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ORIGINAL RESEARCH

Botulinum Toxin Utilization, Treatment Patterns, and Healthcare Costs Among Patients with Spasticity or Cervical Dystonia in the US

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ABSTRACT

Introduction: Spasticity and cervical dystonia (CD) are movement disorders with considerable direct and indirect healthcare cost implications. Although several studies have discussed their clinical impact, few have calculated the economic burden of these disorders. This study aimed to understand treatment/injection patterns of botulinum toxins type A (BoNT-As) and the characteristics, healthcare resource utilization (HCRU), and costs among patients with spasticity or CD.

Methods: Retrospective analyses were conducted using administrative healthcare claims from the IQVIA PharMetrics® Plus database, from October 1, 2015 to December 31, 2019. Eligible patients were selected based on Healthcare Common Procedure Coding System codes for BoNT-A (index date) and ICD-10 diagnosis codes for spasticity or CD with 6 months of continuous enrollment pre-index and 12 months post-index. Patients were stratified into adult spasticity, pediatric spasticity, and CD cohorts, and were evaluated for injection patterns, HCRU, and costs in the post-index period.

Results: Overall, 2452 adults with spasticity, 1364 pediatric patients with spasticity, and 1529 adults with CD were included. Total mean all-cause healthcare costs were US$42,562 (adult spasticity), $54,167 (pediatric spasticity), and $25,318 (CD). Differences were observed in the cost of BoNT-A injection visits between toxins, with abobotulinumtoxinA (aboBoNT-A) having the lowest injection cost across all indications.

Conclusions: AboBoNT-A had the lowest injection visit costs across indications. These results are suggestive of real-world resource utilization patterns and costs, and, while helpful in informing insurers' BoNT-A management strategies, further research into cost differences is warranted.

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PLAIN LANGUAGE SUMMARY

Spasticity is an abnormal, involuntary muscle tightness due to extended muscle contraction. This resistance in movement can be caused by stroke, multiple sclerosis, or traumatic injuries to the brain or spinal cord. Cervical dystonia is a form of sustained involuntary muscle contractions that result in abnormal or repetitive muscle movements in the neck and upper shoulders. Spasticity and cervical dystonia are both associated with significant decrease in quality of life and work productivity as well as significant economic burden. It is therefore important to understand how disease management impacts these patients. Many studies have shown that botulinum toxins type A (BoNT-As) are safe and effective in reducing muscle tightness and improving normal range of motion. This study was conducted to better understand BoNT-A injection patterns, use of healthcare services, and the resulting costs in patients with spasticity or cervical dystonia.

Keywords: Botulinum toxin A; Cervical dystonia; Healthcare resource utilization; Spasticity; Treatment patterns

Key Summary Points

Why carry out this study?
Both spasticity and cervical dystonia have considerable direct and indirect healthcare cost implications, and, although several studies have discussed the clinical impact of these disorders, few have calculated the economic burden.
Given the burden of spasticity or cervical dystonia in patients with these conditions, it is important to understand the characteristics, healthcare resource utilization, and costs among these patient populations.
What was learned from this study?
These findings demonstrate significantly higher healthcare costs among patients with spasticity or cervical dystonia, and further confirm the economic burden associated with disease management.
Such data are important for managed healthcare systems, as effective treatment of spasticity and cervical dystonia may represent significant opportunities for cost savings in these patient populations.

INTRODUCTION

Spasticity is characterized by a velocity-dependent increase in muscle tone with exaggerated tendon jerks resulting from hyperexcitability of the stretch reflex [1, 2]. Affecting more than a half million people in the United States (US), spasticity is a common complication of upper motor neuron syndrome in people recovering from a stroke, traumatic brain injury, or spinal cord injury [2, 3]. It is estimated that spasticity affects 25% of patients post-stroke, 65–78% of patients with a spinal cord injury, and up to 80% of patients with multiple sclerosis at some point during their clinical course [4–7]. In pediatric patients, spasticity is seen in more than 90% of children with cerebral palsy [8].

Patients with spasticity have impaired motor control, mobility, and function, and are often dependent on their caregivers for daily routine care [9]. In many cases, spasticity requires lifelong medical management, resulting in increased direct (e.g., injection costs) and indirect costs (e.g., work capability), which have a clear impact on patients' and caregivers' lives [9–11]. Management aims to improve patient ease of care, comfort, function, and quality of life with the use of therapeutic interventions and pharmacological therapies [12, 13].

Cervical dystonia (CD) is characterized by involuntary contractions of neck and upper shoulder muscles, resulting in abnormal postures and/or movements of the neck, shoulder,

and head, and has a prevalence of 4.98 per 100,000 people in the US [14–16]. Patients with CD present variable combinations of dystonic postures and movements that alter the normal positions of head, neck, and shoulders, at rest and during volitional tasks [17]. Abnormal movements often combine head turn, tilt, forward or backward shift, flexion or extension, and shoulder elevation [17].

CD is often associated with disability and pain, which have been found to influence patients' physical and mental functions, with a decreased quality of life. A recent study assessing disease burden of CD found substantial negative impacts on employment and work productivity: almost one-third of patients had work status affected and nearly 60% had decreased productivity, particularly associated with CD-related pain [18]. Pain, anxiety, and depression were reported as the main predictors related to decreased quality of life among patients with CD [19, 20].

Botulinum toxins type A (BoNT-As), such as abobotulinumtoxinA (aboBoNT-A), onabotulinumtoxinA (onaBoNT-A), and incobotulinumtoxinA (incoBoNT-A), are first-line pharmacological treatments for the management of spasticity in the upper and/or lower limbs and for CD. Although evidence levels and indications differ across serotypes and brands, all formulations have regulatory approval and are commonly used [15].

Given the potential economic burden of spasticity or CD, it is important to understand the treatment patterns, healthcare costs, and healthcare resource utilization (HCRU) in these patients. Although the safety and efficacy of BoNT-As have been published across many studies, evidence of utilization and costs of these treatments is limited, and large studies using real-world data of BoNT-A use in adult and pediatric patients with spasticity or CD have not been conducted. This study aims to understand the clinical characteristics, BoNT-A utilization, and healthcare economic outcomes in these patient populations.

