# Botulinum Toxin and Pain

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## Contents



**Abstract**

This chapter is focused on analgesic mechanism of action of botulinum toxin type A (BoNT-A) including the action beyond peripheral nerve endings. With the exception of the meninges and possibly urinary bladder, the presence of BoNT-A activity in the periphery, cleaving SNAP25 as a target molecule, up to now was not convincingly shown. In contrast many reports demonstrated BoNT-A activity and the presence of cleaved SNAP25 in the brain and spinal cord. In a model of mirror pain BoNT-A analgesic effect can be achieved even without participation of peripheral nerve ending. Thus generalized hypothesis central or peripheral mechanism of action belongs to history, and there is a need to confirm or dispute the results with meninges, urinary bladder, and possibly with other, especially visceral organs.

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There are two general options for the central actions of BoNT-A:

1. The activity ends by silencing primary sensory neuron thereby stopping the pain information further in the CNS.
2. Or thereafter, indirectly or transsynaptically, BoNT-A triggers smaller or larger neural loops, forming memory of pain in the CNS that could explain the bilateral effects after unilateral peripheral administration, similar effect in mirror image allodynia and the like

Intensive research has shown that peripherally administered BoNT-A reaches the CNS by axonal transport. There is increasing evidence that BoNT-A is preventing pain in a growing range of disorders. In the absence of unexpected findings, or an increase in the uncontrolled use of illicit preparations by uneducated persons, BoNT-A is emerging as a new long-lasting and relatively safe analgesic.

**Keywords**
Analgesia · Axonal transport · Botulinum toxin type A · Botulinum toxin type B · CNS · Pain · SNAP25 · SNARE · Transsynaptic transport

## 1 Introduction

There is enormous advancement in medical science and practice in this twenty-first century: artificial organs, gene therapy, robotic surgery, brain-computer interface, and more. One area is lagging behind, and it is pain, especially chronic pain, the greatest source of human misery and suffering. Hundreds of potential analgesics are being investigated, including opioids and nonsteroidal anti-inflammatory drugs. However, finding analgesics that will work that are strong enough, long enough, and free from serious side effects is a long-standing hope. From the multitude of substances under study, botulinum toxins, especially botulinum toxin type A (BoNT-A), and to a lesser extent BoNT-B, emerge as medicine that might have a special place. This review focuses mostly on BoNT-A.

## 2 How Neurotoxin Became an Analgesic

The beneficial effect of botulinum toxin serotype A (BoNT-A) in pain was first observed in the patients with painful cervical dystonia in 1985 (Tsui et al. 1985) and considered to be a consequence of reduced muscular contraction. However, eventually it becomes evident that the analgesic activity occurs before and lasts longer than the antispastic activity (Freund and Schwartz 2003). From the first observation in 1987, BoNT-A analgesic potency did not attract major attention for a long time. Several large trials, 33 years later, showed that BoNT-A is beneficial in chronic but not episodic migraine (Diener et al. 2000; Dodick et al. 2010). In 2010 FDA approved BoNT-A for chronic migraine.

## 3 BoNT-A Analgesia

A common classification is nociceptive, inflammatory, and chronic pain. However in many cases, this is a continuum. Touching something painfully hot, we remove the hand from the heat; this is the reflex present in life forms even without a brain. If the burn is severe enough, there will be inflammation lasting several days or longer. Especially if something went wrong, acute pain can become chronic, and for a long period we feel an unpleasant sensation; in some cases *traces of memory of pain* develop, and the pain and allodynia can continue after tissue damage is already repaired. Moreover in rare cases, where an amputation of burned body part was necessary, some patients still feel the pain in the extremity which does not exist anymore (*phantom pain*). As hippocampal and other neurons are developing plastic changes underlying the mechanism of memory and learning, nociceptive neurons are also developing plastic changes that can last longer than nociceptive stimuli: memory of the pain. Accordingly chronic pain could be considered a CNS disorder (Tracey and Bushnell 2009; Ji et al. 2013).

The first experimental evidence in vivo of antinociceptive effect of BoNT-A was published in 2004. It was shown that in the rat formalin test, BoNT-A diminished only the second inflammatory phase (Cui et al. 2004). The formalin test consists of an injection of dilute formaldehyde (1% in saline) usually in dorsal surface of one hindpaw, but could be any part of the body. The response is the amount of time the animals spend by movement pointing to painful place, usually licking the injection place. There are two distinct periods of high licking activity, an early phase lasting the first 5 min and a late phase lasting from 20 to 30 min after the injection of formalin.

