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# Reduction in Post-Botulinum Toxin Flu-like Symptoms After Injection with Incobotulinum Toxin

Edwin George

*Wayne State University*, [egeorge@med.wayne.edu](mailto:egeorge@med.wayne.edu)

Natalya Shneyder

*Wayne State University*

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School of Medicine

# Reduction in Post-Botulinum Toxin Flu-like Symptoms After Injection with Incobotulinum Toxin

Edwin George, MD, PhD and Natalya Shneyder, MD  
Wayne State University School of Medicine, Detroit, MI

## ABSTRACT

**OBJECTIVE:** To determine if patients reporting flu-like symptoms (FLS) after botulinum toxin (BoNT) injections are less susceptible to this reaction after incobotulinum toxin.

**BACKGROUND:** Approximately 10% of patients injected with BoNT in our clinic complain of FLS, primarily malaise, myalgias and rhinorrhea, beginning a few days to one week after injection and lasting one week or less. A review by Baizabal-Carvalho et al. (*Toxicon*, 2011, 58:1-7) found rates of FLS between 1.7 and 20% in patients after various preparations of botulinum toxin A, and a subsequent study showed increased cytokines in patients with FLS (*Neurotoxicity Research*, 2013, 24:298-306). Besides the neurotoxin itself, most BoNT preparations contain associated complexing proteins (NAPs), most of which are hemagglutinins. It is thought that NAPs induce the release of inflammatory cytokines, which may cause the FLS. Incobotulinum toxin is a botulinum toxin A preparation where the active peptide is separated from the NAPs (hemagglutinins and non-hemagglutinins) through a series of steps yielding the active neurotoxin with molecular weight of 150 kDa, without accessory proteins.

**DESIGN/METHODS:** Consecutive patients who reported FLS consistently occurring after previous BoNT injections (> two prior treatment sessions, average 21 sessions, patients reporting FLS after “most sessions”) were offered further injections with incobotulinum toxin at similar doses.

**RESULTS:** Six patients were identified as having had FLS and given injections with incobotulinum toxin. Three were cervical dystonia patients, and one each with blepharospasm, hemi-facial spasm and tics secondary to Tourette’s. All reported a satisfactory clinical response similar to their previous injections. One patient had only rhinorrhea, the others had malaise and myalgias. None of the patients experienced flu-like symptoms after incobotulinum toxin injections (16 treatment sessions).

**CONCLUSIONS:** Initial results from this open-label, unblinded series suggests patients who have consistently experienced FLS after BoNT injections are much less likely to do so after injection with incobotulinum toxin.

## REFERENCES

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Wayne State University  
Neurology Movement Disorders  
Neurology.med.wayne.edu



## INTRODUCTION

Clostridium botulinum are anaerobic bacteria that produce botulinum neurotoxins that cause botulism by interfering with synaptic transmission at neuromuscular junctions. Different clostridium botulinum strains produce seven immunologically distinct serotypes of botulinum neurotoxins, but only serotypes A, B, and F have been used for therapeutic purposes. Serotype A is the most frequently used. Three forms of botulinum toxin A are commercially available in the USA: Botox® (Allergan, Irvine, CA), Dysport® (Ipsen Biopharm, Wrexham, UK), and Xeomin® (Merz Pharmaceuticals, Frankfurt, Germany). The non-A serotype, botulinum toxin B, is commercially available as Myobloc® (Solstice Neurosciences, Inc., South San Francisco, CA, USA). Each preparation has a unique pharmacological profiles and set of side effects (Albanese, 2009). Many adverse effects have been reported with botulinum neurotoxin administration, but most of them are related to the mechanism of action of the toxin, including muscle weakness, ptosis, and dysphagia. Systemic reactions following botulinum neurotoxin administration primarily comprise nausea, fatigue, malaise, rash, and flu-like symptoms. Flu-like symptoms refers to a group of symptoms that includes: fever, nonproductive cough, sore throat, myalgia, shivering, chills, malaise, anorexia, and headache (Cox and Subbarao, 1999). Besides the neurotoxin itself, most botulinum neurotoxin preparations contain associated complexing proteins, most of which are hemagglutinins. It is thought that these neurotoxin associated proteins induce the release of inflammatory cytokines, which may cause the flu-like symptoms.

## RATIONALE

Incobotulinum toxin is a botulinum toxin A preparation where the active peptide is separated from the neurotoxin associated proteins (hemagglutinins and non-hemagglutinins) through a series of steps yielding the active neurotoxin with molecular weight of 150 kDa, without accessory proteins. Since it is thought the neurotoxin associated proteins may be responsible for the flu-like symptoms associated with botulinum toxin injections, we decided to offer incobotulinum toxin A injections to patients who had previously reported any of the flu-like symptoms after botulinum toxins.

## METHODS

Consecutive patients who reported flu-like symptoms consistently occurring after previous botulinum toxin injections were offered further injections with incobotulinum toxin at similar doses. All patients included had undergone more than two prior treatment sessions, and the average was 21 sessions/patient. Patients reporting any of the flu-like symptoms after previous injections were asked about the frequency with which the symptoms had occurred. Specific occurrences could not be reliably quantified retrospectively in all cases, but the patients included identified one or more flu-like symptoms as occurring within one week after “most treatment sessions”, and believed they had experienced a consistent pattern of flu-like symptoms after the prior injections.

## RESULTS

Six patients were identified as having had flu-like symptoms and given injections with incobotulinum toxin (3 male, 3 female, mean age 59 years, range 26-80 years). Three were cervical dystonia patients, and one each with blepharospasm, hemi-facial spasm and tics secondary to Tourette’s. All reported a satisfactory clinical response to incobotulinum injections similar to their previous injections. One patient had only rhinorrhea, the others had malaise and myalgias. None of the patients experienced flu-like symptoms after incobotulinum toxin injections (16 treatment sessions).

Indication for Botulinum Toxin Therapy	N	Botulinum toxin	Flu-like Symptoms
Cervical dystonia	2	Onabotulinum toxin A	Myalgias & malaise
	1	Rimabotulinum toxin B	Myalgias & malaise
Blepharospasm	1	Onabotulinum toxin A	Myalgias & malaise
Hemi-facial spasm	1	Onabotulinum toxin A	Rhinorrhea & malaise
Organic tics	1	Onabotulinum toxin A	Myalgias & malaise

## DISCUSSION

This was an open-label, unblinded clinical series with a very small number of patients, so the interpretation is limited. None of the patients identified had been on abobotulinum toxin A (Dysport®). The package insert for Xeomin® (incobotulinum toxin A) indicates that nasopharyngitis and respiratory tract infection were reported in clinical trials at rates greater than for placebo (5% vs. 3%), and although myalgias and malaise were not listed as adverse effects seen in clinical trials, myalgia is mentioned as occurring in post-marketing reports. Nonetheless, rates of flu-like symptoms reported for the other botulinum toxin preparations are higher, similar to our own experience of approximately 10% (*Toxicon*, 2011, 58:1-7). These differences are of uncertain significance, but the cross-over nature of our clinical experience suggests they are real.

## CONCLUSIONS

Initial results from this open-label, unblinded series suggests patients who have consistently experienced flu-like symptoms after injections with other botulinum toxin are much less likely to do so after injection with incobotulinum toxin.

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