METHODS

Study Design and Data Source

This was an observational, retrospective, real-world cohort study, conducted among adult and pediatric patients with spasticity or adults with CD who were treated with a BoNT-A of interest (aboBoNT-A, incoBoNT-A, onaBoNT-A) using claims data from the IQVIA PharMetrics® Plus database from October 1, 2015 through December 31, 2019. The selection window for patients was April 1, 2016 through December 31, 2018. The index date was the date of the first BoNT-A claim with extremity, trunk, or neck locations. Each patient had a 6-month (180-day) baseline (pre-index period) and 12-month (360-day) follow-up (post-index period) starting on the index date (Fig. 1).

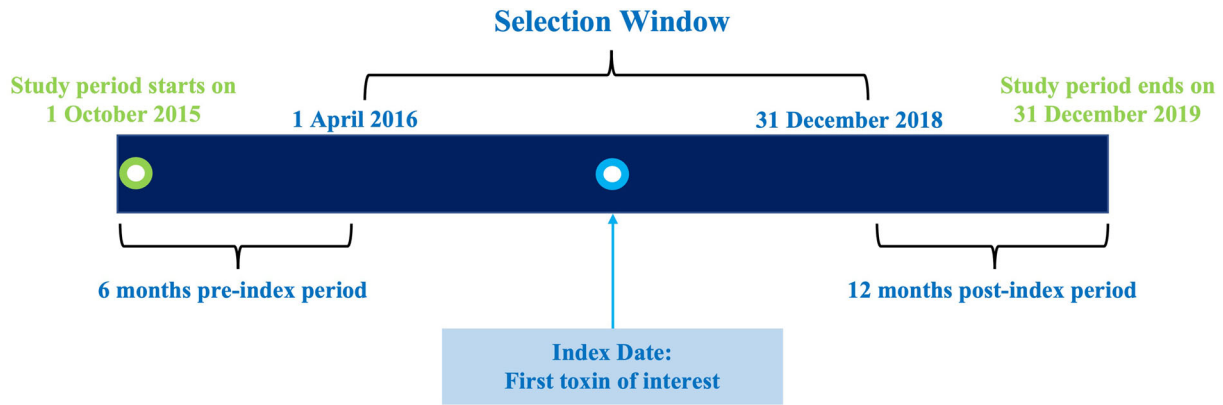

Fig. 1 Study design schematic

The PharMetrics Plus database is characteristic of the commercially insured population in the US in terms of age and gender. All data are compliant with the Health Insurance Portability and Accountability Act to guard patients' privacy. As this was a retrospective claims study in which all data were de-identified according to regulations, ethics approval and consent to participate were not required. The PharMetrics Plus database is owned by IQVIA. Several of the authors are IQVIA employees and have full access to use of the PharMetrics Plus database.

Eligibility Criteria

The study sample was selected from patients who had at least one claim for aboBoNT-A, incoBoNT-A, or onaBoNT-A based on Healthcare Common Procedure Coding System or National Drug Codes during the selection window, in addition to a 6-month pre-index and a 12-month post-index period (starting on the index date) of continuous health plan enrollment with medical and pharmacy benefits. Patients with spasticity were at least 2 years old at the index date, and patients with CD were at least 18 years old at the index date.

Included patients had (1) at least one International Statistical Classification of Diseases and Related Health Problems (ICD)-10 diagnosis code in any position for spasticity; (2) a diagnosis code in any position for traumatic brain injury, spinal cord injury, stroke, multiple sclerosis, or cerebral palsy; or (3) at least one diagnosis code in any position for CD, during the pre-index period or up to 7 days past the index date.

Patients with spasticity or a spasticity etiology also had a Current Procedural Terminology (CPT) code indicating toxin location in the neck (64616, without ICD-10 diagnosis code G243), an extremity (64642–64645), or the trunk (64646–64647) on the injection date. Patients with CD also had a CPT code indicating neck injection (64616, with ICD-10 diagnosis code G243 indicating CD).

Patients were excluded from the study sample if they had more than one type of BoNT-A on the index date, data quality issues (i.e., invalid age, gender), a diagnosis code in any position for migraine, blepharospasm, chronic sialorrhea, neuromuscular bladder, or a prescription claim for a 5-hydroxytryptamine 1 (5-HT_1) agonist or calcitonin gene-related peptide antagonist on the index date or during the pre-index period. Patients were also excluded if there was evidence of both spasticity and CD; however, patients with a diagnosis code for cervicalgia (M542) or torticollis (M436), both of which otherwise indicate evidence of spasticity, and a diagnosis code indicating CD, were retained in the CD cohort.

After meeting the study criteria, patients were stratified into 3 mutually exclusive cohorts: adult spasticity ($\geq$ 18 years of age on the index date with evidence of spasticity), pediatric spasticity ($<$ 18 and $\geq$ 2 years of age on the index date with evidence of spasticity), and adult CD ($\geq$ 18 years of age on the index date with evidence of CD).

Study Measures: Baseline Characteristics

The demographic characteristics assessed included age, gender, geographic region, payer type, health plan type, and index year. Clinical characteristics included Charlson Comorbidity Index (CCI; as continuous and categorical measures), selected comorbidities of interest, spasticity etiology, selected medications of interest, and devices of interest (i.e., splint or cast, assistive device). Pre-index all-cause HCRU and healthcare costs were evaluated and included pharmacy utilization and total pharmacy costs, outpatient visits [emergency room (ER) visits, physician office visits] and total outpatient medical costs, and inpatient utilization (inpatient stays, average length of stay) and total inpatient medical costs.

Study Measures: Post-index Outcomes

BoNT-A injection characteristics were evaluated (by patient and by injection), including the prescribing provider specialty, BoNT-A type, total cost of injection and by toxin, use of sedative anesthesia and with other adjuvants, and location for injection (for the spasticity

cohort). Injection patterns were evaluated, including time to switch (among patients who switched to a new non-index BoNT-A within 180 days), and injection intervals (among patients who received second and third injections). Injection-related healthcare costs included costs associated with the injection visit and the toxin, as well as costs associated with guidance techniques, anesthesia, and ultrasound.

Rates and frequency of HCRU and direct medical costs were examined over the 12-month post-index period. HCRU categories included pharmacy as reported by prescription fills, outpatient services (physician office visits, ER visits, laboratory/pathology tests, radiology examinations, surgical services, and ancillary services use), and inpatient visits. All-cause total costs included pharmacy, outpatient, and inpatient costs. All costs were converted to 2020 USD using the medical component of the Consumer Price Index.