On the basis of (1) this experiment in which analgesic effect of BoNT-A in vivo was shown only in the second, inflammatory phase of formalin test, (2) different in vitro studies showing inhibitory action of BoNT-A, (3) first evidence of analgesic effect of BoNT-A in patients, and (4) knowledge that BoNT-A inhibits the release of the acetylcholine at the neuromuscular junction, it was suggested that the analgesic mechanism in the sensory nerve is the same as it is in motor nerve: enzymatic blockade of neurotransmitter release (Aoki 2003, 2015). This idea was that both inflammation and pain is associated with peripheral release of inflammatory mediators and neurotransmitters like glutamate. However BoNT-A has antinociceptive effect in pain induced by intraplantar injection of capsaicin or carrageenan but no visible effect on inflammation. Thus, it was concluded that the *mechanism of the antinociceptive action of BoNT-A might be much more complex than the suggested inhibition of transmitter release in the periphery* (Bach-Rojecky and Lacković 2005). Contrary to BoNT-A, the skeletal muscle relaxant dantrolene produced more motor impairment than analgesia (Favre-Guilmard et al. 2009). Apparently, release of inflammatory substances and neurotransmitters involved in inflammation is separate from BoNT-A antinociceptive effect.

The most common model to study chronic pain in experimental animals is chronic constriction injury (CCI) of a nerve that results in mononeuropathy with long-lasting pain hypersensitivity and allodynia. There are a number of reports

showing that BoNT-A reduces pain in CCI (Bach-Rojecky et al. 2005, 2010; Shinoda et al. 2007; Kitamura et al. 2009; Filipović et al. 2012).

In the first of those report, a peripheral application of BoNT-A (7 U/kg) significantly reduced thermal and mechanical hypersensitivity in rats with the partial sciatic nerve transection (Bach-Rojecky et al. 2005). Treatment with high dose of BoNT-A was associated with faster nerve regeneration (Marinelli et al. 2010).

## 4 Axonal Transport of BoNT-A

BoNT-B and tetanus toxin at molecular level cleave the same SNARE protein: VAMP/synaptobrevin. However BoNT-B produces flaccid paralysis, while tetanus toxin has clinically opposite effect, spastic paralysis. The basic difference is the existence of retrograde axonal transport of tetanus toxin in contrast to BoNT-s. This shows fundamental importance of the existence of axonal transport of BoNT-s.

First publication of central effect of peripherally applied BoNT dates to 1956 and was published in *Byulleten Eksperimental'noi Biologii i Meditsiny* (USSR). Soviet scientist V. V. Michailov found that administration of BoNT to experimental animals causes defect in brain stem reflexes (Michailov 1956, cit. by Tyler 1963). In 1963 Tyler published a case report in *Science* reporting that electrical stimulation of multiple peripheral nerves elicited "H" reflexes in a patient, 61 years old, with botulism. The author emphasized that *this "central" action of botulinum toxin is similar to that suggested for tetanus toxin* (Tyler 1963). Two years later Polley et al. (1965) found that BoNT-A has a depressant effect on the cortical electrical activity of monkeys.

To evaluate if peripherally applied BoNT-A can reach the CNS, the radioiodinated BoNT-A was prepared and observed in the spinal cord after peripheral injection (Habermann 1974; Wiegand et al. 1976). After unilaterally injected sublethal doses of $^{125}$I-BoNT-A into gastrocnemius muscle of the cat, most radioactivity was localized in the spinal cord ipsilateral to radioactivity injection, as well as ventral roots innervating the injected muscle (Wiegand et al. 1976). Nearly 30 years later, distribution of radiolabeled holotoxin and only the active 150 KDa free toxin was investigated at the same experiment. However, almost no radioactivity was found in the brain (Tang-Liu et al. 2003).

Evidence for axonal transport was investigated in vitro. Using rat hippocampal neurons cultured in microfluidic devices, Koizumi et al. (2014) studied uptake and transfer of BoNT-A heavy chain in compartmentalized platforms. The simple system consists of two tiny chambers connected by a narrow passage. In one chamber neuronal soma is placed, while in another nerve terminals will grow. Passage between these chambers is so narrow that cell soma cannot pass through and it is retained in soma chamber. In such system Koizumi found activity-dependent uptake of BoNT-A Hc in the terminal chamber that led to a significant increase in SNAP25 cleavage detected in the soma chamber. Blocking autophagosome formation or acidification with wortmannin or bafilomycin A1, respectively, inhibited the activity-dependent retrograde transport of BoNT-A-Hc.

