments in basic sciences, clinical research, and treatment applications in the field of botulinum toxins. More specifically, the topics presented in this report include the well established use of botulinum toxins in spasticity and cervical dystonia with emphasis on recent clinical trials and treatment algorithms, the more recently established efficacy of botulinum toxin A in chronic migraine, but also new promising applications in peripheral neuropathic pain and in Parkinson disease with regards to tremor and sialorrhea. Novel versions of botulinum toxins are also largely covered.

I am confident that these various and balanced presentations illustrate the high quality and dynamism of preclinical and clinical research in the field of botulinum toxins and will be of great interest to all medical doctors and researchers interested in botulinum toxins and their applications.

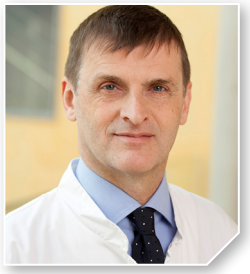
Enjoy reading

Nadine Attal

Biography

Nadine Attal, MD, PhD, is Professor of Therapeutics and Pain in University Versailles Saint Quentin, France and responsible for the Center of Evaluation and Treatment of Pain in Ambroise Paré Hospital, Boulogne-Billancourt. She is also a member of the INSERM U-987 Research Unit on Pain directed by Didier Bouhassira. Her research activity mainly focuses on neuropathic pain and pain management. She has coordinated several international guidelines on neuropathic pain and authored more than 140 peer-reviewed papers in high impact factor journals (H index 50). She is a Council member of the International Association for the Study of Pain and of the the French Society of Pain and member of the scientific committee of the European Academy of Neurology. She has been appointed knight (« Chevalier de la légion d'honneur ») in 2016.

Conflict of Interest Statement:
Nadine Attal has disclosures with Sanofi Pasteur MSD, MSD, Grunenthal, Aptynix, and Ipsen, unrelated to this conference, in the past 36 months (scientific advice or speakers bureau).



Incobotulinum toxin A for patients with sialorrhea

Interview with
Prof. Wolfgang Jost, MD, PhD,
conducted on 18 February 2019 by Dr Yvette Zwick

In his presentation at the TOXINS 2019 convention in Copenhagen, Prof. Jost (Parkinson-Klinik Ortenau, Germany) covered the topic of hypersalivation. Last year, incobotulinum toxin A was the only botulinum toxin preparation in the USA to receive approval for sialorrhea without restrictions on the underlying cause.

Are neurotoxins the gold standard for treatment of patients with sialorrhea? Would you also recommend any other drug?
Botulinum toxin injections are most likely the most efficacious and the least side effect-associated therapeutic option. Anticholinergics such as glycopyrrolate may also be used but are currently not approved and are, of course, associated with side effects due to their systemic effects.

Did it take long to enroll 184 patients when initiating the SIAXI trial or is sialorrhea a rather common phenomenon?
Sialorrhea is a common symptom, particularly in patients with Parkinson's disease. Recruiting patients was never a problem because the afflicted suffer tremendously. Due to the extraordinary therapeutic success, patients willingly participated, staying on to the end of the study.

How long does it take until one learns the injection technique? What is the greatest danger (worst side effect) of a poor injection technique?
The injection technique is easy to learn. Thanks to ultrasound guidance, the salivary glands can be well identified. The main problem of poor injection technique would be a lack of efficacy. In case of targeting the submandibular gland, there would also be the potential danger of dysphagia. With ultrasound guidance, however, this shouldn't happen.

When targeting the submandibular gland, you recommended longer needles in older patients. What is the reason?
The anatomy of the neck varies considerably. In people with slender and long necks as well as firm connective tissue, the submandibular gland lies very superficial. As time goes by and the patients get older, the distance between skin and gland might get wider, thus requiring a longer needle.

In the SIAXI study, both ultrasound guidance and anatomical landmark guidance revealed similar outcomes. Why do you personally prefer ultrasound?
The fact that there were no differences between ultrasound and anatomical landmark guidance, confirms the safety of the method. It could, however, also be based on the fact that the clinicians were skilled. In general, I use ultrasound guidance when injecting to be sure that the injection ends up where it belongs. It is not all about avoiding side effects, but also about achieving an effect.

What happens in case of unilateral injections? Couldn't that be generally done to prevent side effects such as dry mouth? Or do you always have to inject bilaterally?
I would generally suggest bilateral injections. Dry mouth was not an issue in the study and it is not in clinical practice. If less of an efficacy is desired, it is rather recommended to use a lower dosage, distributed into the four most important salivary glands.

There are several serotypes of botulinum toxins. Have other botulinum toxins ever been used to manage intractable sialorrhea?
Other botulinum toxins are also used for treatment of sialorrhea, some in trials, too, however, not in controlled approval-relevant studies. The newest botulinum toxin has not yet been investigated in sialorrhea, it first has to prove superiority when used for the classical indications.
Whether other botulinum toxins are superior to incobotulinum A remains to be determined and is subject to further investigations. However, there is no urgent need because the current neurotoxin is highly efficient with an efficacy that is sufficiently long lasting.

At this year's election, you became a member of the board of directors of the International Neurotoxin Association (INA). What will be your tasks in the next four years until your term ends in 2023? What are your personal goals you want to achieve as director?
I am sure that we will see enormous dynamics in this sector in the next few years. Development of innovative toxins, modified botulinum toxins, respectively, will offer new possibilities. At the same time, we have to protect us against botulinum toxins of poor quality. Development in research provided us with many new insights which will eventually be internalised in our therapies. A huge problem seems to be the promotion and encouragement of new talent, of both young researches who are willing to work as scientists and of clinicians who are willing to treat the numerous patients who can benefit from botulinum neurotoxins.

Pain

What does pain have to do with toxins? Clinical evidence for analgesic effects of botulinum neurotoxins has been reported early on in their use. When used for cosmetic reasons, it had been accidentally noted that neurotoxins exerted additional analgesic effects in migraine patients. Pain reduction, exceeding the sole effect of muscle relaxation, was also observed when neurotoxins were injected for relief of muscle tension in neurological disorders. Two potential – central and peripheral – mechanisms have been attributed to botulinum toxin's analgesic actions.

Mechanisms of pain

In his keynote lecture, Prof. Stephen McMahon (King's College London, United Kingdom) talked about two important processes, i.e. peripheral and central sensitisation. He asked, "if you are trying to develop a therapy, where should you be targeting your therapies to alleviate pain? We do not have a very complete answer to that question," he conceded, "but the data that we do have, strongly suggest that peripheral mechanisms are important for many patients." Prof. McMahon concluded that while most patients presumably have a peripheral mechanism driving their chronic pain, the remaining patients may have a central mechanism that dominates. "You might want to stratify those patients to treat them better," he added.

Prof. McMahon presented data relating to neuropathic pain: "It is a small trial, but I think it is indicative of a range of data in the literature. It shows the effect of local anaesthetic block – of lidocaine block – on neuropathic pain behaviour in a smaller group of (mainly diabetic) patients, either with peripheral nerve injury or polyneuropathy. What it shows is that all these patients got a complete, albeit temporary relief of pain by blocking their peripheral nervous system. This is not to say that central pain states are unimportant. I think you can treat chronic pain very effectively with centrally active compounds. We do that with antidepressants, for instance. But the important point is that those central abnormalities seem to be driven in many patients by peripheral abnormalities." Therefore, it is a logical conclusion, he stated, to address peripheral pain in most patients.