Statistical Analyses

Descriptive analyses were used to examine the study measures. Categorical variables were reported in frequency (*n*) and percentage (%), whereas continuous variables were reported with mean, standard deviation (SD), and median. HCRU and costs were expressed as both the proportion of patients with such utilization and as per patient mean, SD, and median. Utilization and costs were calculated on a per-patient basis, averaged across the cohort. A generalized estimating equation (GEE) model was developed to examine the costs associated with each toxin visit in the adult spasticity cohort while controlling for age group, gender, payer type, and geographic region. Analyses were conducted using SAS Release 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Study Sample and Baseline Patient Characteristics

Applying the algorithm for patient selection, a total of 18,922 patients were identified, of which 5345 met the study inclusion/exclusion criteria. Eligible patients were divided into 3 cohorts: adult spasticity ($N = 2452$), pediatric spasticity ($N = 1364$), and CD ($N = 1529$) (Fig. 2).

Most patients in the CD cohort were female (69.5%), as were adult patients with spasticity (54.7%), whereas fewer than half (42.4%) of patients in the pediatric spasticity cohort were female. The mean (SD) age for the adult spasticity cohort was 46.9 (16.0) years, 8.9 (4.5) for the pediatric spasticity cohort, and 52.9 (11.8) years for the CD cohort (Table 1).

The most commonly reported comorbidities in the adult and pediatric spasticity cohorts were, respectively, paraplegia/hemiplegia (36.1%, 31.6%) and cerebrovascular disease (26.5%, 9.8%). In the CD cohort, the most common comorbidity of interest was diabetes (8.4%). The most common spasticity etiologies in the adult spasticity cohort were stroke (28.2%) and cerebral palsy (16.5%). Cerebral palsy was the dominating etiology in the pediatric spasticity cohort (83.9%). The most common medications of interest in the adult spasticity cohort were muscle relaxants (45.0%), antidepressants (40.5%), and anti-epileptics (37.8%). Anti-epileptics (31.8%) were the most frequently utilized medication among pediatric patients with spasticity. In the CD cohort, antidepressants (35.9%), anti-epileptics (34.1%), and muscle relaxants (33.6%) were the most commonly reported medications (Table 2).

Baseline All-cause HCRU and Healthcare Costs

Pre-index all-cause prescription fills and outpatient office visits were high in all cohorts. The proportion of patients with at least one prescription fill was 94.6% in the adult spasticity cohort, 83.1% in the pediatric spasticity cohort, and 96.1% in the CD cohort. The mean number of pre-index prescription fills was 21.3 in the adult spasticity cohort, 11.0 in the pediatric spasticity cohort, and 18.4 in the CD cohort. Physician office visits occurred in 94.6% of the adult spasticity cohort, 98.8% of the pediatric spasticity cohort, and 95.1% of the CD cohort.