In another study in compartmented cultures of sympathetic neurons from rat superior cervical ganglion, neurons were examined after focal application of BoNT-A. A majority of cleaved SNAP-25 was seen locally, but some appeared along neurites and accumulated in the soma over several weeks. Neurite transection prevented movement of BoNT-A. However, spontaneous or evoked transmission to cell bodies was not inhibited by retrogradely migrated BoNT-A except with high doses. This was interpreted as the lack of evidence for a direct central action of BoNT-A (Lawrence et al. 2012). Opposite results in those two experiments might be addressed to the methodological differences; however, hippocampal (Koizumi et al. 2014) or sympathetic neurons (Lawrence et al. 2012) are not pain-transmitting sensory neurons.

Quantity of BoNT-A used in experimental animals or in human studies is very low, in picograms or low nanograms range that is not possible to trace to individual neurons. Development of antibody against BoNT-A enzymatic product cl-BoNT-A enabled tracing augmented signal and presence cl-SNAP25 in spinal cord and nuclei of cranial nerves (Antonucci et al. 2008; Matak et al. 2011, 2012, 2019).

Percutaneously, injected *formalin* into trigeminal ganglia destroyed all nerves, and after that BoNT-A had no behavioral effect, and no cl-SAP25 was detected upstream of the ganglia. Although rough this experiment excludes the possibility that BoNT-A can bypass trigeminal ganglia and reach trigeminal nucleus by some alternative route.

Cleaved SNAP25 in caudal trigeminal nuclei disappeared after sensory denervation, induced by transcutaneous application of *capsaicin* into trigeminal ganglia (Matak et al. 2014). Finally, the analgesic effect of BoNT-A in the formalin test, in bilateral pain as well, as in CC test, and cl-SNAP25 in the brain was prevented with intraneuronal application of axonal transport blocker colchicine (Bach-Rojecky and Lacković 2009; Filipović et al. 2014). These observations exclude passive spreading of BoNT-A along axons, establishing existence of axonal transport and partial overlapping with the capsaicin sensitive, i.e., vanilloid receptor.

## 5 BoNT-A Target Molecule

Most peripheral terminals of sensory neurons in the skin, viscera, and autonomic ganglia of guinea pig and mice lack immunoreactivity for SV2, SNARE (including SNAP25), or glutamate transporters. In dorsal root ganglia, most small neurons with immunoreactivity for both substance P and CGRP lacked immunoreactivity for SNAP25. Thus, molecular machinery considered essential for vesicular uptake and exocytotic release of glutamate or other neurotransmitters is not expressed at detectable levels by most peripheral sensory neurons containing SP and CGRP in rodents and guinea pig (Morris et al. 2005).

Marinelli et al. (2012) after peripheral administration of BoNT-A, together with the behavioral effects on CC neuropathic pain, found immunofluorescence of the cl-SNAP-25 in all tissues examined, from the peripheral nerve endings, sensory ganglia. Interestingly in the skin sections of naive mice intraplantarly injected only

with saline, there was almost undetectable staining of cl-SNAP25. However in naïve mice injected with BoNT-A, intense GFAP staining in hindpaw nerve endings was accompanied by a diffuse staining of cl-SNAP25. High magnification images show a punctuate staining, interpreted as localization of cl-SNAP25 in the peripheral nerve terminals. Whether those peripheral nerves were sensory or autonomic was not identified. Appearance of cl-SNAP25 is expected effect of BoNT-A protease. On the contrary "punctate staining" as well as presence of any cl-SNAP25 in BoNT-A naïve mice raises the question about the specificity of anti cl-SNAP25 antibody (Marinelli et al. 2012).

Examination of cl-SNAP25 immunohistochemistry in guinea pig bladder after in vivo intramural injection of a toxin showed SNAP25 immunoreactive fibers abundant throughout the bladder tissue in the mucosa and muscular layer. Double labeling showed that toxin cleaves the SNAP25 protein mainly in cholinergic (parasympathetic) but also in adrenergic and sensory fibers (Coelho et al. 2012).