Prof. McMahon also talked about the growing interest in neurotoxins, particularly in botulinum toxin A, which may affect nociceptor function in multiple ways, i.e. by receptor trafficking in nociceptor terminals, retrograde transport and cell-to-cell-signalling, trans-ganglionic transport and neurotransmitter release, trans-synaptic transport and block of CNS neurotransmission, and by a direct effect on peripheral non-neuronal cells. Botulinum toxin A has been clinically licensed and tested in many pain states, including migraine, headache, musculoskeletal pain (back pain), trigeminal neuralgia, (peripheral) neuropathic pain, diabetic painful neuropathy, and osteoarthritis. In animal models, botulinum toxin A reversed mechanical hyperalgesia of neuropathic pain (diabetic neuropathy) and inflammatory pain, as in carrageenan (additive in nutrition extracted from red seaweed) inflammation [1], and in human volunteers it has shown to alter pain perception [2]. Increasing evidence for pain reduction derives from case reports and clinical trials, demonstrating efficacy of botulinum toxin when treating patients suffering from neuropathic pain, including post-herpetic neuralgia, post-traumatic and postoperative neuropathies, as well as trigeminal neuralgia.

1. Favre-Guilmard C, et al. Eur J Pain. 2017 May;21(5):927-937.
2. Paterson K, et al. Ann Neurol. 2014 Apr;75(4):591-6.

Pain subsides before effect on muscles become apparent

Prof. Nadine Attal (University Versailles Saint Quentin, France) focused on emerging clinical uses for botulinum toxin A in relation to pain. She reminded the audience that "botulinum toxin acts directly on acetylcholine release at the neuromuscular junction, and, for this reason, it has been used for several decades now in many conditions associated with increased muscle tone. This includes disorders such as blepharospasm, strabismus, and cervical dystonia in particular." Several clinical observations suggested that botulinum toxin might also relief a number of conditions associated with chronic muscle pain, such as chronic low back pain, shoulder pain, or myofascial pain, in particular.

Potential mechanism of muscular pain

"One of the suggested mechanisms of muscular pain is that increased muscle tension is responsible for ischaemia due to compression of muscle and blood vessels. This, in turn, increases the release of a number of neuromodulators, including bradykinin and ATP, which might sensitise nociceptors," Prof. Attal explained.

According to Prof. Attal, one characteristic molecular feature accounts for the classical effects of botulinum toxin on dystonia and on muscle pain, and that is the internalisation

and fixation on SNAP-25 and inhibition of acetylcholine exocytosis. Furthermore, pronounced analgesic effects appear even before the drug's effect on muscle contraction [1].

Directly reducing nociceptive activity

She speculated that beyond its well-known effect on muscle contraction, botulinum toxin might also exert a direct anti-nociceptive effect that is completely independent from its well-known classical effect on muscle tone. Many animal studies testing this hypothesis have started to emerge. In the formalin test model, peripheral injection of botulinum toxin in animals improved nociceptor behaviour in a dose-dependent manner, suggesting that this indeed is an anti-nociceptor effect [2]. Peripheral injections of botulinum toxin in further animal models suggested that botulinum toxin might have an effect on neurogenic inflammation and may be effective in many pain conditions. Another experimental pain model, mimicking what happens in chronic pain states, revealed its effect on TRPV1 receptors, which may explain why botulinum toxin A is able to reduce capsaicin-evoked pain in human skin in healthy volunteers. Botulinum toxin-pretreated subjects experienced reduced pain when capsaicin was applied [3-5].

Neuropathic pain – unmet medical need

"All this data from animal and human observations prompted us some years ago to explore the potential activity of botulinum toxin in peripheral neuropathic pain. Several conditions are associated with peripheral neuropathic pain, for example, post-herpetic neuralgia, polyneuropathy, postsurgical neuropathic pain, and radicular pain. Recent clinical trials and a recent meta-analysis have shown that the number of responders to current treatment options compared with placebo is relatively low". Prof. Attal emphasised that these conditions are very difficult to treat and this is why she urged that other therapeutic options are needed.

In patients with peripheral neuropathic pain, a first randomised, double-blind, placebo-controlled trial was published in 2008 [6]. Patients with peripheral neuropathic pain were selected on the basis of allodynia in the painful area. The neurotoxin was injected subcutaneously or deep intra-dermally. The results of this pilot study revealed indeed some efficacy of botulinum toxin vs placebo. The effect set in approximately 7 days after the initial set of injections and effects were remained even after 24 weeks [6]. Based on a meta-analysis of small but convincing clinical studies published in 2015 [7], "we proposed to recommend botulinum toxin A as a last choice; however, to recommend it with some limitations" (third-line recommendation for patients with peripheral neuropathic pain with a local pain generator).

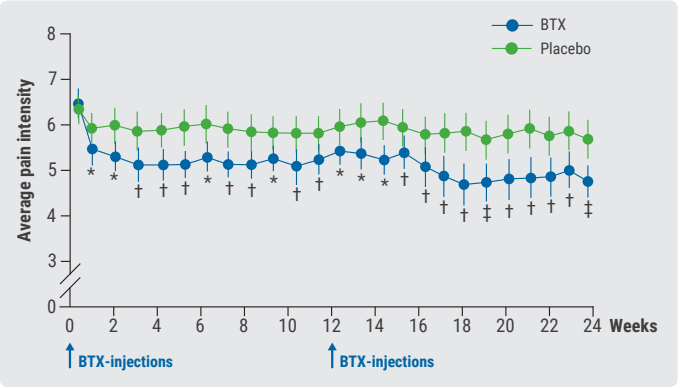
In patients with post-herpetic neuralgia, the neurotoxin also demonstrated some efficacy compared with saline and placebo, its efficacy also lasting up to 3 months (VAS score) [8]. However, for treatment of patients with trigeminal neuralgia, botulinum toxin A is not yet recommended by scientific societies [9].

Repeated injections

Since data on efficacy and safety of repeated administrations of botulinum toxin A were lacking, Prof. Attal designed another double-blind, randomised trial [10]. She pointed out that repeated injections are essential when treating chronic pain patients. She added: "We wanted to determine whether a second injection could have the same or even better efficacy." Thus safety and efficacy of repeated injections of botulinum toxin A (2 successive administrations within 12 weeks) was evaluated in patients with moderate-to-severe peripheral neuropathic pain (limited to a maximum area of 240 cm^2 due to dose limitations of 300 units of botulinum toxin A in this study, to avoid any potential side effects). A total of 152 patients were screened and 68 patients with moderate to severe peripheral neuropathic pain were randomised. In three centres, in Paris, Limoges, and Sao Paulo, the patients received multiple subcutaneous injections of botulinum toxin A into the painful area. Clinical assessment was performed via specific validated neuropathic pain questionnaires and quantitative sensory testing. At baseline and at one month, intradermal fibre density (IENFD) was evaluated at the painful and the control side by skin punch biopsy. At the same timepoints, levels of calcitonin gene-related peptide (CGRP) and substance P (SP) – substances involved in neurogenic inflammation – were evaluated at the painful side.