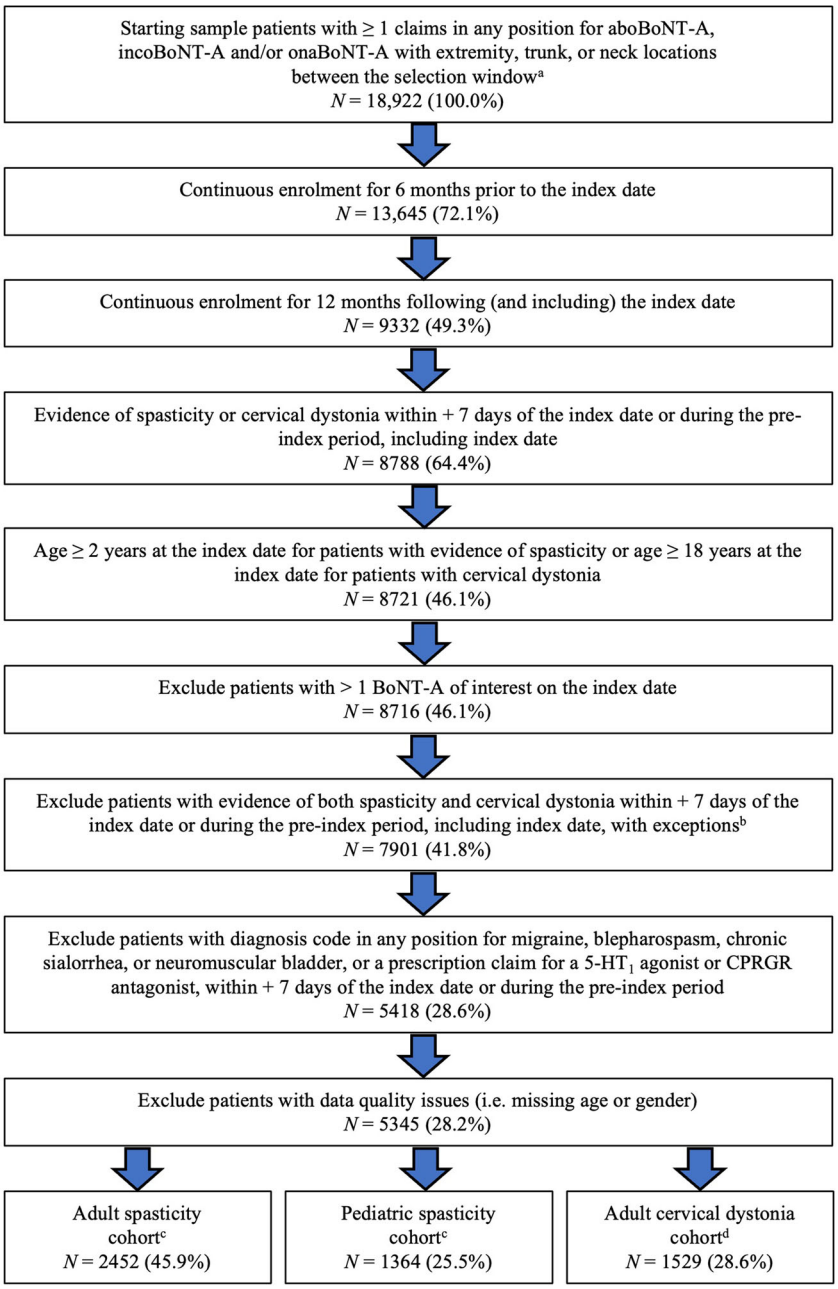

Fig. 2 Attrition of the study sample. [a]First toxin claim during the selection windows was the index date. [b]ICD-10 diagnosis codes M542 (cervicalgia) or M436 (torticollis) (both of which otherwise indicate evidence of spasticity) AND an ICD-10 diagnosis code indicating cervical dystonia were retained in this step in the cervical dystonia cohort. [c]Defined as ≥ 1 claim with a diagnosis of spasticity or ≥ 1 claim with a diagnosis of spasticity etiology (TBI, SCI, stroke, MS, or CP) within + 7 days of the index date or during the pre-index period AND ≥ 1 CPT code of 64616 (without ICD-10 diagnosis code G243), 64642, 64643, 64644, 64645, 64646, or 64647. [d]Defined as ≥ 1 claim with a diagnosis of cervical dystonia within ± 7 days of the index date or during the pre-index period, including index date AND CPT codes of 64616 on the same date as index (injection) date. *5-HT1* 5-hydroxytryptamine 1, *aboBoNT-A* abobotulinumtoxinA, *BoNT-A* botulinum toxin type A, *incoBoNT-A* incobotulinumtoxinA, *onaBoNT-A* onabotulinumtoxinA

Table 1 Baseline demographic characteristics

	Study cohorts					
	Adult spasticity $N = 2452$		Pediatric spasticity $N = 1364$		Cervical dystonia $N = 1529$	
	n	%	*n*	%	*n*	%
Age						
Mean	46.9		8.9		52.9	
SD	16.0		4.5		11.8	
Median	50		8		54	
Age group (years)						
2–10	0	0.0	851	62.4	0	0.0
11–17	0	0.0	513	37.6	0	0.0
18–34	638	26.0	0	0.0	122	8.0
35–44	308	12.6	0	0.0	204	13.3
45–54	548	22.3	0	0.0	470	30.7
55–64	730	29.8	0	0.0	551	36.0
≥ 65	228	9.3	0	0.0	182	11.9
Gender						
Female	1342	54.7	578	42.4	1063	69.5
Male	1110	45.3	786	57.6	466	30.5
Geographic region						
Northeast	460	18.8	225	16.5	313	20.5
Midwest	908	37.0	561	41.1	470	30.7
South	703	28.7	436	32.0	507	33.2
West	381	15.5	142	10.4	239	15.6
Payer type						
Commercial	1456	59.4	731	53.6	941	61.5
Medicaid	83	3.4	45	3.3	28	1.8
Medicare risk	83	3.4	0	0.0	48	3.1
Self-insured	811	33.1	582	42.7	487	31.9
Other/unknown	19	0.8	6	0.4	25	1.6
Health plan type						
Consumer-directed healthcare	10	0.4	9	0.7	8	0.5
HMO	341	13.9	140	10.3	181	11.8
Indemnity	46	1.9	34	2.5	35	2.3

Table 1 continued

	Study cohorts					
	Adult spasticity $N = 2452$		Pediatric spasticity $N = 1364$		Cervical dystonia $N = 1529$	
	n	%	*n*	%	*n*	%
POS	182	7.4	98	7.2	95	6.2
PPO	1859	75.8	1076	78.9	1187	77.6
Other/unknown	14	0.6	7	0.5	23	1.5
Index year						
2016	1269	51.8	718	52.6	867	56.7
2017	642	26.2	333	24.4	348	22.8
2018	541	22.1	313	22.9	314	20.5
2019	0	0.0	0	0.0	0	0.0

HMO health maintenance organization, *POS* point-of-service, *PPO* preferred provider organization, *SD* standard deviation

The mean number of physician office visits was 14.2 in the adult spasticity cohort, 21.3 in the pediatric spasticity cohort, and 9.4 in the CD cohort.

Pre-index inpatient and pharmacy costs comprised the majority of healthcare costs across the 3 cohorts. Mean inpatient costs were \$9378 in the adult spasticity cohort, \$6695 in the pediatric spasticity cohort, and \$1437 in the CD cohort. The mean pharmacy costs were \$5708 in the adult spasticity cohort, \$3829 in the pediatric spasticity cohort, and \$3830 in the CD cohort. Mean all-cause total healthcare costs were \$23,813 in the adult spasticity cohort, \$22,370 in the pediatric spasticity cohort, and \$10,083 in the CD cohort (medians \$7777, \$9035, and \$5141, respectively) (Fig. 3).

Cost and Utilization of BoNT-A Injections

At the patient level, the mean costs of visits during the post-index period using aboBoNT-A and incoBoNT-A were lower than for onaBoNT-A in all cohorts. For example, the adult spasticity cohort had mean total costs of \$5104 for visits using aboBoNT-A, compared with \$7311 for visits using incoBoNT-A and \$7658 for visits using onaBoNT-A. The pediatric spasticity and CD cohorts both had lower total costs of visits with aboBoNT-A (\$6076 and \$5888) and incoBoNT-A (\$3768 and \$5440) compared with visits with onaBoNT-A (\$9266 and \$6275).

At the injection level, the mean cost of injection visits in the adult spasticity cohort using aboBoNT-A was \$2054, compared with \$3220 for visits using incoBoNT-A and \$3103 for visits using onaBoNT-A. In the pediatric spasticity cohort, the mean total cost of injection visits using aboBoNT-A was \$3504, compared with \$2655 for visits using incoBoNT-A and \$4806 for visits using onaBoNT-A. In the CD cohort, the mean total cost of injection visits using aboBoNT-A was \$2101, compared with \$1947 for visits using incoBoNT-A and \$2239 for visits using onaBoNT-A (Fig. 4).

The pediatric spasticity cohort had the highest total mean cost for a BoNT-A injection visit (\$4669), compared with \$3049 in the adult spasticity cohort and \$2204 in the CD cohort. In adult patients with spasticity, most injections were in an extremity (81.4%), with 16.7% in the neck and 9.4% in the trunk; similar trends were also observed in the pediatric spasticity cohort (98.9%, 9.6%, and 5.8%, respectively) (Table 3).

