Supplement Article

Medicine

OPEN

Treatment of neurogenic detrusor overactivity and overactive bladder with Botox (onabotulinumtoxinA)

Development, insights, and impact

Victor Nitti, MD[a,*], Cornelia Haag-Molkenteller, MD, PhD[b], Michael Kennelly, MD[c], Michael Chancellor, MD[d], Brenda Jenkins, MS[e], Brigitte Schurch, MD[f]

Abstract

Neurogenic detrusor overactivity (NDO) is a complication of multiple sclerosis, spinal cord injury (SCI), stroke, head injury, and other conditions characterized by damage to the upper motor neuronal system. NDO often leads to high bladder pressure that may cause upper urinary tract damage and urinary incontinence (UI). Prior to the use of onabotulinumtoxinA, oral anticholinergics and surgical augmentation cystoplasty were the treatment options. Overactive bladder (OAB) is non-neurogenic and affects a much larger population than NDO. Both NDO and OAB negatively impact patients' quality of life (QOL) and confer high health care utilization burdens. Early positive results from pioneering investigators who injected onabotulinumtoxinA into the detrusor of patients with SCI caught the interest of Allergan, which then initiated collaborative clinical trials that resulted in FDA approval of onabotulinumtoxinA 200U in 2011 for NDO and 100U in 2013 for patients with OAB who inadequately respond to or are intolerant of an anticholinergic. These randomized, double-blind, placebo-controlled trials for NDO showed significant improvements in UI episodes, urodynamic parameters, and QOL; the most frequent adverse events were urinary tract infection (UTI) and urinary retention. Similarly, randomized, double-blind, placebo-controlled trials of onabotulinumtoxinA 100U for OAB found significant improvements in UI episodes, treatment benefit, and QOL; UTI and dysuria were the most common adverse events. Long-term studies in NDO and OAB showed sustained effectiveness and safety with repeat injections of onabotulinumtoxinA, the use of which has profoundly improved the QOL of patients failing anticholinergic therapy and has expanded the utilization of onabotulinumtoxinA into smooth muscle.

Abbreviations: AEs = adverse events, AUA = American Urological Association, CDC = Centers for Disease Control and Prevention, CIC = clean intermittent catheterization, FDA = Food and Drug Administration, IDC = involuntary detrusor contraction, I-QOL = Incontinence Quality of Life Questionnaire, MS = multiple sclerosis, NDO = neurogenic detrusor overactivity, OAB = overactive bladder, PVR = post-void residual urine volume, QOL = quality of life, SCI = spinal cord injury, UI = urinary incontinence, UTI = urinary tract infection, UUI = urgency urinary incontinence.

Keywords: botulinum toxin, neuromuscular agents

This manuscript was funded by AbbVie. AbbVie was involved in the manuscript concept and participated in writing, reviewing, and approval of the final version.

No honoraria or payments were made for authorship.

V Nitti has served as an investigator for Allergan plc, Astellas, and Medtronic. C Haag-Molkenteller was formerly employed by Allergan plc and owns stock in the company; now employed at Urovant Sciences Inc. M Kennelly has received grants from and served on research studies and as a consultant for Allergan plc, Astellas, Boston Scientific, and Coloplast; has received grants from and served on research studies for Amphora, Axonics, Cook Myosite, Dignify Therapeutics, Ipsen, Taris, Uro1, FemPulse, and EBT Medical; and has served as a consultant for Laborie and Urovant. M Chancelor has financial relationships with Cook Myosite, Inc. and Lipella Pharmaceuticals, Inc. B Jenkins is a full-time employee of Allergan, an AbbVie Company, and owns stock in the company. B Schurch has received an investigator-initiated trial grant from Allergan plc.