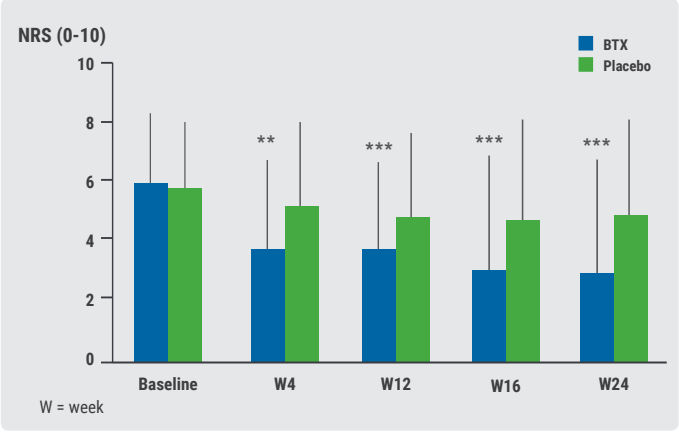
Results showed that 2 successive administrations of botulinum toxin A, each consisting of several injections, significantly decreased pain intensity over a period of 24 weeks compared with placebo ($P<0.0001$). A sustained analgesic effect in peripheral neuropathic pain was reported (Figure 1).

Figure 1 Effects of botulinum toxin A vs placebo on the primary study endpoint, average pain intensity over a 24-week period of time [12]



Moreover, analgesic efficacy was enhanced by a second administration 12 weeks after the first. Almost a quarter of the patients who only demonstrated little improvement after the first administration, responded favourably to the second administration. This finding suggests that 2 administrations of botulinum toxin A may be essential before concluding that a patient with neuropathic pain does not respond to the therapy. Evaluation of the questionnaires revealed that botulinum toxin A had a very significant and prolonged effect on paroxysmal pain; not only on pain intensity but also on number of paroxysmal pain (Figure 2). Botulinum toxin A significantly reduced allodynia (P=0.0002) and relieved hyperalgesia to mechanical stimuli on the painful side compared with placebo (P=0.03). Efficacy on average pain intensity during the study duration was greater in participants with allodynia than in those without allodynia at study entry. Neuropeptide concentrations (CGRP, SP) in skin punch biopsies were similar in both treatment arms and were not modified by botulinum toxin A injections [10].

Figure 2 Effects of botulinum toxin A on paroxysmal pain (Neuropathic Pain Symptom Inventory) vs placebo [12]



Predictors of response

When searching for predictors of response to botulinum toxin A, it was observed that patients who seemed to be the best responders were those who had very little evidence for thermal deficit at baseline, Prof. Attal explained. Moreover, presence, intensity, and severity of (mechanical) allodynia at baseline was a predictor of response to botulinum toxin A. Prof. Attal added that "this was also confirmed by a more objective marker of fibre loss which is skin punch biopsy." The less impairment of intra-epidermal fibre density at baseline and the more preserved nociceptive function, the better the response to botulinum toxin A [10].

Take-home message

Prof. Attal concluded that there is strong experimental rationale for the use of botulinum toxin A as an analgesic. Moreover, there is growing clinical evidence for its use in neuropathic pain. She emphasised that the safety profile is excellent and that its mechanisms of action might be central. She wondered, "who could be the ideal patient for botulinum toxin?" According to her, ideal candidates would be "patients with peripheral, maybe central, neuropathic pain, or trigeminal neuralgia, irresponsive to conventional therapy. This is off label! Preserved nociceptive function and mechanical allodynia seem to be a very good predictor for response, at least from our study. Patients also with paroxysmal pain are most likely very good responders for this drug."

1. Tsui JK, et al. Can J Neurol Sci. 1985 Nov;12(4):314-6.
2. Cui M, et al. Pain. 2004 Jan;107(1-2):125-33.
3. Morenilla-Palao C, et al. J Biol Chem. 2004 Jun 11;279(24):25665-72.
4. Tugnoli V, et al. Pain. 2007 Jul;130(1-2):76-83.
5. Gazerani P, et al. Pain. 2006 Jun;122(3):315-25.
6. Ranoux D, et al. Ann Neurol. 2008 Sep;64(3):274-83.
7. Finnerup NB, et al. Lancet Neurol. 2015 Feb;14(2):162-73.
8. Xiao L, et al. Pain Med. 2010 Dec;11(12):1827-33.
9. Cruccu G, et al. Neurology. 2016 Jul 12;87(2):220-8.
10. Attal N, et al. Lancet Neurol. 2016 May;15(6):555-65.

Migraine

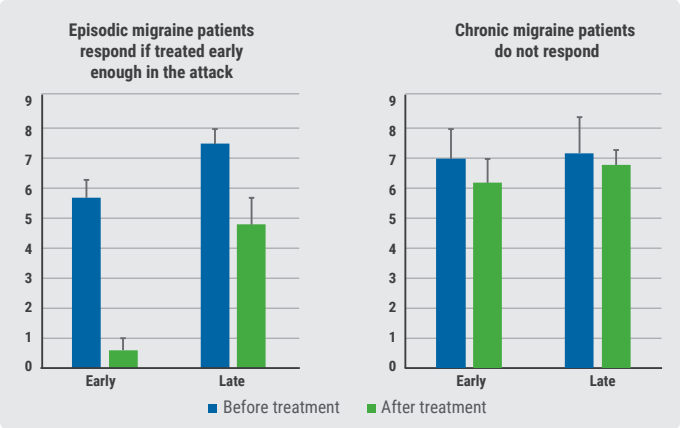
According to Dr Patricia Pozo-Rosich (Vall d'Hebron University Hospital, Spain), "the earlier you treat and the younger the patient is, the better." However, "defeating migraine pain with triptans is a race against developing allodynia," Prof. Rami Burstein (Harvard Medical School, USA) added. Both speakers shared their knowledge of migraine pathophysiology and gave new insights into emerging treatment options, particularly focusing on the convincing data of botulinum toxin A in the PREEMPT studies. Since 2010, botulinum toxin A has been approved for patients with chronic migraine, both by the FDA and EMA.

Migraine, a condition affecting more women than men, affects approximately 15% of the population during their most productive periods of their lives. The migraine brain is altered structurally and functionally with many neuronal systems functioning abnormally (i.e. generalised neuronal hyperexcitability). Migraine attacks often begin with a prodromal phase and an aura accompanied by transient focal, cortically mediated, neurological symptoms, developing gradually and resolving completely. Symptoms may include throbbing headache, nausea, vomiting, photophobia, abnormal sensitivity to noise and smell, allodynia, paraesthesia, and numbness (when the somatosensory cortex is affected), tremor and unilateral muscle weakness (when the motor cortex or basal ganglia are affected), and aphasia (involvement of speech area). The aura phase may last 5 minutes to 1 hour per aura type. The whole headache attack may last between 4 and 72 hours. Peripheral sensitisation is responsible for throbbing pain, while central sensitisation in the spinal cord mediates skin hypersensitivity and muscle tenderness. Sensitisation of thalamic trigeminovascular neurons results in whole-body allodynia. Cortical spreading depression – with a slowly propagating wave of alternating neuronal depolarisation and hyperpolarisation, vascular constriction, and dilation – is a neurovascular event underlying migraine aura.

Lessons learned from triptan therapy

Episodic migraine patients do respond to triptan if treated early enough in the attack before establishment of central sensitisation. Chronic migraine patients, after establishment of central sensitisation, however, do not respond to 5-hydroxytryptamine (5-HT)1B/1D receptor agonists, the current standard acute treatment for migraine (Figure 1). The reason for this is that, as the disease progresses, the chronic state of central sensitisation leads to interictal allodynia and background headache, Prof. Burstein explained the underlying mechanism.

