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DRUG USE EVALUATION: UTILIZATION OF BOTULINUM TOXIN

There are currently four botulinum toxin (BoNT) products available in the United States: abobotulinumtoxinA (ABO), incobotulinumtoxinA (INC), onabotulinumtoxinA (ONA), and rimabotulinumtoxinB (RIM). They are used for a variety of FDA approved and off label indications. The goal of this drug use evaluation is to quantify the use of BoNT in OHP that lacks evidence for benefit or is not currently funded by OHP in order develop prior authorization criteria for the FFS program.

Background:

There are seven serologically distinct forms of BoNT, A through G. Each neurotoxin works at a distinct site. Botulinum toxins now play a role in the management of a variety of medical conditions.[1] Three distinct serotype A botulinum toxin (BoNT A) products, ABO, INC, ONA, and one serotype B botulinum toxin (BoNT B) product, RIM, have been approved by the U.S. Food and Drug Administration (FDA) (Table 1). The most recent preparation approved is INC in 2010. Due to the unique manufacturing process used to produce each product, they are chemically, pharmacologically, and potentially clinically distinct. Moreover, units of biological activity are unique to each BoNT product and cannot be compared or converted into units of another product. In addition, there are no universally accepted safe dose conversion ratios. BoNTs are used for a variety of conditions including, blepharospasm, cervical dystonia, strabismus and upper limb spasticity, where the goal of therapy is to reduce contraction of striated or smooth muscle. [1] All of the products have a black box warning in their labeling regarding the risk of BoNT spreading beyond the site of injection, resulting in adverse events and death in some cases. BoNT A has become first line therapy for cervical dystonia and blepharospasm.[2] Not all patients respond well to BoNT A though, and 5 to 10% become resistant to it.[3] In these cases, BoNT B is an alternative to BoNT A. [2] Head to head studies comparing the efficacy and safety of different BoNT formulations are limited.[4] However, there is evidence that ABO and ONA are similar in efficacy for the treatment of cervical dystonia, blepharospasm, and spasticity.[5]

Table 1: FDA approved Indications

Drug	FDA approved indications*
OnabotulinumtoxinA (Botox®)	Prophylaxis of chronic migraines, upper limb spasticity, cervical dystonia, axillary hyperhidrosis, bladder dysfunction (detrusor over activity associated with a neurologic condition or overactive bladder), blepharospasm, strabismus
AbobotulinumtoxinA (Dysport®)	Cervical dystonia
RimabotulinumtoxinB (Myobloc®)	Cervical dystonia
IncobotulinumtoxinA (Xeomin®)	Cervical dystonia, Blepharospasm

The use of BoNT has been evaluated for prophylaxis treatment of migraines. Common prophylactic treatments for migraines include beta-blockers, tricyclic antidepressants, antiepileptic drugs, and lifestyle management. ONA is the only BoNT approved by the FDA for the prophylactic treatment of chronic migraine. There is lower quality evidence that unspecified BoNT A products may be associated with benefit in the prophylaxis of chronic daily migraine headaches (15 or more headaches per month), but results are inconsistent.[6–8] In addition, the clinical significance remains uncertain, as the absolute reduction in the number of headaches is only 2 to 3 headaches per month.[6] A recent draft technology assessment on controversies in migraine management by the Institute for Clinical and Economic Review (ICER) confirms this.[9] The systematic review and meta-analysis demonstrated a small clinical improvement with BoNT compared to placebo injections, with a reduction in 2.3 migraine headache days per month.[9] None of the BoNT formulations are approved for the prophylactic treatment of chronic tension-type headache or intermittent migraine attacks, and there is moderate quality evidence of no benefit of prophylaxis with BoNT A in these patients.[6–8]

There are additional uses of BoNT that may be considered appropriate for patients who have tried and failed other more conservative or more effective treatments. This includes use in anal fissures, and urinary incontinence due to detrusor over activity associated with a neurologic condition. [5] Table 4 also describes indications in which there is no evidence to support the use of BoNT or evidence of no benefit. Cosmetic procedures involving BoNT injections and treatment of primary axillary hyperhidrosis are not covered by OHP. BoNT has been studied in a number of other disorders where there is evidence of no benefit or insufficient evidence to recommend its use. This includes gastroparesis, restless legs syndrome, benign prostatic hyperplasia, lower back pain, and spasmodic dysphonia.[5]

Methods:

This is a descriptive, observational study to determine prevalence of diagnoses associated with patients with BoNT claims. The study population includes all patients with 1 or more paid FFS or encounter drug, professional or outpatient claim for BoNT (Appendix 1) in the calendar year 2013. Patients were excluded if they were also enrolled in Medicare Part D as identified by a benefit package of BMM or BMD or if they were eligible for less than 75% of days during the calendar year.