Utilization of anesthesia and guidance therapies differed across the cohorts. In the adult

Table 2 Baseline clinical characteristics

	Study cohorts					
	Adult spasticity $N = 2452$		Pediatric spasticity $N = 1364$		Cervical dystonia $N = 1529$	
	n	%	*n*	%	*n*	%
Charlson comorbidity index (CCI)						
Mean	1.6		0.9		0.5	
SD	1.9		1.2		1.1	
Median	1		0		0	
0	1065	43.4	751	55.1	1109	72.5
1–2	688	28.1	457	33.5	346	22.6
3–4	489	19.9	145	10.6	57	3.7
5–6	160	6.5	9	0.7	9	0.6
7+	50	2.0	2	0.1	8	0.5
Comorbidities						
Myocardial infarction	31	1.3	0	0.0	4	0.3
Congestive heart failure	52	2.1	4	0.3	13	0.9
Peripheral vascular disease	92	3.8	11	0.8	32	2.1
Cerebrovascular disease	649	26.5	134	9.8	22	1.4
Dementia	67	2.7	28	2.1	14	0.9
Chronic pulmonary disease	60	2.4	12	0.9	42	2.7
Diabetes	285	11.6	3	0.2	128	8.4
Paraplegia and hemiplegia	885	36.1	431	31.6	11	0.7
Renal disease	112	4.6	18	1.3	45	2.9
Anxiety	345	14.1	64	4.7	273	17.9
Ataxia	57	2.3	34	2.5	10	0.7
Convulsions/seizure disorders	349	14.2	404	29.6	19	1.2
Depression	414	16.9	15	1.1	209	13.7
Hypertension	740	30.2	16	1.2	391	25.6
Hyperlipidemia	603	24.6	2	0.1	357	23.3
Sleep disorders	368	15.0	99	7.3	182	11.9
Transient ischemic attack	42	1.7	1	0.1	7	0.5
Coronary artery disease	114	4.6	0	0.0	40	2.6
Spasticity etiology						
Multiple sclerosis	161	6.6	0	0.0	N/A	N/A

Table 2 continued

	Study cohorts					
	Adult spasticity $N = 2452$		Pediatric spasticity $N = 1364$		Cervical dystonia $N = 1529$	
	n	%	*n*	%	*n*	%
Traumatic brain injury	153	6.2	35	2.6	N/A	N/A
Spinal cord injury	69	2.8	4	0.3	N/A	N/A
Stroke	692	28.2	52	3.8	N/A	N/A
Cerebral palsy	405	16.5	1145	83.9	N/A	N/A
Other/unknown	972	39.6	128	9.4	N/A	N/A
Medications of interest						
NSAIDs	383	15.6	62	4.5	348	22.8
Opioid analgesics	643	26.2	96	7.0	501	32.8
Opioid/NSAID combination therapies	224	9.1	93	6.8	119	7.8
Antidepressants	993	40.5	84	6.2	549	35.9
Anti-epileptics	926	37.8	434	31.8	522	34.1
Benzodiazepines	423	17.3	140	10.3	317	20.7
Muscle relaxants	1,104	45.0	263	19.3	514	33.6
Baclofen, delivered orally	719	29.3	225	16.5	187	12.2
Tizanidine	270	11.0	20	1.5	153	10.0
Cyclobenzaprine	172	7.0	1	0.1	213	13.9
Trihexyphenidyl	48	2.0	46	3.4	55	3.6
Dopamine receptor antagonists	186	7.6	44	3.2	96	6.3
Beta blocker	390	15.9	8	0.6	251	16.4
Other treatments/devices of interest						
Splint or cast	32	1.3	49	3.6	10	0.7
Assistive device (cane, walker, or crutch)	308	12.6	223	16.3	17	1.1
Any treatments/devices of interest (composite)	332	13.5	268	19.6	23	1.5

CCI Charlson comorbidity index, *NSAID* non-steroidal anti-inflammatory drug, *SD* standard deviation