Figure 1 Lessons learned from triptan therapy in episodic and chronic migraine [1]

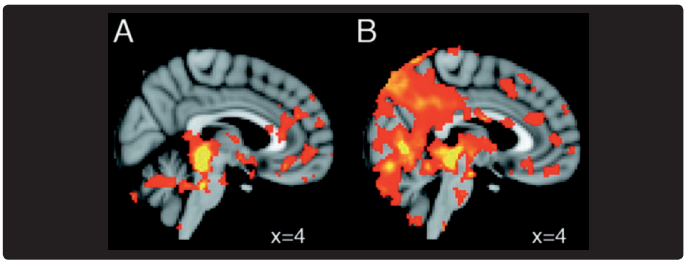


1. Burnstein R, et al. Ann Neurol. 2004 Jan;55(1):19-26.

Central and peripheral mechanisms in migraine

Prof. Anthony Dickenson (University College London, United Kingdom) focused on similarities and differences between migraine and other types of chronic pain. He talked about central and peripheral mechanisms in migraine and explained that pain needs a peripheral drive for central processing. Pain is a sensory and emotional response. In migraine, there is evidence for peripheral and central sensitisation. Peripheral sensitisation, a reduced threshold for stimulation of the peripheral sensory neurons, contributes to the pathophysiology of chronic migraine. He showed his audience the changes that occur in the brain, the altered functional MRI resting-state connectivity in periaqueductal grey networks in migraine (Figure 1).

Figure 1 Altered functional MRI in the brain in migraine [1]



1. Mainero C, et al. Ann Neurol. 2011 Nov;70(5):838-45.

Pain and sensory mechanisms

Prof. Cristina Tassorelli (University of Pavia, Italy) talked about primary headaches: cluster, tension-type headache, benign cough headache, and migraine.

Migraine is a complex disorder characterised by recurring attacks whose initiation depends on endogenous and exogenous factors. It is a disturbance of sensory processing involving the meninges, cortex, thalamus, hypothalamus, brainstem nuclei, and cranial pain pathways. There are endogenous factors involved such as hyperexcitability of the cortex. In addition, there is participation of exogenous factors: peripheral stress, dietary products, and environmental changes may also initiate migraine through activation of sensory afferents. There is also activation of the trigeminovascular afferent fibres of the trigeminal ganglion, release of neurotransmitters from peripheral nerve terminals of trigeminovascular afferents, and vasodilation of the meningeal vessels. Plasma extravasation and mast cell degranulation lead to secretion of other pro-inflammatory substances in the dura (neurogenic inflammation). Activation of neurons in the trigeminal nucleus caudalis and in brain regions are associated with pain perception.

Migraine-related disability

A severe migraine attack is as disabling as quadriplegia, schizophrenia, or dementia, Prof. Tassorelli emphasised. Migraine-related disability is high and so is headache medication overuse, as shown by the years of life lost because of the disease [1]. Migraine is the third cause of disability in individuals below the age of 50.

Prof. Tassorelli pointed out that the antinociceptive effect of onabotulinum toxin A is distinct from its neuromuscular activity. Its biochemical effect, cleavage of SNAP-25 to impair synaptic vesicle fusion and neurotransmitter release, is the same at both sensory and motor nerve terminals. The toxin may suppress peripheral sensitisation, thereby possibly inhibiting central sensitisation [2,3].

Onabotulinum toxin A blocks peripheral acetylcholine release at presynaptic cholinergic nerve terminals. The therapeutic benefit is muscle relaxation. Onabotulinum toxin A also blocks the release of neurotransmitters associated with the genesis of pain and reduces the cell surface expression of ion channels and sensory receptors. Its treatment benefit is pain reduction.

1. GBD 2015 Neurological collaborator Group. Lancet Neurol. 2017 Nov;16(11):877-897.
2. Aoki KR. Headache. 2003 Jul-Aug;43 Suppl 1:S9-15.
3. Whitcup SM, et al. Ann N Y Acad Sci. 2014 Nov;1329:67-80.

Predictors of response

Dr Pozo-Rosich tried to clarify whether there are clinical, molecular, or neurophysiologic predictors of response to botulinum neurotoxin in chronic migraine. In a prospective, multicentre study in which 79.3% of the patients treated with onabotulinum toxin A every 12 weeks for one year showed more than a 50% reduction in number of headaches per month, she observed that disease duration of less than 1 year increased the chances of treatment response. Unilaterality of pain, fewer days of disability per month, and milder headache at baseline correlated with a good outcome [1].

She recommended that the primary endpoint in controlled trials investigating preventive treatment in chronic migraine should either be defined as one or a combination of the following: change in migraine days, change in moderate-to-severe headache days, or responder rate. Dr Pozo-Rosich suggested that these three potential endpoints, if not selected as primary endpoints, should be considered as secondary endpoints. She said that efficacy can be assessed as improvements in headache frequency and intensity, in acute medication intake reduction, in better response to analgesics, in disability rates, and in frequency of associated symptoms/comorbidities such as depression. Pre-treatment evaluation, early response after 3 to 6 months, and long-term response after one year all have relevance as potential time points for assessing response to migraine prevention treatment. In addition, tolerability and adverse events should be evaluated and the non-responder rate determined.

What does a patient need?

Dr Pozo-Rosich continued that patients desperately want to stop the migraine cycle. They want to plan and programme their lives, be able to pack their luggage with more clothes than pills, and tolerate noises and lights. Other study participants mentioned that they wish to forget the anxiety they feel of not knowing when the next migraine will hit.

Thus, an efficient preventive measure for migraine first of all needs to be effective and tolerable, facilitate adherence, be persistence in effect, and should be designed for migraine, she said. Onabotulinum toxin A is a treatment specifically approved for the prophylaxis of chronic migraine in adults. When it comes to dosing, it became apparent over the years that 195 units are better than 155 units (no increase in secondary effects, improvement in disability).

1. Pozo-Rosich P, et al. Poster 216, TOXINS 2019, Copenhagen, Denmark, 16-19 January, 2019.

Spasticity

"Spasticity is a costly thing to have", Dr Anthony Ward (University Hospital of North Staffordshire, United Kingdom) said in his lecture, focusing on treatment considerations in focal and multi-focal spasticity.

Features of spasticity are shortened overactive muscles, muscle spasms, stiff limbs, hypertonia, limb posture change, weakness masked by stiffness, loss of fine motor control, and fatigue, Dr Ward reminded the audience. Among the impacts of adult spasticity are an impaired ability to perform everyday tasks, decreased mobility associated with pain, sleep disturbances, and mood changes, which all lead to a reduced quality of life.

Why treat spasticity?

According to Dr Ward, botulinum toxin injections are indicated for improvement of function (i.e. mobility, dexterity) and symptom relief to ease pain (i.e. muscle shortening, tendon pain, postural effects). He suggested this therapeutic approach for decreasing spasms, avoiding unnecessary treatments, reducing complications, facilitating therapy, delaying/preventing surgery, and reducing caregiver burden when handling the patients [1]. Toxin treatment may also allow better toleration of splints and physical treatment, he added.

Do not hesitate, treatment is safe

In the BEST trial, Dr Ward et al. looked at costs. "While it looks expensive, it actually is good for the patients. Post-stroke patients with spasticity are expensive anyway, because these patients need intermittent rehabilitation." Even 4 years after a stroke occurred, clinically meaningful outcomes can still be achieved by rehabilitation methods, he emphasised. For post-stroke patients, standard of care is important, he said, pointing out that that botulinum toxin A is an important adjunctive treatment to standard of care. Addition of botulinum toxin A after preparing muscles for treatment with physical therapy can significantly improve patients goal achievement [2]. Dr Ward urged: "start treatment immediately. Do not wait, we know that treatment is safe." Early mobilisation is important in stroke patients.