In addition, professional and outpatient claims from January 1, 2012 through April 30, 2014 were used to classify each patient into the mutually exclusively categories in Table 4 in priority: 1) Evidence-supported first-line use 2) Evidence-supported second-line use 3) Unclear benefit 4) Limited evidence of no benefit and/or not funded by OHP and 5) no identified diagnosis. Patients could have more than one diagnosis within each of the 5 categories.

Profiles in the Second-Line and Unclear categories were manually reviewed to make a final determination of the indication that BoNT was used for and the appropriateness of that therapy. Patients using BoNT for

migraine were deemed "appropriate" if there was claims evidence of a trial of 3 alternative prophylactic medications. It was not possible to determine the number of migraines experienced per month from claims data, and relied on the ICD-9 codes for "Chronic" vs "Episodic" to make the assumption that patients with "Chronic" migraines experienced at least 15 episodes per month. Patients using BoNT for neurogenic bladder were deemed "appropriate" if there was claims evidence of a neurological cause and a prior trial of antimuscarinic drug.

Results:

There were 558 unique patients identified for this study. After exclusion of 275 Medicare patients and 24 patients that were eligible for Medicaid coverage less than 75% of the study period, there was a unique study population of 272 patients.

Table 2 displays the demographics. The majority of study patients were adults (73%), Caucasian (84%), female (65%) and were enrolled in Coordinating Care Organizations [CCO] (84%). The study population is similar to all Medicaid BoNT users with the exception of age and CCO enrollment. The Medicare exclusion resulted in a study population that was generally younger than all BoNT users (mean age 31.5 years versus 43.3 years). Children were also more prevalent in the study population (27% versus 14%). Study patients were also more likely to be enrolled in a CCO (84% versus 68%).

TABLE 2: PATIENT DEMOGRAPHICS

		All BoNT Patients		Study BoNT Patients	
	n=	**558**	**%**	**272**	**%**
Age					
	Mean (min-max)	43.3	0-90	31.5	0-67
	< 13	52	9.3%	49	18.0%
	13-18	24	4.3%	24	8.8%
	19-64	397	71.1%	196	72.1%
	> 64	85	15.2%	3	1.1%
Sex					
	M	196	35.1%	95	34.9%
	F	362	64.9%	177	65.1%
Ethnicity					
	Caucasian	482	86.4%	227	83.5%
	Non-Caucasian	76	13.6%	45	16.5%
Claims Source*					
	FFS	183	32.8%	43	15.8%
	Encounter	381	68.3%	229	84.2%

* 6 patients from the "All BoNT Patients" group had both FFS and Encounter claims. So, the total percent is >100%.
BoNT = botulinum toxin

Table 3 displays utilization by product and claim source. As expected, most were billed on professional or outpatient claims and more than $709,000 was reimbursed to providers during calendar year 2013. Of this number, about $541,000 was paid on CCO claims and the $168,000 was paid on FFS claims. The average CCO claim cost of $627 was $173 (28%) more than the average FFS claim cost of $454. Finally, over 86% of market share by claim count is associated with ONA.

TABLE 3: **All BoNT Product Utilization - Pharmacy and Medical, Calendar Year 2013**

Pharmacy		**FFS**			**CCO**		
HSN	**Description**	**Patient Count**	**Claim Count**	**Sum Amt Paid***	**Patient Count**	**Claim Count**	**Sum Amt Paid***
004867	ONABOTULINUMTOXINA (BOTOX, BOTOX COSMETIC)	2	2	$191	2	2	$2,146
036477	ABOBOTULINUMTOXINA (DYSPORT)	1	1	$157			
036687	INCOBULINUMTOXINA (XEOMIN)						
021869	RIMABOTULINUMTOXINB (MYOBLOC)						
Medical		**FFS**			**CCO**		
Proc Code	**Description**	**Patient Count**	**Claim Count**	**Sum Amt Paid***	**Patient Count**	**Claim Count**	**Sum Amt Paid***
J0585	Injection, Onabotulinumtoxina, 1 Unit	163	308	$157,322	346	746	$483,150
J0586	Injection, Abobotulinumtoxina, 5 Units	13	35	$7,098	13	39	$11,195
J0587	Injection, Rimabotulinumtoxinb, 100 Units	1	3	$0	3	7	$18,739
J0588	Injection, Incobotulinumtoxin A, 1 Unit	10	21	$3,305	24	70	$26,191
	Unique by Plan Type	183	370	$168,073	381	864	$541,420
	Unique, FFS/MCO Combined	558	1234	$709,493			

* Rebate revenues are not included in this figure.