[a] Division of Female Pelvic Medicine and Reconstructive Surgery, Departments of Urology and Obstetrics and Gynecology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA, [b] Urovant Sciences, Inc., Irvine, CA, USA, [c] Urology, Urogynecology, Female Pelvic Medicine and Reconstructive Surgery, Atrium Health, Charlotte, NC, USA, [d] Urology, Beaumont Hospital, Royal Oak, MI, USA, [e] Allergan, an AbbVie company, Irvine, CA, USA, [f] Neurourology Unit Department of Neurosciences, Centre Hospitalier Universitaire Vaudois, Université de Lausanne, Lausanne, Switzerland

** Correspondence: Victor Nitti, Professor of Urology and Obstetrics and Gynecology, Chief of Female Pelvic Medicine and Reconstructive Surgery, and Fellowship Director, Division of Female Pelvic Medicine and Reconstructive Surgery, Departments of Urology and Obstetrics and Gynecology, David Geffen School of Medicine at UCLA, 200 Medical Plaza, Suite 140, Los Angeles, CA 90095, USA (e-mail: VNitti@mednet.ucla.edu).*

How to cite this article: Nitti V, Haag-Molkenteller C, Kennelly M, Chancellor M, Jenkins B, Schurch B. Treatment of neurogenic detrusor overactivity and overactive bladder with Botox (onabotulinumtoxinA): Development, insights, and impact. Medicine 2022;102:S1(e32377).

Received: 31 August 2022 / Accepted: 1 December 2022

http://dx.doi.org/10.1097/MD.0000000000032377

1. Overview of neurogenic detrusor overactivity and overactive bladder

Neurogenic detrusor overactivity (NDO; formerly called detrusor hyperreflexia) is a common manifestation of neurologic conditions including spinal cord injury (SCI) and multiple sclerosis (MS), and may also occur after stroke, head injury, and other conditions characterized by damage to the upper motor neuronal system.[1,2] This can lead to urinary incontinence (UI), repeated urinary tract infections (UTIs), vesicoureteral reflux, and high bladder pressures that may result in damage to the upper urinary tract.[3,4] NDO is estimated to affect 50% to 90% of patients with MS, and 70% to 84% of patients with SCI.[3,5]

In contrast to NDO, overactive bladder (OAB) is not caused by an obvious neurological condition (often of unknown origin) and is defined as "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of UTI or other obvious pathology."[6] OAB is predicted to affect over 500 million people worldwide,[7] with a high prevalence in the adult population, ranging from 17% to 32% in various countries,[8–11] that increases with age.[9,11] Results from a number of studies suggest that the incidence is the same among men and women,[9,10,12,13] although a few have observed a higher incidence in women (39% vs 24% in men in Colombia[8] and 30% vs 16% in men in the US[11]). Of those with OAB, more than one-third have UI.[12,13]

Although OAB is far more common than NDO, both conditions cause a substantial burden, with negative impacts on patients' quality of life (QOL) and increased health care resource utilization and costs.[14–19] Patients with OAB with UI have higher psychological stress, anxiety, and depression compared with healthy controls or those with OAB with minimal or no symptoms.[17,20,21] The cost of OAB with urgency UI in the United States is estimated to be $82.6 billion in 2020, which includes direct costs such as medical care and incontinence pads and indirect costs such as losses in work productivity.[22,23]

The following historical narrative was compiled based on review of the literature and interviews with the authors, and the quoted portions reflect the personal observations and reflections of the individuals who were interviewed. In some instances, this article describes uses for which Allergan has not sought and/or received regulatory approval in individual countries and are mentioned for historical context or background only.

2. Unmet need for the treatment of NDO and OAB

For NDO, the first line of treatment is oral anticholinergic (antimuscarinic) medication for patients with SCI, often in association with the use of clean intermittent catheterization (CIC) for those with emptying problems (detrusor sphincter dyssynergia).[24] MS patients usually begin with behavioral therapy and lifestyle changes along with anticholinergic or β3-adrenoceptor agonist medication. In more advanced cases with coexistent detrusor sphincter dyssynergia, MS patients may eventually progress to CIC use. Prior to the use of onabotulinumtoxinA for NDO, the next treatment option for patients who failed anticholinergics was an invasive surgical augmentation cystoplasty procedure. This major reconstructive surgery involves enlarging the bladder, usually with a segment of bowel, and can lead to serious complications such as cystoplasty perforation, urinary tract stones (with excess mucus production), bowel disturbances, and electrolyte abnormalities.[25]

Dr. Schurch, who was the Head of Neuro-Urology at the Swiss Paraplegic Centre, University Hospital Balgrist in Zurich, Switzerland when she conducted the first work using onabotulinumtoxinA in patients with NDO: There was no intermediate treatment between conservative treatment (antimuscarinics and behavioral therapy) and cystoplasty. There was a need to find something in between.