1. Ward AB. J Rehabil Med. 2003 May;(41 Suppl):60-5.
2. Ward AB, et al. J Rehabil Med. 2014 Jun;46(6):504-13.

ASPIRE: High patient and clinician satisfaction

Dr Gerard Francisco (TIRR Memorial Hermann Hospital, USA) focused on real-world onabotulinum toxin A treatment utilisation. He evaluated efficacy across multiple aetiologies of spasticity from the Adult Spasticity International Registry (ASPIRE) study. Dr Francisco examined data – derived from the international, multicentre, prospective, observational registry – from adult patients with spasticity either due to stroke (56%), multiple sclerosis, cerebral palsy, traumatic brain injury, spinal cord injury, or other illnesses, treated with onabotulinum toxin A. In total, 730 participants, of whom 37% were previously treatment-naïve to botulinum toxins, received at least one onabotulinum toxin A treatment. Total dosages per treatment session ranged from 45 to 1,038 units. The most common symptoms prompting treatments were equinovarus foot and clenched fist (in stroke). Most physicians and patients reported being "satisfied" or "extremely satisfied" with treatment that helped manage spasticity. The majority of physicians and patients stated they would "definitely" or "probably" continue therapy. No new safety signals were identified.

These 1-year interim data from the ASPIRE study, presented by Dr Francisco, continue to support safety and effectiveness of onabotulinum toxin A treatment for spasticity in clinical practice. Despite variation in dosing, patient and physician satisfaction across aetiologies was high.

Cervical Dystonia

A much discussed topic in Copenhagen was cervical dystonia, the most frequent focal dystonia in clinical practice with a prevalence of approximately 50 per million. Women are far more frequently affected by this painful chronic condition, characterised by involuntary patterned contractions of cervical musculature, resulting in postural changes of the head, neck, and shoulder. Disease onset peaks in the fourth and fifth decades of life. In up to 25% of the patients, there is a family history of this disorder that is mainly managed by repeated botulinum toxin injections.

Diagnosis and treatment

Prof. Alberto Albanese (Humanitas Research Hospital, Italy) recounted his historical knowledge on early observations about cervical dystonia, which dates back to Dante and Virgil who met the seers: "Each of them appeared strangely distorted between the chin and the start of the chest, since the head was reversed towards the body, and they had to move backwards, since they were not allowed to look forward." Prof. Albanese explained that in cerebellar processing of neck proprioceptive information, the effects of combined cerebellar and cortical stimulation in cervical dystonia patients are opposite from those in healthy volunteers. Phenomenological subtypes of cervical dystonia include stiff head and neck, i.e. caput and collum obstitum.

Diagnosis of cervical dystonia is based on clinical features: rotational posture (torticollis) and lateral tilt (laterocollis). Still, the average interval between symptom onset and diagnosis is 44 months, as there are no validated diagnostic criteria and a lack of confirmatory diagnostic testing [1]. Cervical dystonia may increase in severity depending on activity/posture. That is why it is important to assess patients with regard to action and posture, Prof. Cynthia Comella (Rush University Medical Center, USA) said.

All botulinum toxin products labelled for cervical dystonia

Prof. Albanese welcomed the fact that all botulinum toxin products are labelled for cervical dystonia. Unique to dystonia affecting the cervical region is that high doses are required compared with other focal dystonia, he added. Prof. Comella further mentioned deep brain stimulation. Surgical procedures, however, are a second-line alternative. She emphasised that no oral medications, such as levodopa, anticholinergics, baclofen, clonazepam, or tetrabenazine have been approved for use in cervical dystonia and adverse effects are frequent. According to Prof. Comella, botulinum toxin is the treatment of choice. Treatment of peripheral muscles with botulinum toxin A can lead to modification of brain-motor-control, she said. Originally it was assumed that botulinum toxin reduced pain only by the decrease of muscle spasms. However, the current understanding is that it can also directly act on nociceptors by inhibiting the release of neuropeptides. Botulinum toxin A demonstrated improvement in clinical scores and a reduction of pain. In an open-label study, including 97 patients with focal dystonia and hemifacial spasm, 64% of the patients experienced moderate or marked improvement in motor symptoms and 74% in pain symptoms after treatment with botulinum toxin A. According to a Cochrane review of botulinum toxin A therapy for cervical dystonia, there is an average of 18.7% Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) improvement from baseline at 4 weeks after injection [2]. Recommendations for managing cervical dystonia in patients with a poor response to botulinum toxin by the British Neurotoxin Network consist of improvements in practice by using a flexible, non-stereotype strategy and correct botulinum toxin targeting with the lowest dose required.

Determination of dominant abnormal movement

Prior to botulinum toxin treatment, Prof. Albanese suggested identification of the primarily involved muscles as opposed to compensatory activity for simple cases. His rule of thumb: muscles that cause the most dominant movement of head/neck and are clinically hyperactive and painful should be injected. The injection technique has to be precise. Movement (affected and compensatory muscles), weakness (lack of activation, atrophy), and pain (contraction, stretching, independent of muscle activity) are to be assessed. For clinical examination, initial inspection serves to allow detection of hypertrophy/atrophy and recognition of the muscles involved in abnormal postures and movements. Palpation is used for identification of size and activation of superficial muscles, and evoked muscle pain.

For complex or unclear cases, Prof. Albanese recommends the use of electromyography (EMG) mapping. EMG recordings show muscle activity at rest and during voluntary tasks.

Ultrasound may be used for visual recognition of muscles and their contractile activity, and to measure muscle size (quantify botulinum toxin-induced atrophy). EMG and ultrasound may be used for targeting, especially when targeting deep muscles.

Treatment algorithm

Prof. Albanese was convinced that there was a need to develop practical management guidelines for botulinum toxin injections with the aim to increase patient satisfaction and to assess whether EMG in combination with ultrasound would help in targeting dystonic muscles in patients with cervical dystonia. As currently no consensus exists on the practical issues involved in performing guided injections, he proposed a new algorithm based on simultaneous support of EMG plus ultrasound in botulinum toxin injections. After conducting a prospective 12-week study in which patients with cervical dystonia received botulinum toxin treatment according to the algorithm, the speaker concluded that algorithm-based treatment is feasible and efficacious.

A randomised, double-blind study, comparing botulinum toxin injections administered with and without EMG guidance, revealed that those in the EMG guided group had a greater magnitude of improvement and a larger number of patients with a marked improvement [3].

1. Tideringston et al. J Neurol Sci (2013).
2. Castelão M et al. Cochrane Database Syst Rev. 2017 Dec 12;12:CD003633.
3. Comella CL et al. Neurology. 1992 Apr;42(4):878-82.

Anterocollis posture and deep cervical muscle injections

Dr Laxman Bahroo (Georgetown University Medical Center, USA) talked about anterocaput, a head flexion of the skull base on the cervical spine, as well as anterocollis, a forward flexion of the neck and head that involves the cervical vertebrae and the skull, which remains undertreated. Anterocollis represents approximately 6.8% of the abnormal posture seen in cervical dystonia and presents several challenges to the neurotoxin injector.

Anterocollis is more common in females (67%) than in males. Aetiologies include neuroleptic exposure and parkinsonism syndromes. Dr Bahroo stressed the importance to differentiate this distinct abnormal posture from other similar looking postures such as anterocaput. In anterocollis posture, various muscles are involved, i.e. the scalenes, the longus capitus, and the longus colli muscle. Accurate distinction is important as the various postures involve different combinations of muscles.