Table 4 displays the number of unique patients by exclusive diagnostic evidence category. Prior to the manual review, the prevalence of diagnoses were similar in the study and all BoNT users (not shown). Over 73% of study patients had a claim for a diagnosis supported by evidence and <4% had claims for diagnoses that are not funded by the OHP or evidence of no benefit of BoNT. BoNT was used by a single patient for "Other disorder of binocular eye movements", a diagnosis where BoNT has unclear benefit. Of note, 22.8% of study patients used BoNT for diagnoses where it is not recommended first-line and the majority had a migraine diagnoses. Not shown in Table 4 is that of the total 43 FFS patients included in this study, 90.7% (n=39) of the patients were prescribed therapy according to supported evidence. This is in comparison to just

67.7% (n=155) of the 229 CCO patients. In CCO patients, the second most common category was in second line use of BoNT.

TABLE 4: DIAGNOSTIC CATEGORY DISTRIBUTION

ICD-9	Diagnostic Category	n=	%
Evidence or guidelines supporting BoNT use first-line		**199**	**73.2**
333.6x *333.7x* *333.81* *333.83* *333.89*	*Genetic torsion dystonia* *Acquired torsion dystonia* *Blepharospasm* *Spasmodic torticollis* *Other fragments of torsion dystonia*	86	31.6
 340.xx *341.0* *342.xx* *343.xx* *344.0x* *344.1* *344.2* *344.4x* *344.5* *378.73*	*Secondary spasticity and strabismus in other neuromuscular disorders* *Multiple sclerosis* *Neuromyelitis optica* *Spastic hemiplegia, Other specified hemiplegia,* *Cerebral palsy* *Quadriplegia and quadraparesis* *Parapalegia,* *Diplegia of upper limbs,* *Monoplegia of upper limb,* *Unspecified monoplegia* *Strabismus in other neuromuscular disorders*	132	48.5
Evidence for BoNT use is second-line or in specific circumstances only		**62**	**22.8**
596.5x, *788.3x*	*Other functional disorders of bladder (e.g. Hypertonicity of bladder, Neurogenic bladder NOS, Detrusor sphincteric dyssynergia).* *Urinary incontinence*	9	3.3
346.xx	*Migraine*	46	16.9
530.0 *530.5*	*Achalasia and cardiospasm* *Dyskinesia of esophagus*	4	1.5
728.85 *727.81*	*Spasm of muscle;* *Contracture of tendon (sheath)*	3	1.1
527.7	*Disturbance of salivary secretion (sialorrhea)*	0	0.0
Low quality or insufficient evidence of unclear benefit		**1**	**0.4**
787.2x	*Dysphagia*	0	0.0
378 (excluding 378.73)	*Other disorders of binocular eye movements (e.g. Esotropia, Exotropia, mechanical strabismus, sixth nerve palsy).*	1	0.4
Limited Evidence of no benefit and/or not funded OHP indications		**10**	**3.7**
333.xx (excluding 333.6x, 333.7x,333.81, 333.83,333.89) *307.2x* *351.xx* *478.75* *478.79*	*Other extrapyramidal disease and abnormal movement disorders (excluding torsion dystonias)* *Tics* *Facial nerve disorders* *Laryngeal spasm* *Spastic Dysphonia*	8	2.9
705.xx *780.8*	*Disorders or sweat glands (e.g. Focal hyperhidrosis)* *Generalized hyperhidrosis*	1	0.4
565.0	*Anal fissure*	0	0.0
723.xx *724.xx* *729.1*	*Other disorders of cervical region* *Other and unspecified disorders of back* *Myalgia and myositis, unspecified*	2	0.4
339.xx *307.8x*	*Other headache syndromes (e.g. tension headache)* *Pain disorders related to psychological factors (e.g. tension headache)*	0	0.0
536.3	*Gastroparesis*	0	0.0
600.xx	*Hyperplasia of prostate*	0	0.0
335.20	*Amyotrophic sclerosis.*	0	0.0
None of selected conditions		**0**	**0**

