Decrease in Therapeutic Effect Among Botulinumtoxin Type A Agents: Analysis of the FDA Adverse Event Reporting System Database

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BACKGROUND

- There are three FDA (Food and Drug Administration) approved botulinum toxin type A (BoNT-A) agents: onabotulinumtoxinA (Botox®; Allergan, Inc.; initial FDA approval 1989), abobotulinumtoxinA (Dysport®; Galderma Laboratories, L.P. for cosmetic; initial FDA approval 2009), and incobotulinumtoxinA (Xeomin®; /Bocouture®, Merz Pharmaceuticals GmbH; initial FDA approval 2010).
  - Specific potency units, dosing, and reconstitution are unique for each botulinum toxin type A agent[3–6].
  - Published literature comparing BoNT-A agents for antibody formation, resistance, and loss of effect is lacking.
  - IncobotulinumtoxinA is the only botulinum toxin type A (BoNT-A) agent that has removed the unnecessary proteins, leaving just the 150 kDa active component.
- The FDA Adverse Event Reporting System (FAERS) is an open access data-base, which contains passive adverse event surveillance data reported to the FDA by health professionals, consumers, or pharmaceutical manufacturers, and helps to support the FDA's post-approval safety surveillance program[7, 8].
  - FAERS is the world's largest pharmacovigilance database to date, with over 9 million adverse events reported just since 2004[9].
- The aim of this analysis was to assess the BoNT-A agents for decreased therapeutic effect over time.

METHODS

- The United States FDA adverse event reporting system (FAERS) database was utilized.
- The analysis was conducted on data between March 2014 and September 2017.
  - BoNT-A cases were included when it was considered the "Primary Suspect" drug.
- The primary outcome was relative incidence of decreased therapeutic effect, defined as presence of either 'therapeutic response decreased' and/or 'drug effect decreased' being reported as an AE, divided by all cases of AEs (which was the previously mentioned "Preferred Term" (PT) variable, present in the REACTION data file).
- This relative rate methodology has been well described previously in the pharmacovigilance literature.
- All three FDA approved botulinum toxin type A agents were included in the analysis: onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA.
- Data are available for download on the FDA website in 7 separate data files (DEMOGRAPHIC, DRUG, REACTION, OUTCOME, REPORT SOURCE, THERAPY, INDICATIONS), uploaded quarterly.
  - These 98 different data files (14 quarters with 7 data files each) were downloaded into a SQLite database (version 3.24.0) and merged on caseid. AEs in FAERS are coded to match the "PT" level medical terminology preferred by the Medical Dictionary for Regulatory Activities (MedDRA, version 21.0).
- Inclusion criterion was all botulinum toxin type A adverse events reports in which they were considered the "Primary Suspect" drug (coded as "PS" in the ROLE_COD variable of the DRUG data file).
- Exclusion criterion included having insufficient information reported to identify which botulinum toxin type A agent was utilized or any of the following AEs being reported: 'Product preparation error', 'Wrong technique in product usage process', 'Incorrect dose administered', 'Product storage error', or 'Poor quality drug administered'.
  - Those specific AEs were excluded from the analysis in order to reduce confounding, as they were considered possible alternative causes of decreased therapeutic effect.
- Similar indications were combined into one category whenever possible. For example, 'skin wrinkling', 'skin cosmetic procedure', and 'face lift' were all categorized under 'cosmetic' for indication.
  - Additionally, AEs listed as "Botox Cosmetic" without a given indication were assumed to be for cosmetic use.
  - IncobotulinumtoxinA and abobotulinumtoxinA did not have this assumption made, as the specific cosmetic names of those products was not a selectable option for reporters of AEs.
  - OnabotulinumtoxinA and Botox Cosmetic® were combined under onabotulinumtoxinA for this analysis, as they contain the same active ingredient.

RESULTS

- A total of 12,280 BoNT-A cases were included across a wide array of cosmetic and therapeutic indications.
- Presence of AEs involving decreased therapeutic effect for incobotulinumtoxinA was 2.2% (15/689); for abobotulinumtoxinA was 9.2% (79/858); and for onabotulinumtoxinA was 11.6% (1,247/10,733).
- Relative incidence of decreased therapeutic effect for patients on >1 year of treatment versus <1 year for incobotulinumtoxinA was 0.0% (0/10) vs 4.5% (13/291); for abobotulinumtoxinA was 11.9% (36/302) vs 4.3% (11/257); and for onabotulinumtoxinA was 19.6% (504/2,577) vs 10.1% (539/5,350).