Injections with botulinum toxin under various guidance modalities resulted in improvement of posture with mild side effects (mild dysphagia). However, anterocollis is often excluded from pivotal trials studying botulinum toxins. Moreover, botulinum toxin treatment may be limited by the occurrence of dysphagia. In addition, doses are not well known because these muscles are not commonly injected. Depending on the targeted muscles and the botulinum toxin that is injected, dose may vary considerably (Table 1).

Table 1 Botulinum toxin dose, depending on the muscle and the drug that is used

Muscles	Onabtx	Incbtx	Abobtx	Rimabtx
SCM	20-50 Units	20-50 Units	40-120 Units	1000-3000 Units
Scalene	5-30 Units	5-30 Units	20-100 Units	500-2000 Units
Longus Colli	15-30 Units	15-30 Units	20-60 Units	
Longus Capitis	5-15 Units	5-15 Units	20-60 Units	

Dr Bahroo reported that the sternocleidomastoid and the scalene muscles are commonly injected in anterocollis but may not provide significant benefit [1]. Case reports of failure indicated that the sternocleidomastoid and/or the scalene anterior muscle were the only muscles that had been injected. If posture does not respond to standard sternocleidomastoid/scalene injections, Dr Bahroo recommended that the lower sternocleidomastoid should also be targeted. He mentioned two case reports describing injections targeting the lower sternocleidomastoid in "refractory" anterocollis patients who had had a limited response to upper sternocleidomastoid injections after 3 injection cycles. In these patients, when the lower sternocleidomastoid (i.e. sternal and clavicular heads) was injected under EMG guidance, posture improved without side effects [2].

A literature review indicated that refractory anterocollis involves the deep cervical muscles (i.e. the longus colli and longus capitus muscles). If posture is refractory, one should consider targeting the longus capitus muscle/longus colli muscle with guidance, Dr Bahroo added. Thus, he advised that consideration is given to injections in these muscles in cases of anterocollis that do not improve with sternocleidomastoid and scalene injections. With injections targeting the longus capitus muscle and the longus colli muscle, sustained improvement was demonstrated in "refractory" anterocollis neck posture in several case reports. Yet, the deep cervical muscles are located in the retropharyngeal space presenting an additional challenge in accurate and successful injection of these muscles. Nonetheless, they may be successfully targeted using several guidance methods including EMG, CT, ultrasound, and fluoroscopy, with sustained benefit over several treatment cycles [3-7].

Guidance necessary to reach deep cervical muscles

According to Dr Bahroo, reasons for potential anterocollis treatment failures are incorrect characterisation of posture,

lack of appropriate muscle identification, incorrect targeting of muscles, and issues with guidance. Guidance is important given the deep location of muscles, and there are various ways to target deep cervical muscles. There is no consensus, however, on which technique is best in terms of accuracy since there is no comparison.

1. Marion M-H, et al. Pract Neurol. 2016 Aug;16(4):288-95.
2. Peng-Chen Z, et al. Neurologist. 2016 Mar;21(2):30-1.
3. Herting B, et al. Mov Disord. 2004 May;19(5):588-90.
4. Ulzheimer JC, et al. Klin Neurophysiol 2007; 38-P67
5. Allison SK, Odderson R. Ultrasound Q. 2016 Sep;32(3):302-6 .
6. Glass GA, et al. Parkinsonism Relat Disord. 2009 Sep;15(8):610-3 .
7. Bhidayasiri R. Parkinsonism Relat Disord. 2011 Nov;17 Suppl 1:S20-4 .

Daxibotulinum toxin in isolated cervical dystonia

Currently available treatments for cervical dystonia call for injection of botulinum toxin about 3 to 4 times a year. Is there a chance to achieve longer-lasting effects and to prolong injection intervals? A phase 2 trial with an investigational product, daxibotulinum toxin A for injection (RT002), revealed a clinically significant mean reduction of 38% from baseline in the TWSTRS total score and of 34% in the TWSTRS severity score at week 4 across all patients.

Dr Atul Patel (Kansas City Bone & Joint Clinic, USA) presented the results of the open-label, dose-escalating phase 2 study with a low (100-240 units) and a high-dose (300-450 units) daxibotulinum toxin A group in 37 patients with moderate-to-severe isolated cervical dystonia. Safety and preliminary efficacy of daxibotulinum toxin A as well as efficacy duration were assessed. The results demonstrated improvement in signs and symptoms. Clinically meaningful reductions in TWSTRS-severity, -disability, and -pain subscales were consistent and observed at all time points. At week 24, an average reduction in the TWSTRS total score of 30% and in the TWSTRS severity score of 20% was reported. Observed effects (median duration of effect defined as maintaining at least 30% of the treatment benefit attained in week 4) lasted for more than 24 weeks in both dose groups. Daxibotulinum toxin A for injection appeared to be generally safe and well tolerated across all cohorts and dose groups through week 24 with no increase in treatment-emergent adverse events upon dose escalation. This also positively affected quality of life. Daxibotulinum toxin A may provide a long-lasting symptom reduction in cervical dystonia [1,2].

1. Patel AT, et al. Poster 205, TOXINS 2019, Copenhagen, Denmark, 16-19 January, 2019.
2. Jankovic J, et al. Mov Disord Clin Pract. 2018 Apr 26;5(3):273-282.

Parkinson

A long list of symptoms present in Parkinson's disease may be targeted with botulinum toxins to alleviate the burden of disease. Studies investigated its efficacy in tremor, sialorrhea, dystonia, freezing of gait, camptocormia (bent spine syndrome), urinary dysfunction, constipation, eyelid opening apraxia, blepharospasm, and in dysphagia, a condition highly prevalent in Parkinson's disease (up to 81%) which can cause serious complications.

Tremor

It might be time to reconsider botulinum toxins for tremor, as botulinum toxin injections adapted to the patients are effective in controlling tremor and at the same time avoid wrist extensor inhibition and the occurrence of weakness in the hand.

Hand tremor is a common movement disorder that may be caused by essential tremor, Parkinson's disease, or dystonia. Hand tremor may be very disabling and is often associated with an impairment of quality of life despite optimal therapy. Dr Nicki Niemann (Baylor College of Medicine, USA) stressed the fact that tremor treatment with oral drugs is often limited by lack of efficacy and systemic side effects [1]. Invasive procedures, such as deep brain stimulation and MRI-guided ultrasound thalamotomy, are reserved for severe and disabling tremor.

Early clinical trials with botulinum toxin in essential tremor showed a clinically moderate improvement of tremor amplitude. However, relatively high rates of side effects were also seen. Benefits were limited by clinically significant weakness, particularly of extensor muscles and wrist weakness, which were attributed to the injection techniques [2, 3]. With modification of the injection technique, botulinum toxin has been increasingly used for treatment in patients with focal tremor with good outcomes and favourable long-term safety [4-6].

Onabotulinum toxin A in hand tremor

Dr Niemann performed a retrospective review of patients with refractory hand tremor who had been treated with onabotulinum toxin A injections between 2010-2018 in at least two sessions. He obtained data on muscle selection, dose, and response to prior injection from 91 patients (i.e. 53 with essential tremor, 6 with Parkinson's disease, 31 with dystonia, and 1 patient with cerebellar outflow tremor) in whom tremor was optimised prior to the first onabotulinum toxin A injection. In 97.8% of the patients, forearm flexors were injected and 2.2% received injections other than the forearm flexors. EMG was used in only 5.5% of the patients, while all other patients were injected relying on surface anatomy. It was demonstrated that patients had sustained benefits during an average follow-up period of 2.5 years. In most patients, marked or moderate improvement of tremor severity and function on the peak-effect rating and global-effect rating scales was reported.