## 6 Transsynaptic, Cell-to-Cell Transport of BoNT-A

Bomba-Warczak et al. (2016) investigated the potential distal effects of BoNT-A, BoNT-D, and tetanus toxin, using hippocampal neurons grown in compartmentalized microfluidic devices. Neurons are placed in soma chamber. After 2 weeks axons were found in the opposing axon chamber. When the axon chamber was incubated with BoNT-A, intensive cleavage was observed in the soma chamber. Using axotomy of cultured neurons and specific antibody against BoNT-A, it was found that all three toxins are taken up, via two separate pathways: (1) usual synaptic vesicle recycling pathway that leads to local effects and (2) a distinct secondary uptake pathway that directs these toxins into non-acidified organelles that mediated retrograde transport to the soma chamber. Toxins were then released into the media, where they exerted their effects upon upstream neurons. These discoveries reveal that BoNT-A and -E similar to tetanus toxin undergo interneuronal transfer and transcytosis in an active form producing long-distance effects (Bomba-Warczak et al. 2016).

In vivo evidence for transsynaptic transport of BoNT-a was found in the CNS or motoric system (Antonucci et al. 2008; Caleo et al. 2018). Possibility of transsynaptic transport in sensory system is discussed together with mirror pain.

## 7 Bilateral Effect of BoNT-A Following Unilateral Injection

Effect of BoNT-A was studied in polyneuropathic pain caused by experimental streptozotocin diabetes (Bach-Rojecky et al. 2010; Favre-Guilmard et al. 2017) and paclitaxel-induced peripheral neuropathy (Favre-Guilmard et al. 2009). In both conditions neuropathic pain develops in both legs, and BoNT-A applied unilaterally reduced pain on both side.

Mirror pain or mirror-image allodynia occurs in the healthy body region contralateral to the site of nociceptive stimuli. This is still a mysterious phenomenon that occurs in association with many clinical pain syndromes and in different animal models of pathological pain.

Sluka et al. (2001) developed model of mirror pain induced by repeated intramuscular administration of acidic saline. Two unilateral injections of low pH saline, 5 days apart, caused a pH-dependent bilateral mechanical, but not heat, hyperalgesia lasting 30 days. Histopathological changes were minimal showing that such chronic muscle-induced pain is unrelated to tissue damage. Lidocaine injection into the gastrocnemius muscle or unilateral dorsal rhizotomy had no effect on the contralateral mechanical hyperalgesia. Apparently after second injection, some memory of the pain has been developed (Sluka et al. 2001).

Injection of 3% carrageenan in the muscle or knee produced hyperalgesia to mechanical and heat stimuli ipsilaterally, which lasted 7–8 weeks and spread to the contralateral side 1–2 weeks after injection. Histologically acute inflammation after 1 week transforms to chronic. Interestingly hyperalgesia that spreads to the contralateral side appeared at the same time period as the inflammation transforms from acute to chronic (Radhakrishnan et al. 2003).

In acidic saline, mirror pain ipsilateral injection of BoNT-A had a bilateral effect, while contralateral injection diminished pain only on that side. Injection of colchicine into the ipsilateral sciatic nerve bilaterally prevented antinociceptive activity of the BoNT-A. However, when colchicine was injected into the sciatic nerve opposite to the site of pain induction and BoNT-A injection, it did not prevent the BoNT-A antinociceptive effect on either side. This observation eliminated possible contribution of the contralateral peripheral nerve endings to the BoNT-A effect. After sciatic nerve was transected, BoNT-A in a dose as low as 0.5 U/kg was injected into the proximal part of a distally cut sciatic nerve, which reduced mirror pain hypersensitivity on the contralateral side. This observation surprisingly demonstrates that BoNT-A antinociceptive effect is independent from peripheral nerve endings (Bach-Rojecky and Lacković 2009).

Bilateral effect of BoNT-A was also demonstrated in mirror pain induced by carrageenan (Favre-Guilmard et al. 2017). In all models tested, BoNT-A alleviates the pain bilaterally.