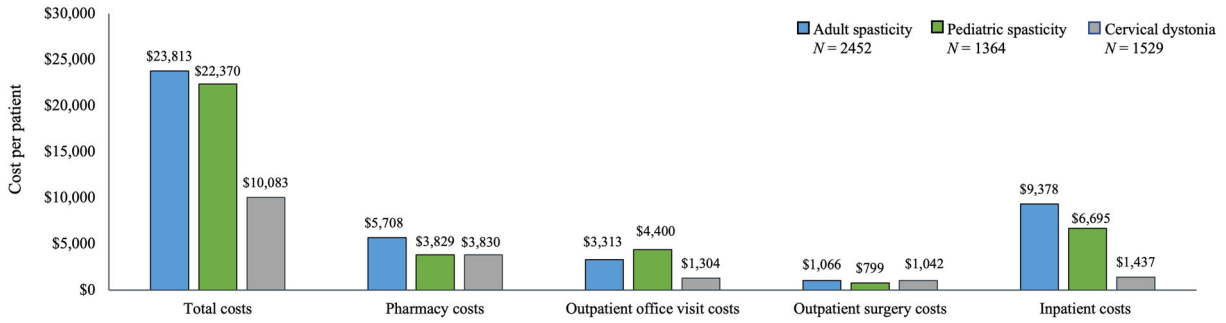

Fig. 3 Pre-index mean all-cause healthcare costs

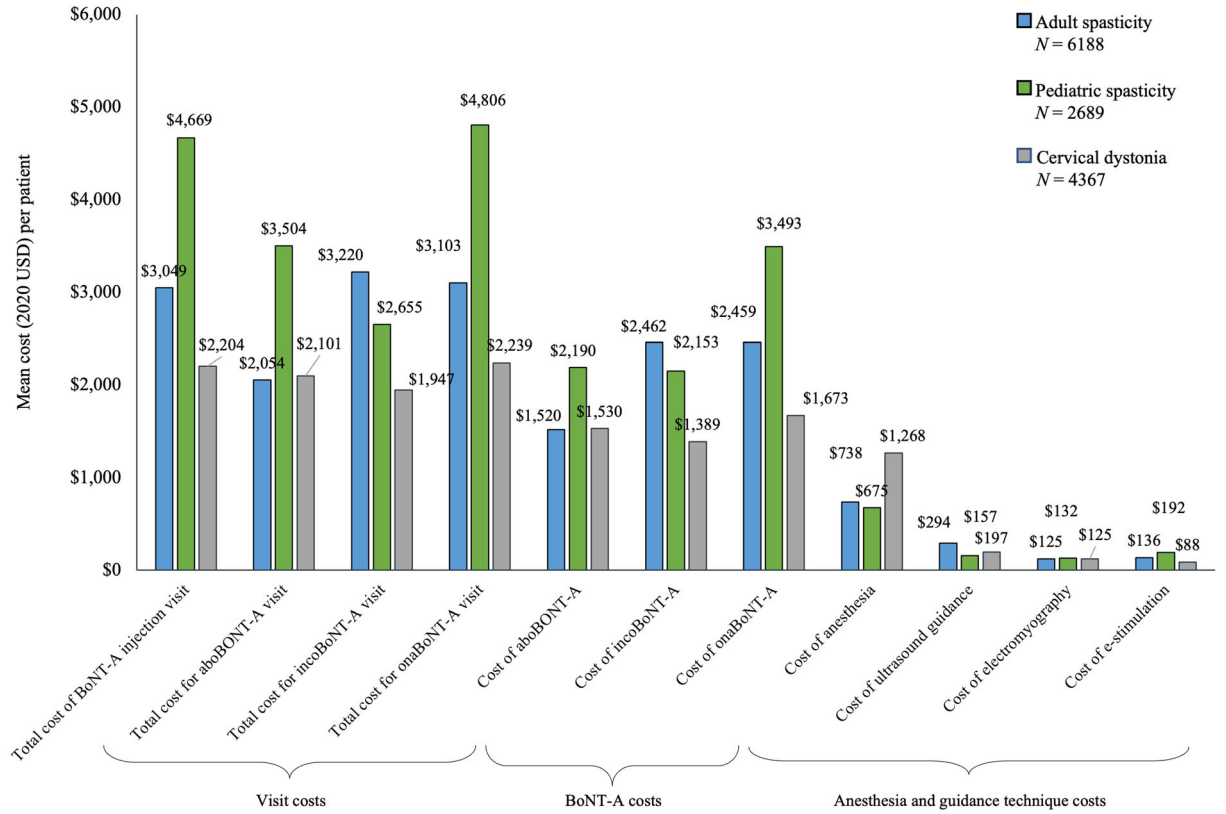

Fig. 4 Cost of BoNT-A injection visits across cohorts (injection level). *aboBoNT-A* abobotulinumtoxinA, *BoNT-A* botulinum toxin type A, *incoBoNT-A* incobotulinumtoxinA, *onaBoNT-A* onabotulinumtoxinA

spasticity cohort, anesthesia was used in 2.8% of injection visits, ultrasound in 4.9%, electromyography in 61.6%, and electrostimulation in 6.8%. However, in the pediatric spasticity cohort, anesthesia was used in 29.3% of injection visits, ultrasound in 11.0%, electromyography in 27.9%, and electrostimulation in 24.8%. In the CD cohort, anesthesia was used in 0.2% of injection visits, ultrasound in 3.8%, electromyography in 62.3%, and electrostimulation in 0.5%. The cost of these therapies also varied by cohort. The median cost of anesthesia ranged from $617 in the adult spasticity cohort, to $541 in the pediatric spasticity cohort and $410 in the CD cohort. The median cost of ultrasound varied from $111, $52, and $133 across the cohorts, respectively, with lowest

Table 3 Injection characteristics at injection level

	Study cohorts					
	Adult spasticity $N = 6188$		Pediatric spasticity $N = 2689$		Cervical dystonia $N = 4367$	
	n	%	*n*	%	*n*	%
Provider specialty for BoNT-A injection						
Primary care	388	6.3	168	6.2	131	3.0
Neurologist	1895	30.6	183	6.8	2219	50.8
Orthopedic surgeon	20	0.3	14	0.5	5	0.1
Physiatrist (PM&R)	1610	26.0	382	14.2	524	12.0
Others	2284	36.9	1946	72.4	1489	34.1
BoNT-A type						
aboBoNT-A	338	5.5	210	7.8	213	4.9
incoBoNT-A	268	4.3	44	1.6	422	9.7
onaBoNT-A	5582	90.2	2435	90.6	3732	85.5
Anesthesia	172	2.8	788	29.3	9	0.2
Ultrasound guidance	304	4.9	299	11.1	167	3.8
Electromyography	3812	61.6	749	27.9	2718	62.3
Electrostimulation	422	6.8	667	24.8	21	0.5
Adjuvant injectables						
Sedative anesthesia	119	1.9	281	10.5	8	0.2
Other adjuvants	132	2.1	245	9.1	21	0.5
Location of BoNT-A injection						
Neck (no cervical dystonia)	1031	16.7	155	5.8		
Trunk	579	9.4	259	9.6		
Extremity	5039	81.4	2659	98.9		

aboBoNT-A abobotulinumtoxinA, *BoNT-A* botulinum toxin type A, *incoBoNT-A* incobotulinumtoxinA, *onaBoNT-A* onabotulinumtoxinA, *PM&R* physical medicine and rehabilitation

median costs observed for electromyography ($103, $91, and $109, respectively).

While few patients switched to another type of BoNT-A (0.5% in the adult spasticity cohort, 1.1% in the pediatric cohort, and 0.8% in the CD cohort), during the post-index period most patients had a second injection (68.4%, 58.6%, and 75.1%, respectively) and many had a third (48.6%, 28.3%, and 59.9%) (Table 4). On average, patients in the adult spasticity cohort had 2.5 injections, compared with 2.0 in the pediatric spasticity cohort and 2.9 in the CD cohort.