Dr. Chancellor, who was a Professor of Urology at the University of Pittsburgh, Pittsburgh, PA when he first used onabotulinumtoxinA for the treatment of patients with NDO: If the pills didn't work, which was very frustrating, you essentially had to jump right to bladder augmentation... Bladder augmentation is a major reconstructive surgery, and sometimes the solution is worse than the problem... patients needed a safer, simpler solution. Many patients would rather put up with a diaper and incontinence rather than have a major reconstructive operation.

Intravesical instillations of the vanilloids capsaicin[26,27] and resiniferatoxin[28–30] showed some initial promise for NDO, but capsaicin caused pain, hematuria, and autonomic hyperreflexia in some patients[26,27,31] and did not receive regulatory approval. Resiniferatoxin was withdrawn from the market because it adhered to its plastic packaging.[32] Oxybutynin instillations also showed some effectiveness[33] but were not widely used due to limited availability of commercial preparations.[31] Thus, there was a great unmet need in the NDO population for treatment of raised bladder pressures and UI.

There was a great unmet need prior to onabotulinumtoxinA in the OAB population as well. The first-line treatment for OAB is behavioral therapy, but it is difficult to maintain patient participation over the long term.[34] Oral medications, including anticholinergics and, more recently, β3-adrenoceptor agonists, are commonly used as a next step because most patients' treatment goals are not met with behavioral therapy alone. However, adherence to anticholinergics is poor, which may be due to a lack of efficacy or incidence of side effects such as dry mouth and cognitive dysfunction.[34–36] Furthermore, exposure to anticholinergics over time is associated with an increased risk of dementia[37] and of falls and fractures in patients with OAB, especially in elderly patients.[38]

3. Early use of onabotulinumtoxinA as a treatment for NDO and OAB and its development program

Dr. Schurch, along with Drs. Daniel Schmid and Manfred Stöhrer, was the first to attempt treatment of NDO with onabotulinumtoxinA.[39]

Dr. Schurch: It was always on my mind that it should be possible to treat NDO because I was aware, from the literature, of historical work from Justinus Kerner who described the evolution of botulism and also described bladder paralysis.[40] *I also read a lot of papers on basic science on the effect of botulinum toxin on the release of acetylcholine in smooth muscle. My primary idea was when I inject Botox into the bladder, it would block the acetylcholine release which is responsible for bladder contraction.*

The idea also coincided with research in which investigators injected onabotulinumtoxinA to treat detrusor-sphincter dyssynergia[41] and palmar hyperhidrosis.[42] In November 1997, Dr. Schurch's group submitted a protocol to her institution's ethics committee to inject onabotulinumtoxinA for neurogenic bladder in patients with SCI who were using CIC and were non-responders to anticholinergics. The group began cautiously, utilizing a protocol similar to the one used for palmar hyperhidrosis,[42] but amended their protocol to increase the dose and number of injections when they saw no result with 30U, eventually increasing to 300U.

The results from this initial study in 21 patients were presented at the Joint Meeting of the International Continence Society (ICS), the International Urogynecological Association, and the International Children's Continence Society in Denver, Colorado in 1999[43] (Fig. 1) and were published in full in 2000.[39,44] At week 6 following injection, 17/19 patients were completely continent, and significant improvements from baseline in urodynamic parameters were observed.

Dr. Haag-Molkenteller, who was the Vice President of Global Drug Development and Therapeutic Area Head for Urology at

Figure 1. Dr. Schurch presenting her talk, "Botulinum A toxin in the treatment of detrusor hyperreflexia in spinal cord injured patients: a new alternative to medical and surgical procedures?," at the Joint Meeting of the International Continence Society, the International Urogynecological Association, and the International Children's Continence Society in August 1999 in Denver, CO. Photo provided by Dr. Schurch.