## 8 Convergence Point of Pain in Trigeminal Region

Different types of pain in trigeminal region caused by formalin injection in a whisker pad, temporomandibular inflammation caused by injection of CFA, or infraorbital nerve constriction injury, much less occipital nerve constriction injury results in neurogenic inflammation of cranial dura (Filipović et al. 2012, 2014; Lacković et al. 2016) characterized by dural extravasation measured by appearance of proinflammatory cells and plasma protein extravasation in meningeal tissue. This phenomenon accompanies selectively only pain in extracranial trigeminal region and cannot be induced by pain in other parts of the body, as well as it is absent in spinal

meninges. Apparently neurogenic inflammation of cranial meninges is a common, convergence point of different types of pain in trigeminal region. Application of BoNT-A abolishes pain behavior and in parallel abolishes the dural inflammation. Immunohistochemically, cl-SNAP25 was found in nerve elements of cranial dura, where it was colocalized with CGRP (Lacković et al. 2016). Those observations create the intriguing question how peripherally applied BoNT-A arrived to dura. BoNT-A effect can be prevented by colchicine injected into the trigeminal ganglion, indicating toxin's axonal transport (Filipović et al. 2012). Still the question remains how BoNT-A crosses from trigeminal extracranial nerve endings to trigeminal nerve endings in dura. Namely, meninges and extracranial trigeminal regions are innervated by separate sensory neurons (Shimizu et al. 2012). The logical conclusion seems that there is transsynaptic transport of retrogradely transported BoNT-A through peripheral branch of trigeminal nerves to trigeminal branches of the same nerve innervating dura. Transcytosis within the trigeminal ganglion after its peripheral injection has been suggested (Kitamura et al. 2009; Shimizu et al. 2012). However, transcytosis in the trigeminal sensory nuclei cannot be excluded (Matak and Lacković 2015; Ramachandran and Yaksh 2014). The third option is extracranial extensions of the nerves innervating the meninges. It is relatively less known that some nerves from dura have extracranial projections through sutures of the skull bones (Kosaras et al. 2009). Using electrophysiological techniques applied on those extracranial nerve terminals of experimental animals, it was found that BoNT-A achieves electrophysiological effects consistent with antimigraine effect (Burstein et al. 2017). Retrograde transport of BoNT-A through those dural extracranial nerves, passing to dura and trigeminal ganglia, seems as a third possibility. However, appearance of BoNT-A activity (cl-SNAP25) in dura after single injection in rat temporomandibular joint (Lacković et al. 2016), or vibrissal pad (Filipović et al. 2012), which is far away from skull sutures, indicates that extracranial extensions of dural nerves could not be only source of BoNT-A activity on meningeal nociceptors. In vitro spontaneous cholinergic neurotransmission is blocked over 80% by 1 pM BoNT-A despite cleaving only less than 20% of the SNAP25 (Lawrence et al. 2013). Clearly only a portion of SNAP25 needs to be cleaved to induce near-complete synaptic silencing.

The effect of BoNT-A beyond first, peripheral sensory neuron has been only fragmentarily investigated. Administration of BoNT-A into the rat whisker pad was without effect on 10 brain regions related to sensation of pain. The only significant effect was increase of concentration of noradrenaline in striatum and serotonin in hypothalamus (Ibragić et al. 2016). Whether this can play a role in reported BoNT-A efficacy for the treatment of depression remains to be investigated (Stearns et al. 2018).

Antinociceptive effects of BoNT-A in formalin and sciatic CC pain were abolished by low dose of intrathecal naltrexone or selective μ-antagonist naloxonazine. Additionally BoNT-A-induced decrease in dorsal horn c-Fos expression was prevented by naltrexone. Apparently this is a central effect because naltrexone abolished the effect of BoNT-A on pain and dural plasma protein extravasation, whereas peripherally acting methylnaltrexone did not. However,

methylnaltrexone decreased the antinociceptive effect of morphine only partially in the second phase of the formalin test and had no significant effect on morphine-mediated reduction in dural neurogenic inflammation (Drinovac Vlah et al. 2018). BoNT-A enhances the analgesic effects of morphine on inflammatory pain and antagonizes tolerance induced by morphine in mice. Since the effects of BoNT-a on the opioid system were prevented by antagonist and augmented by agonist (morphine) (Vacca et al. 2012), it is clear that normal tone of endogenous opioid system, involving central μ-opioid receptor, is required for antinociceptive activity of BoNT-A.

Cl-SNAP25 has been identified in parasympathetic (pre- and postganglionic), sympathetic, and afferent fibers in the urinary bladder. BoNT-A reduces the release of acetylcholine from parasympathetic, norepinephrine from sympathetic, and glutamate and neuropeptides from sensory neurons (Cruz 2014).

Chronic pain is associated with glial activation: hypertrophy, proliferation, and upregulation of glial markers/mediators that modulate excitatory and inhibitory synaptic transmission (Rojewska et al. 2018). In vivo in sciatic nerve and dorsal root ganglia application of BoNT-A diminished neuroimmunological changes, activation of microglia/macrophages. The title of one publication emphasized the importance of glia: *Glia and pain: is chronic pain a gliopathy* (Ji et al. 2013)?