Table 4 Treatment patterns for BoNT-A injections

Treatment patterns	Study cohorts					
	Adult spasticity $N = 2452$		Pediatric spasticity $N = 1364$		Cervical dystonia $N = 1529$	
	n	%	*n*	%	*n*	%
Switch to another BoNT-A[a]	13	0.5%	15	1.1%	12	0.8%
Time (days) to switch						
Mean (SD)	108.1 (31.4)		140.0 (29.3)		119.2 (33.5)	
Median	105		152		118	
Second BoNT-A injection	1678	68.4%	799	58.6%	1149	75.1%
Time (days) between index and second injections						
Mean (SD)	124.1 (57.5)		168.8 (72.9)		115.5 (49.1)	
Median	99		148		99	
Third BoNT-A injection	1191	48.6%	386	28.3%	916	59.9%
Time (days) between second and third injections						
Mean (SD)	111.0 (33.4)		128.1 (36.1)		103.1 (27.3)	
Median	99		120		95	

BoNT-A botulinum toxin type A, *SD* standard deviation

[a]A switch was defined by the study team as a BoNT-A injection administered within 180 days that was different than the BoNT-A type administered as the index treatment. The date of the new non-index toxin prescription was the date of switch

All-cause HCRU and Costs Over the 1-year Post-index Period

HCRU during the post-index period was high in each cohort. All patients had at least one prescription claim. The mean number of prescription fills was 45.5 in the adult spasticity cohort, 24.1 in the pediatric spasticity cohort, and 38.9 in the CD cohort. Nearly all patients (98.9% in the adult spasticity cohort, 99.6% in the pediatric spasticity cohort, and 98.2% in the CD cohort) had at least one physician office visit. The mean number of office visits was 25.7 in the adult spasticity cohort, 40.8 in the pediatric spasticity cohort, and 17.0 in the CD cohort.

Total mean all-cause healthcare costs were $42,562 in the adult spasticity cohort, $54,167 in the pediatric spasticity cohort, and $25,318 in the CD cohort (Fig. 5). Median all-cause total costs were $21,480, $28,467, and $15,030, respectively (Fig. 6). The adult spasticity cohort had mean pharmacy costs of $15,977 (median $8152), the pediatric spasticity cohort $11,915 (median $5107), and the CD cohort $11,164 (median $6632). Outpatient medical costs accounted for a majority of the post-index costs among adult (45.6%) and pediatric patients (56.6%) with spasticity, whereas pharmacy costs (44.1%) accounted for a plurality of costs among patients with CD.

Findings from a GEE model examining the costs of BoNT-A toxin visits among adult patients with spasticity showed that patients with an injection of incoBoNT-A had 1.4 times higher adjusted costs [adjusted cost ratio: 1.426; 95% confidence interval (CI) 1.244–1.634; $P < 0.001$], and patients with an injection of onaBoNT-A had 1.5 times higher adjusted costs

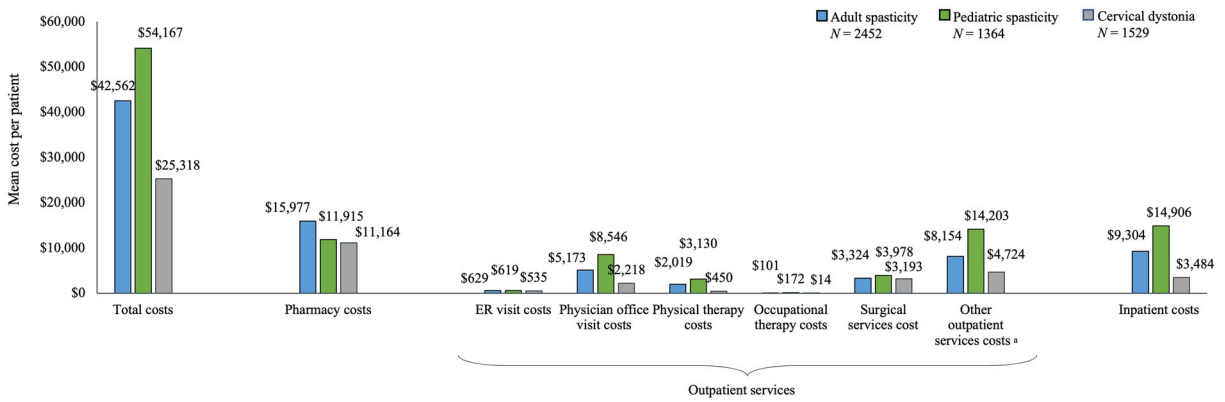

Fig. 5 Post-index mean all-cause healthcare costs. [a]Including laboratory/pathology and radiology visits and other outpatient services. *ER* emergency room

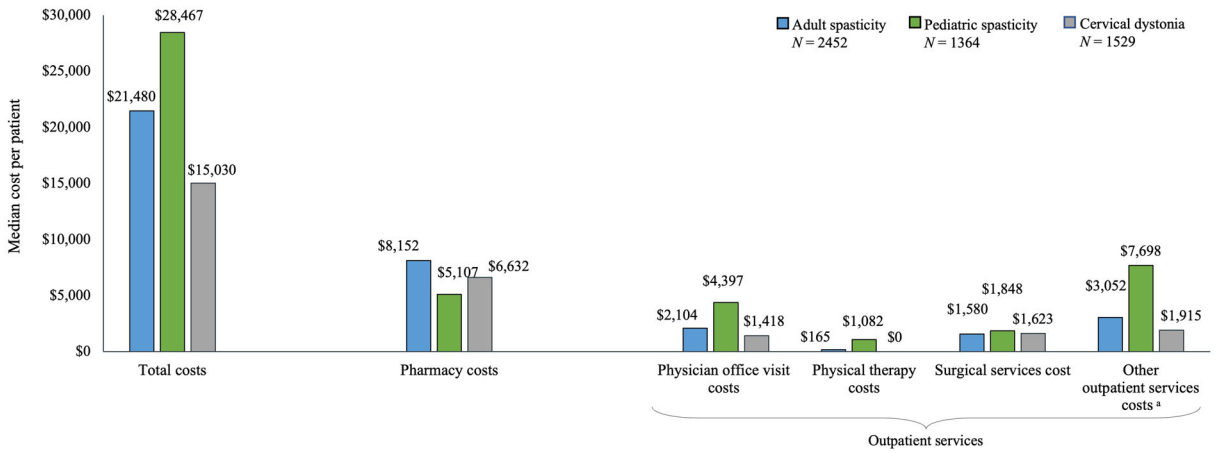

Fig. 6 Post-index median all-cause healthcare costs. [a]Including laboratory/pathology and radiology visits and other outpatient services. Emergency room visits and inpatient medical costs are not presented here as patients in both cohorts had a median cost of $0

(adjusted cost ratio: 1.523; 95% CI 1.385–1.675; $P < 0.001$), compared with patients with an injection of aboBoNT-A. Younger patients had higher adjusted costs of the toxin visit compared with older age groups, and Medicaid enrollees had statistically lower adjusted costs compared with self-insured enrollees.