Allergan during the registrational studies for onabotulinumtoxinA treatment of NDO and OAB: [Dr. Schurch] received a standing ovation from the ICS audience in Denver for this idea.

Dr. Schurch: The abstract had a really fascinating impact to all people who read it and heard the talk, and all the people after this meeting said, "We want to start; we want to try."

Allergan became interested in this use for onabotulinumtoxinA and sponsored the phase 2 study for NDO, which tested two onabotulinumtoxinA doses (200U and 300U) and placebo in a total of 59 patients.[45] This small study showed similar efficacy and safety with both doses, which led Allergan to test both doses in the phase 3 program, even though testing two doses led to the need for a greater number of patients for the trials. In the context of this trial, an acceptable safety profile was observed, with UTI rates of 21%, 32%, and 14% for onabotulinumtoxinA 300U, onabotulinumtoxinA 200U, and placebo, respectively.

At this time, awareness of the work of Dr. Schurch and her colleagues spread, and other physicians began to use onabotulinumtoxinA off-label in their own practices.

Dr. Kennelly, who was the Director of Urology at the Charlotte Institute of Rehabilitation in Charlotte, NC when he first used onabotulinumtoxinA for the treatment of patients with NDO: After reading Drs. Schurch, Stöhrer, et al initial manuscript regarding Botox for the use of neurogenic detrusor overactivity,[39,44] I was very intrigued. Subsequently, I got the opportunity to meet with Dr. Stöhrer at the 2000 SIU [World Congress of the Société Internationale d'Urologie], where we talked in depth about the article and logistics of performing intradetrusor Botox. And after doing my research I began offering intradetrusor Botox in January 2001 for my SCI and MS patients who were scheduled to undergo an augmentation cystoplasty. These patients were on maximal anticholinergic medications but still they were having leakage of urine and high bladder pressures. In order to get a better quality of life and improve their kidney reserve, they were planning to undergo an irreversible surgical augmentation cystoplasty procedure. As Botox is a minimally invasive procedure, I thought it could possibly be an alternative and fulfill an unmet medical need for these patients. For the first 10 patients, I basically replicated the original trial study design utilizing Botox 300U as was mentioned in the article.

Results from Dr. Kennelly's initial work on 10 patients were published in a paper that showed significant urodynamic improvements. Further, 5/10 (50%) patients were continent without anticholinergics and 3/10 (33%) restarted anticholinergics but at less than half the dose at week 12.[46]

Dr. Chancellor: I was in charge of urinary dysfunction in neurourology at the University of Pittsburgh. I had three female patients with MS, but I didn't know how to treat them since they did not want surgery. I'd heard of the toxin; I think I'd read Brigitte's paper. But it was really the neurologist who heads up the MS center [at the University of Pittsburgh], who was performing Botox [injections for spasticity] at the time, said, "Mike, have you thought about using Botox on these [patients]?" So then I researched it on my own and then found out it seems reasonable... I injected these three women the next week, and obviously they were a home run or otherwise I wouldn't have continued it.

The success of these three patients spurred Dr. Chancellor to investigate the mechanisms of action of botulinum toxin on the bladder through laboratory experiments on rats.[47,48]

Dr. Chancellor: Everybody says, "benchtop to bedside" but I did the exact reverse. The three women did wonderfully, so I went right to Professor William de Groat, who has been the foremost neuropharmacologist in the world for 30 years now, and I shared with him my experience... So the week after the women got much better, we started doing rat experiments. We were looking at muscle contractility strip studies and acetylcholine, norepinephrine, and ATP release. We found that the bladder smooth muscle relaxed better than the skeletal muscle from the urethra. So it was because of the initial patient success and my good fortune to work with one of the best scientists in the world that we were able to start a whole slew of rat experiments.