## 9 Emerging New Analgesic

Preclinical studies on experimental animals suggest specific pharmacological and pharmacotherapeutic characteristics:

A. A unique characteristic of BoNT-A is a long-lasting analgesic effect. In experimental animal analgesic, effect lasts up to 3 weeks or longer, in human 3 months and more.
B. BoNT-A has no effect on acute, reflexive, painful stimuli regardless of the cause (thermal, mechanical, chemical) that has important warning function and is vital to the life of the organism. In preclinical research first phase of formal test is the best known example.
C. Antinociceptive activity of BoNT-A is achieved at a lower dose than neuroparalytic activity and occurs usually with delay of 3–5 days after peripheral administration. The lowest effective antinociceptive dose of BoNT-A in rats is 3.5 U/kg after peripheral intraplantar administration (Bach-Rojecky et al. 2005), while a dose of 30 U/kg cause muscular weakness (Cui et al. 2004). Because BoNT-A has both analgesic and muscle relaxing/paralytic activity, the behavioral outcome, which is measured in experimental animals, is the balance between the two. This is probably the reason that up to now, there is no any reliable dose response of BoNT-A analgesic activity.
D. BoNT-A has a long-lasting analgesic effect in chronic pain of different origin like inflammatory pain, including neurogenic pain of the meninges, neuropathic pain, chronic visceral pain arising from inflammation, benign and malignant tumors, etc.

E. Regardless of the cause of chronic pain, up to now there are no negative results published. Accordingly, in experimental animals, it seems that BoNT-A has beneficial effect on all types of chronic pain, hyperalgesia, and allodynia.

In experimental animal beneficial effect of BoNT-A was reported in a model of trigeminal neuropathy (Filipović et al. 2012), trigeminal mandibular disorder (Lacković et al. 2016) or streptozotocin diabetes (Bach-Rojecky et al. 2010), and dozens more.

After registration for treatment of chronic migraine, analgesic effects of BoNT-A have been studied in many human disorders. In a short survey of PubMed in the 5-year period (Dec 2012–Oct 2019), we found 23 clinical trials in 14 painful disorders and 30 review-type publication (review, systemic review, meta-analysis, Cochrane, etc.) focused on 18 indications.

According to the American Academy of Neurology (AAN), the quality and risk of bias of clinical trials are evaluated and are categorized into Classes I, II, III, or IV. Quality and risk of bias decrease and increase, respectively, from Class I to Class IV studies. Moreover, recommendations for treatments can be formed after evaluation and classification of the evidence from strong to weak (level A to C), based on the quality and quantity of all the available scientific evidence.

Level of evidence for efficacy of BoNT-s in different pain syndromes using the recommended efficacy criteria from the Assessment and Therapeutic Subcommittee of the American Academy of Neurology is as follows (Safarpour and Jabbari 2018):

There is a level A evidence (effective) for BoNT therapy in

- Post-herpetic neuralgia
- Trigeminal neuralgia
- Posttraumatic neuralgia

There is a level B evidence (probably effective) for:

- Diabetic neuropathy
- Plantar fasciitis
- Piriformis syndrome
- Pain associated with total knee arthroplasty
- Male pelvic pain syndrome
- Chronic low back pain and male pelvic pain
- Neuropathic pain secondary to traumatic spinal cord injury

BoNT-s are possibly effective (Level C – one class II study):

- For female pelvic pain
- Painful knee osteoarthritis
- Post-operative pain in children with cerebral palsy after adductor release surgery
- Anterior knee pain with vastus lateralis imbalance

## 10 Conclusion

This review is focused on mechanism of action of BoNT-A including the action beyond peripheral nerve endings. With the exception of meninges and possibly urinary bladder, the inactivation of peripheral SNAP25, as a target molecule, is not convincingly demonstrated. In a model of mirror pain, BoNT-A analgesic effect can be achieved even without participation of peripheral nerve ending. Finding of axonal transport of BoNT-A from periphery to the CNS opens the way for new discoveries of its action beyond first sensory neuron, as well as new discoveries about chronic pain and formation of the memory of pain. There is increasing evidence that BoNT-A is preventing pain in a growing range of disorders. In the absence of unexpected findings, or an increase in the uncontrolled use of illicit preparations by uneducated persons, BoNT-A is emerging as a new long-lasting and relatively safe analgesic.

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