Table 1: Botulinum toxin type A patient demographics (n = 12,280)

Variable	n	Value (%)
Age, mean in years (SD)	5206	49.4 (14.7)
Gender		
Female	10338	84.2%
Male	1215	9.9%
Unknown	727	5.9%
Drug		
OnabotulinumtoxinA	10733	87.4%
AbobotulinumtoxinA	858	7.0%
IncobotulinumtoxinA	689	5.6%
Indication		
Cosmetic	8047	65.5%
Therapeutic (all indications)	3032	24.7%
Unknown	1201	9.8%
Length of Therapy, mean in years (SD)	8850	0.9 (1.7)
Country		
USA	9934	80.9%
All other countries	646	5.3%
Unknown	1700	13.8%

Figure 1: Decreased Effect (All)

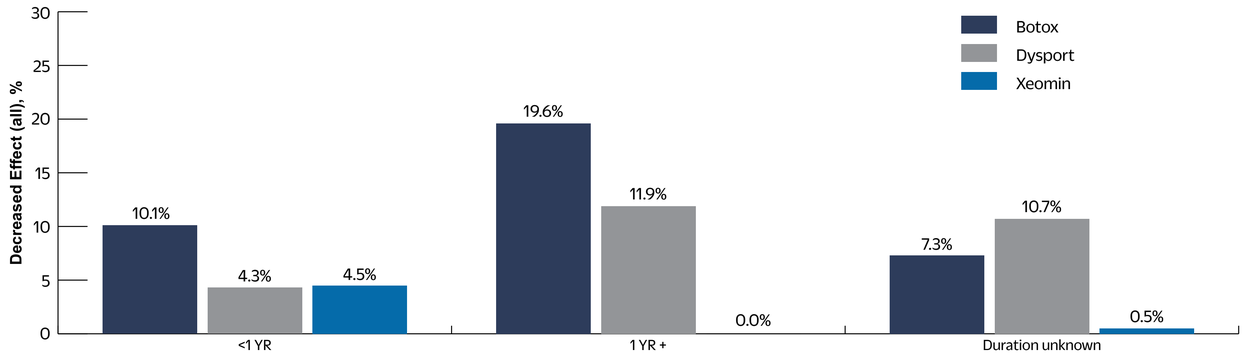
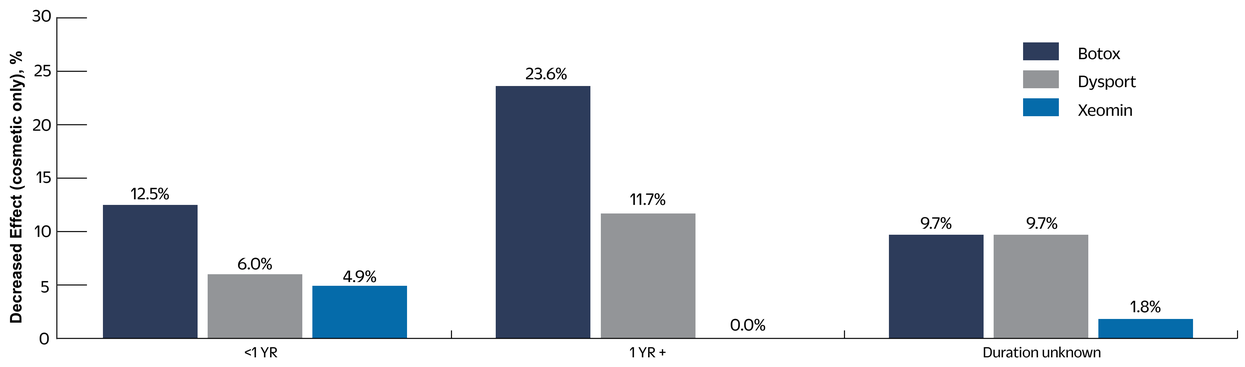


Figure 2: Decreased Effect (Cosmetic only)



DISCUSSION

- The percentage of BoNT-A adverse events involving decreased therapeutic response was higher with longer lengths of therapy in the present analysis
- Studies have shown that hemagglutinin components present in BoNT-A complexing proteins can elicit an immunogenic response[8]. Additionally, literature has suggested that even in patients with pre-existing positive neutralizing antibody titres from past BoNT-A therapy, the majority have their titres return to undetectable levels while on incobotulinumtoxinA therapy in a similar fashion to cessation of BoNT-A therapy[9].
- A recent long term study in 596 BoNT-A patients showed that incobotulinumtoxinA-only patients had zero (0%) development of neutralizing antibodies versus 15.1% for all other patients[10].
- Relative rates used in this analysis should not be confused with true incidence rates. A validated methodology has not been established to calculate true incidence rate from pharmacovigilance databases.
- There are several limitations to the present analysis. It was a retrospective analysis of a pharmacovigilance database with optional reporting requirements. Additionally, given the nature of these optional reporting requirements, there was a high degree of missing data for some variables. Included within this was missing data for length of therapy on incobotulinumtoxinA. Other limitations include different lengths of time since product approvals, different FDA indication mixes, and variability in market share.
  - More important than total numbers of AEs for such pharmacovigilance database analyses is the relative rate of the AE of interest for each respective drug. Therefore, the difference in total AEs reported between drugs is an inherent limitation of such pharmacovigilance analyses, but not unexpected.
  - It should be noted this analysis was exploratory. The aim was not to establish causality with this pharmacovigilance database retrospective study, but rather identify associations that would be of interest to decision makers and safety experts.

CONCLUSIONS

- **Based on these preliminary findings, the decrease in BoNT-A therapeutic effect over time warrants further study.**

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Disclosure: This analysis was unfunded. Dr Kazerooni was an employee of Merz North America, Inc. at the time this analysis was conducted.