Sixty-two patients (22.8%) were using BoNT for a second line therapy. The two most common conditions were either overactive bladder (9 patients, 3.3%) or migraine (46 patients, 16.9%). Upon manual review of the migraine patients, 14 (30.4%) met criteria for appropriate BoNT use, while 32 (69.6%) did not. Of the 9 patients categorized under overactive bladder, 4 (44.4%) were classified as having neurogenic etiology, with prior use of antimuscarinic therapy, and 5 (55.6%) failed to meet this criteria. Three patients had diagnoses of both contracture of tendon and abnormality of gait, not associated with an associated musculoskeletal condition such as cerebral palsy. There is insufficient evidence evaluating the efficacy and safety of BoNT for these conditions not associated with a neurologic or musculoskeletal condition.[10] Lastly, there were 4 patients using BoNT for achalasia (1.5%). BoNT could be appropriate in achalasia patients who are not candidates for the other surgical treatments (older patients with multiple comorbidities).[11] It could not be determined if these patients were appropriate from the claims data.

Discussion:

Overall, the patients utilizing BoNT carry multiple, complex medical problems and many were severely disabled. From these data it was determined the majority of patients using BoNT (73.2%) were associated with diagnoses with strong supporting evidence, and an additional 6.6% utilized BoNT appropriately for second line therapy. The remaining 20.2% either had unclear benefit, no benefit, or used BoNT inappropriately for secondary treatment according to treatment guidelines.[8,9,12,13,14] Literature describing BoNT utilization, as well as use of other appropriate preventive medications, in Medicaid programs is lacking.[15]

The off-label indications continue to expand for BoNT in both neurological and non-neurological disorders. This could greatly impact the future OHP costs associated with BoNT. The majority of BoNT cost was in the CCO patient population ($541,420), as was the majority of inappropriate use (~33% of CCO patients versus 9% of FFS patients). Much of the inappropriate use in the CCOs was associated with chronic migraine where the clinical benefit is debatable.[9] The remaining inappropriate use was largely in patients with overactive bladder, but to a much smaller degree than chronic migraine.

Due to the retrospective and descriptive design of this study, there are certain limitations of importance. It should be noted that claim data can only associate patients with the same drugs and diagnoses but does not indicate the specific diagnosis a drug is prescribed for. In addition, the study period only extends back to January 1, 2012 and it is possible that prior utilization may reduce the amount of "inappropriate" use for migraine or neurogenic bladder. A total of 18% of the Medicaid study patients were less than 13 years of age. Medicare patients were excluded. This, in addition to the high-risk nature the population, could result in a higher percentage of appropriate use than what might be seen in non-Medicaid populations.

Overall the majority of patients in our study population had claims evidence of using BoNT appropriately. However, a significant portion (20.2%), primarily from CCOs, did not. This is predominantly driven by use for prevention of chronic migraine. Currently, prior authorization for use of BoNT in chronic migraine and other

off-label indications is required in many other state Medicaid programs and could help curb inappropriate use in the Oregon Medicaid population.[16]

Recommendation:

1) Consider implementing prior authorization criteria in FFS to limit use to evidence supported diagnoses.

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Appendix 1:– Drug Identifiers

HSN	Generic Drug Name
004867	ONABOTULINUMTOXINA (BOTOX, BOTOX COSMETIC)
036477	ABOBOTULINUMTOXINA (DYSPORT)
021869	RIMABOTULINUMTOXINB (MYOBLOC)
036687	INCOBULINUMTOXINA (XEOMIN)

ProcCode	Descriptions
J0585	Injection, onabotulinumtoxinA, 1 unit
J0586	Injection, abobotulinumtoxinA, 5 units
J0587	Injection, rimabotulinumtoxinB, 100 units
J0588	Injection, incobotulinumtoxinA, 1 unit
52287	Cystourethroscopy, with injection for chemodenervation of the bladder
64612	Chemodenervation of muscle; muscle(s) innervated by facial nerve, unilaterial (For blepharospasm, hemifacial spasm)
64615	Chemodenervation of muscle; muscle(s) innervation by facial trigeminal, cervical spinal and accessory nerves, bilaterial (For chronic migraine)
64616	Chemodenervation of muscle; neck muscle(s) excluding muscles of the larynx, unilateral
64617	Chemodenervation of muscle(s); larynx, unilateral, percutaneous, includes guidance by needle
64642-64647	Chemodenervation of extremity or truck muscles
64650	Chemodenervation of endocrine glands; both axillae
64653	Chemodenervation of endocrine gland; other areas
67345	Chemodenervation of extraocular muscle
46505	Chemodenervation of internal anal sphincter
95873	Electrical Stimulation for guidance in conjunction with chemodenervation
95874	Needle electromyography for guidance in conjunction with chemonervation