Dr Niemann concluded that by avoiding injections into forearm extensors, clinically significant wrist and finger weakness was largely avoided while tremor reduction was maintained. Onabotulinum toxin A injections were safe and effective in the treatment of hand tremor [7].

1. Schneider SA, Deuschl G. Neurotherapeutics. 2014 Jan;11(1):128-38.
2. Jankovic J, et al. Mov Disord. 1996 May;11(3):250-6.
3. Brin MF, et al. Neurology. 2001 Jun 12;56(11):1523-8.
4. Jankovic J. Mov Disord. 2017 Aug;32(8):1131-1138.
5. Mittal SO, et al. Mayo Clin Proc. 2017 Sep;92(9):1359-1367.
6. Samotus O, et al. Can J Neurol Sci. 2018 Jan;45(1):11-22.
7. Niemann N, Jankovic J. Poster P2.28, abstract 197, TOXINS 2019, Copenhagen, Denmark, 16-19 January, 2019.

Sialorrhea

In his presentation, Prof. Wolfgang Jost (Parkinson-Klinik Ortenau, Germany) discussed approved and unapproved uses of botulinum neurotoxins. He showed ways to manage intractable sialorrhea, a troublesome and disabling symptom associated with various neurological conditions.

Every adult produces up to 1.5 litres of saliva per day by the sublingual, the parotid (1/4-1/3, serous), but mainly by the submandibular gland (≥2/3, mucous and serous), according to Prof. Jost. While sialorrhea refers to excessive saliva production, drooling means unintentional loss of saliva from the mouth, he explained.

Common causes of sialorrhea are Parkinson's disease, stroke, amyotrophic lateral sclerosis, traumatic brain injury, or cerebral palsy. Consequences of sialorrhea may be of a social or medical nature. Embarrassment, social isolation, stigmatisation, perioral skin breakdown, pneumonia due to aspiration of saliva, choking, and dehydration, all may lead to increased morbidity and mortality as well as an impaired quality of life.

Multidisciplinary management of sialorrhea consists of speech therapy, which is moderately helpful, functional dysphagia therapy, oral motor training, intra-oral devices, irradiation, oral/transdermal anticholinergics such as atropine or scopolamine, or surgery in therapy-resistant cases. In Europe, 320 µg/ml glycopyrronium is approved for children only. Neither oral drugs nor patches are currently approved by the FDA or EMA for treatment of chronic, troublesome sialorrhea in adults.

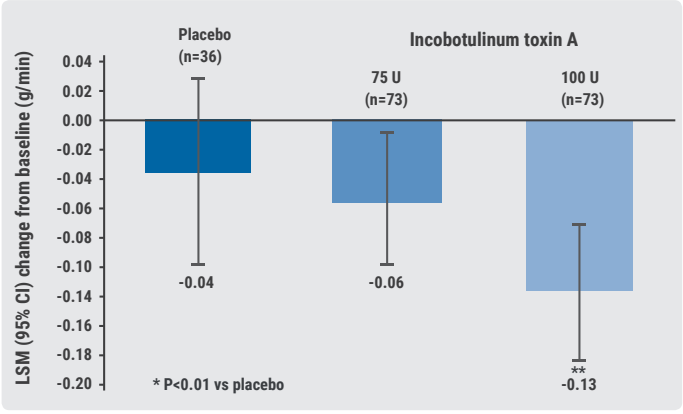
However, botulinum neurotoxin type A has been effectively used to reduce saliva production in patients with sialorrhea since 1999 [1]. Many trial data confirmed safety and efficacy of botulinum toxin A and botulinum toxin B formulations in sialorrhea therapy. In the summer of 2018, incobotulinum toxin A has been approved by the FDA for the treatment of patients suffering from sialorrhea. It was the only botulinum toxin preparation in the USA to receive approval for hypersalivation without restrictions on the underlying cause. EMA approval is anxiously awaited. Prof. Jost manages sialorrhea with the help of botulinum toxin injections, and showed pictures of the injection technique for the submandibular gland. While the gland is very superficial in younger patients, longer needles are recommended in older patients. According to Prof. Jost, an ultrasound-guided injection of 100 units incobotulinum toxin A is recommended, distributed in the parotid and submandibular salivary glands.

SIAXI – incobotulinum toxin A effective and safe in sialorrhea

For evaluation of efficacy and safety of incobotulinum toxin A treatment in patients with sialorrhea under more rigorous conditions, Prof. Jost initiated the randomised, multicentre, double-blind, placebo-controlled, pivotal phase 3 study SIAXI with an extension period of dose-blinded active therapy [2]. The study population consisted of 184 adult patients without clinically relevant dysphagia but with chronic troublesome sialorrhea for at least 3 months prior to screening. Hypersalivation was related either to idiopathic, familial, or atypical Parkinson syndromes, stroke, or traumatic brain injury. After salivary glands had been identified, injections were administered using ultrasound guidance in 56.5% of the total study population. Although investigators were encouraged to use ultrasound for guidance of injections, both injections with and without ultrasound guidance (anatomical landmark guidance) were similarly effective as revealed by the results. For treatment, patients received either placebo (n=36) or incobotulinum toxin A (n=74 in both groups), distributed bilaterally in the parotid and submandibular glands in a single injection cycle (16 ± 2 week duration). Two dosages of incobotulinum toxin A (75 units

and 100 units) were evaluated. Each treatment consisted of 4 injections into the bilateral parotid and submandibular salivary glands in a 3:2 ratio to avoid worsening of any pre-existing swallowing problems due to salivary thickening.
Prof. Jost presented the clinically meaningful primary efficacy data. The results of the co-primary endpoints of the main study period confirmed efficacy of incobotulinum toxin A. This was demonstrated by improved scores of the Global Impression of Change Scale (GICS) and the reduction of unstimulated salivary flow rate by incobotulinum toxin A (Figure 1).

Figure 1 Change from baseline in unstimulated salivary flow rate (uSFR) in the various treatment groups [2]



The mROMP drooling scores (modified Radboud Oral Motor inventory for Parkinson's disease subscales), assessing the domains speech, swallowing, and salivary control, improved from study baseline over 16 weeks to a greater extent in patients treated with incobotulinum toxin A compared with placebo. Average mROMP speech and swallowing symptoms scores improved only slightly from study baseline to all post-treatment visits. Incobotulinum toxin A therapy resulted in reduction of saliva production without impairing speech or swallowing abilities, as revealed by the mROMP speech and swallowing symptom scores. No unexpected adverse events of special interest occurred during treatment with incobotulinum toxin A.
These data have led to FDA approval of incobotulinum toxin A 100 units in the US for adults with sialorrhea.

1. Jost WH. Poster 115, TOXINS 2019, Copenhagen, Denmark, 16-19 January, 2019.
2. Jost WH, et al. Neurology (2019, in press)

Utility of botulinum toxin in Parkinson's disease beyond sialorrhea

Symptoms treatable with botulinum toxins besides tremor and sialorrhea are blepharospasm, eyelid opening apraxia, dystonia, and urinary dysfunction. For some of these indications level A evidence has already been obtained. In further indications Dr Fernando Pagan (Georgetown University Hospital, USA) suggested more trials to obtain level A evidence.
Further symptoms in Parkinson's disease, requiring clinical trials to establish level A evidence with botulinum toxins are constipation, laryngeal dystonia, freezing of gait, camptocormia, and oral mandibular dystonia, he emphasised.