DISCUSSION

Several randomized clinical trials have reported on the use of BoNT-As for the treatment of spasticity following stroke and other etiologies, with improvements in muscle tone and overall health assessment [21–24]. A large international longitudinal study [Upper Limb International Study (ULIS-III)] showed that patients with upper limb spasticity achieved treatment goals with repeated BoNT-A treatment cycles over 2 years and had significant improvement in several study measures, including spasticity, pain, involuntary movements, and active and passive function [25]. A 2015 study, noting the effectiveness of BoNT-As for patients with CD, concluded that cost-effectiveness studies for these patients in the US were limited and that additional research was needed [26]. A 2020 article comparing cost-effectiveness of aboBoNT-A and onaBoNT-A in 356 adult patients with CD in Europe and Australia indicated that treatment with aboBoNT-A may be less costly

and lead to improved clinical outcomes when compared with onaBoNT-A [27].

The current study appears to be the first large real-world examination of patients with spasticity or CD in the US to address the treatment patterns of BoNT-A, as well as overall healthcare costs and HCRU, because literature regarding healthcare economic outcomes—particularly in large, recent, real-world analyses—are limited.

In this study among patients with spasticity or CD and treated with a BoNT-A, healthcare costs were high and differences were observed in costs associated with each toxin type. AboBoNT-A was associated with the lowest injection costs for patients in each cohort, and adjusted costs from a multivariate model were 40–50% higher with incoBoNT-A and onaBoNT-A. Most patients had more than one BoNT-A injection during the post-index period, and fewer than 1% of patients switched to a different toxin. Among patients with spasticity, most patients had multiple extremity injections.

Mean all-cause post-index healthcare costs were $42,562 and $54,167 in adult and pediatric patients with spasticity, respectively, and $25,318 in patients with CD. Outpatient and pharmacy costs were correspondingly high in each cohort. The mean cost of BoNT-A injections comprised 18.0% of mean total all-cause healthcare costs in the adult spasticity cohort, 17.0% in the pediatric spasticity cohort, and 24.8% in the CD cohort.

The top 10% of patients with the highest costs in the adult spasticity, pediatric spasticity, and CD cohorts incurred 46.6%, 45.4%, and 41.5% of all total healthcare costs among all patients in each sample, representing mean costs of $194,048, $246,621, and $104,888, respectively. Thus, spasticity and CD appear to be associated with an even poorer overall healthcare profile in a small percentage of patients as measured by healthcare economics metrics.

The study reported a high percentage of patients with physical or occupational therapy, particularly among pediatric patients with spasticity. A retrospective Medicaid claims data analysis study of children with cerebral palsy, of whom 69.8% reported a diagnosis of spasticity, showed that the most commonly reported management option among treated children was physical therapy (37.1%), which is consistent with the findings in the current study [28].

Limitations

Claims data can be used to efficiently analyze patient characteristics, treatment patterns, HCRU, and costs, but all claims databases have inherent limitations on generalizability, as claims are generated for the purpose of payment and re-imbursement within the insured population and not for research purposes. The presence of a diagnosis code on a medical encounter or outside claim may not have been conclusive or positive presence of disease, as the diagnosis code may have been incorrectly coded or included as rule-out criteria rather than actual disease. However, this risk was mitigated by the requirement that patients had claims for the toxin and its injection location along with the diagnosis code for the disease.

Given the observational nature of the retrospective study design, all study findings are associative and no causal inferences can be made. Results and conclusions are limited to the patient population and may not be generalizable to other commercially insured populations in the US. Only patients with continuous eligibility were included; thus, patients who did not remain enrolled in the same health insurance plan during the course of the study period were not included in the sample.

The study only captured direct costs reported by administrative claims data. Indirect costs, such as loss of productivity, traveling time, costs to the medical facility, or short-term disability, were not included. The cost of the toxin at the injection level was measured by date of service as the cost of individual injections on the same day could not be distinguished.

CONCLUSIONS

In this retrospective claim analysis of patients with an injection of a BoNT-A and with evidence of spasticity ($N = 2452$ adult and 1364 pediatric) or CD ($N = 1529$), healthcare costs were high and differences were observed in

costs associated with each type of toxin injection. Pharmacy costs contributed approximately 40% of the total mean healthcare costs among adult patients with spasticity or CD. The high healthcare costs were in part influenced by the complexity of the BoNT-A injection procedure, which often requires injections in more than one extremity and commonly requires the use of injection guidance techniques and anesthesia (particularly among pediatric patients with spasticity), all of which represent considerable influences on total healthcare costs for these patients.

Differences were observed in the cost of BoNT-A injection visits across the 3 toxins, with aboBoNT-A associated with the lowest injection costs for patients in each cohort. IncoBoNT-A and onaBoNT-A injections had 1.4 times and 1.5 times higher adjusted costs, respectively, than aboBoNT-A injections in the adult spasticity cohort. Most patients had more than one BoNT-A injection during the post-index period. Second injections occurred after a median of 99 days (adult spasticity and CD cohorts) and 148 days (pediatric spasticity cohort) after the initial injection. Fewer than 1% of patients switched to a different toxin.

These results are suggestive of real-world resource utilization patterns and costs. While helpful to inform insurers' BoNT-A category management strategies, further research is warranted to understand the drivers of these cost differences.

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Disclosures. Michael Hull, Vamshi Ruthwik Anupindi, and Mitchell DeKoven are employees of IQVIA, contracted by Ipsen to conduct this study; Jing He is a former employee of IQVIA, contracted by Ipsen to conduct this study; Jonathan Bouchard is an employee of Ipsen.

Compliance with Ethics Guidelines. This was a retrospective claims study in which all data were de-identified according to regulations. Ethics approval and consent to participate were not required. All data presented are compliant with the Health Insurance Portability and Accountability Act to guard patients' privacy. The PharMetrics Plus database is owned by IQVIA. Several of the authors are IQVIA employees and have full access to use of the PharMetrics Plus database.

Data Availability. The data that support the findings of this study are available from IQVIA PharMetrics Plus database, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of IQVIA.

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