Blepharospasm & eye lid apraxia

In blepharospasms and eye lid apraxia, more common in advanced states of the disease and in atypical Parkinsonism, botulinum toxins are recommended as first-line treatment: onabotulinum and incobotulinum toxin A have level A evidence, abobotulinum toxin A has level B evidence, and rimabotulinum toxin B has level U evidence.

Achalasia, Barrett's oesophagus

Dysphagia is also a well-recognised problem in patients with Parkinson's disease. Numerous theories for its aetiology exist, including abnormal neck posture, achalasia, impairment of motor nucleus of Vagus, Lewy bodies in myenteric plexus oesophagus, as well as Barrett's oesophagus. A total of 36% of symptomatic Parkinson patients are affected. In asymptomatic Parkinson's disease, 15-20% of the patients suffer from dysphagia. Oral and pharyngeal phases are prolonged and multiple attempts to swallow occur. Dr Pagan was convinced that Barrett's oesophagus as well as achalasia are both areas where botulinum toxin could be directly injected into the oesophagus with effects lasting for about 6 months depending on the patient.

Cervical dystonia – level A evidence for all botulinum toxins

Neck and shoulder pain is present in up to 70% of the patients with Parkinson's disease. Dr Pagan pointed out that painful dystonia in Parkinson's disease may affect various areas of the body. Parkinson patients may suffer, for example, from cervical dystonia which can be easily missed. Anterocollis is the most common pattern of cervical dystonia in Parkinsonism, he explained. In cervical dystonia, Dr Pagan emphasised that all botulinum toxins have level A evidence for treatment.

Limb dystonia – unmet need

Patients may also be affected by limb dystonia, which manifests as upper limb dystonia in hand, arm, or shoulder. When lower limbs are affected, toe cramping, foot inversion, and toe extension in 10% of the patients may be observed. Dr Pagan pointed out that for limb dystonia in Parkinson's disease, botulinum toxins do not have level A evidence for treatment, but they improve quality of life for the patients.

Further studies are needed, he urged, because an FDA indication is desperately needed.

Overactive bladder – level A evidence

Bladder dysfunction is also common in patients suffering from Parkinson's disease. Nocturia has been reported in up to 60% of the patients. In Parkinson's disease, detrusor overactivity is the main reason for this problem. Dr Pagan pointed out that botulinum toxin therapy (level A evidence) has shown to increase capacity and improve urgency.

New Versions of Botulinum Toxins

Several serotypes of botulinum toxins (A1, A2, A3, B, C1, D, E, F, and G) exist. Currently available versions of botulinum toxins are serotype A (e.g. onabotulinum toxin A, abobotulinum toxin A, and incobotulinum toxin A) and serotype B (e.g. rimabotulinum toxin B). Prof. Cynthia Comella (Rush University Medical Center, USA) focused on new versions of botulinum toxin.

She started by briefly mentioning an innovative botulinum topical gel (RT001), a substance that first appeared promising in phase 1 and 2 studies, but which failed to meet clinical endpoints during phase 3 clinical trials. The development plan for RT001 was discontinued and it was decided to focus on the injectable botulinum toxin A version RT002. Agents with a prolonged effect in chronic conditions, fewer injection series over time, a reduced waning effect between injections, and improved patient satisfaction might provide a prolonged optimal benefit. A safety and tolerability study in cervical dystonia has been completed which revealed that the investigated agent was well tolerated at both doses [1].

Prof. Comella also talked about botulinum toxin type A2, which may have a higher potency to cleave SNAP-25 cell molecules, yet with only pilot clinical data.

Moreover, she mentioned the clinical development of botulinum toxin serotype E with a potential faster onset of action within one day and a faster waning effect (two to four weeks) than botulinum toxin A. Potential benefits of rapid onset and short duration would allow a rapid relief of symptoms, may contribute to healing after injury, and reduce scar formation by reducing muscle activity. It would further allow pre-testing patterns of injection, prior to injection of longer duration botulinum toxins as well as short-term "boosting" effects in suboptimal results with longer acting botulinum toxins without an overlap at the next injection visit.

She further talked about future indications for botulinum toxin such as atrial tachycardia and atrial fibrillation [2], hip osteoarthritis [3], leg cramps in diabetic neuropathy [4], neuropathic pain (trigeminal neuralgia, post herpetic neuralgia, diabetic neuropathy, post-stroke pain, spinal cord injury), complex regional pain syndrome [5, 6], major depression [7] and essential tremor [8, 9] (Table 1).

Table 1 Clinical applications of botulinum toxin

Dystonia	**Pain**	**Gastrointestinal disorders**
- Blepharospasm	- Chronic migraine	- Gastroparesis
- Hemifacial spasm	- Osteoarthritis	- Delayed gastric emptying
- Cervical dystonia	- Plantar fascilitis	- Achalasia
- Spasmodic dysphonia	- Temporomandibular joint disorders	- Anal fissures
- Limb dystonia	- Neuropathic pain	
- Oromandibular dystonia	- Lower back pain	**Cosmetic**
		- Glabellar rhytides
Strabissmus	**Secretory disorders**	- Horizontal lines on the forehead
	- Sialorrhea	- Lateral canthal lines (crow's feet)
Spasticity	- Rhinorrhea	- Depressed brow
- Upper limb	- Frye's syndrome	- Hypertrophic orbicularis oculi muscle
- Lower limb	- Axillary hyperhidrosis	- Rhytides from upper nasalis muscle contraction
	- Palmar hyperhidrosis	- Nostril flare
Other neurological disorders	**Genital-urinal disorders**	- Drooping nasal tip
- Tic disorders	- Detrusor over activity with/without neurologic condition	- Nasolabial folds
- Tremor	- Pelvic pain	- Vertical perioral rhytides
- Camptocormia	- Erectile dysfunction	- Mouth frown
- Pisa syndrome	- Vulvodynia	- Gummy smile
- Stuttering	- Vaginismus	- Melomental folds (marionette lines)
- Restless leg syndrome		- Mental crease
- Synkinesias		- Peau d'orange chin
- Nystagmus		- Masseteric hypertrophy
- Bruxism		- Horizontal neck lines
		- Platysmal bands on the neck
Depression		

1. Jankovic J, et al. Mov Disord Clin Pract. 2018 Apr 26;5(3):273-282.
2. Romanov A, et al. Heart Rhythm. 2019 Feb;16(2):172-177.
3. Eleopra R, et al. Toxins. 2018 Oct 31;10(11).
4. Restivo DA, et al. Ann Neurol. 2018 Nov;84(5):674-682.
5. Park J, Chung ME. Toxins. 2018 Jun 1;10(6).
6. Park J, Park HJ. Toxins. 2017 Aug 24;9(9).
7. Magid M, et al. J Clin Psychiatry. 2014 Aug;75(8):837-44.
8. Samotus O, et al. Can J Neurol Sci. 2018 Jan;45(1):11-22.
9. Niemann N, Jankovic J. Toxins. 2018 Jul 19;10(7).
10. Samizadeh S, De Boulle K. Clin Cosmet Investig Dermatol. 2018 May 30;11:273-287.
11. Fonfria E, et al. Toxins. 2018 May 18;10(5).