Although NDO can occur in patients with various neurological disorders, the MS and SCI populations were chosen for the onabotulinumtoxinA developmental program. From a trial design perspective, enrolling two representative populations with NDO was more amenable than a diverse population. However, while it was encouraging that other physicians were adopting the use of onabotulinumtoxinA to treat their patients with NDO, the non-approved use made it difficult to recruit patients for the phase 3 NDO trials. That is, patients were not willing to enter a study in which they might receive placebo when they could obtain off-label onabotulinumtoxinA treatment from their physician. In addition, the original protocol for the phase 3 trials mandated that all patients had to be already utilizing CIC to avoid the potential risk of urinary retention, which was an issue because not all MS patients were catheterizing. To improve recruitment, the protocol was later amended to include all MS and SCI patients with NDO.

Allergan worked to design the phase 3 NDO program with key opinion leaders, who then suggested expanding the development program to include patients suffering from OAB. Despite conventional treatment with oral anticholinergic agents, the experts indicated that there were a number of people who were not adequately managed, and onabotulinumtoxinA could provide another treatment option for these patients.

Dr. Nitti, who was Professor of Urology and Obstetrics and Gynecology and the Vice Chairman of the Department of Urology at New York University Langone Medical Center in New York, NY at the time of the registrational trials for onabotulinumtoxinA treatment of OAB: We have the seriousness of the NDO condition, for which Botox offered, we thought, a great potential, and then we had this other condition, OAB,

where there were potentially millions of people, a much larger number of people, that were affected in more of a quality of life way than what can be perceived as a threat to their health, which was the case in NDO. Based upon an early key opinion leader meeting in 2004, enough of an impression was left with the Allergan leadership where... the seed was planted that, maybe we really ought to consider going ahead with an OAB program as well.

Dr. Schurch: We were convinced from our first experience with Botox in OAB[49] *that onabotulinumtoxinA might be an option for this condition as it was for NDO.*

In contrast to the NDO trials, enrollment for the OAB trials was faster than anticipated, reflecting a high unmet medical need in this patient population that was not adequately managed by anticholinergics. However, study design was a big challenge for the trials, especially in identifying the optimal doses and in finding a good balance among efficacy, safety, and clinical judgment for issues such as anesthesia during treatment and criteria for use of CIC. In some instances, the mechanism of action of onabotulinumtoxinA may cause the detrusor to become too relaxed, resulting in incomplete emptying of the patient's bladder and requiring the patient to perform CIC to remove residual urine (this adverse event [AE] was coded as "urinary retention" in the trials). From the perspective of protocol design, it was therefore important to define the volume at which CIC should be initiated, as well as other clinical aspects, in a somewhat standard way but to also allow the physician's clinical judgment in management of their patient.

Dr. Haag-Molkenteller: This was a challenge: How do you implement the study? What is the antibiotic coverage? What is the local anesthesia or is general anesthesia needed? What is the appropriate follow-up period? That was challenging. There were no fully explored treatment paradigms for an injectable drug to treat NDO and OAB since Botox was the first injectable therapy for these conditions. Different centers used different treatment paradigms and different doses, but for drug development one needed to establish a global treatment paradigm and define the doses to be studied, as regulatory approvals are based on broad efficacy and safety information. The diverse approaches various physicians were using in their clinics and that Botox was the first injectable drug for NDO and OAB were challenging for a regulatory development program. At Allergan we needed to develop the drug for global regulatory approvals so patients could be treated according to a standardized approach and following comprehensive efficacy and safety information.

Dr. Nitti: I've never been in a situation where there was that kind of collaboration [between a pharmaceutical company and investigators]. The way that the experts were listened to and the way that their many thoughts and opinions were implemented was really like nothing I'd ever seen. And maybe that's because it was such unchartered territory, because you really had to understand this balance of safety and efficacy, particularly in the overactive bladder population. It was one of the most rewarding projects that I've participated in in my career. It was a very exciting time.

Allergan conducted a dose-finding, phase 2 study for OAB that tested onabotulinumtoxinA 50U, 100U, 150U, 200U, and 300U versus placebo.[50] The onabotulinumtoxinA dose groups ≥100U exhibited efficacy in the primary and secondary outcomes as well as in urodynamic and QOL outcomes.[50–52] Patients treated with onabotulinumtoxinA also exhibited higher patient satisfaction scores and greater goal achievement compared with placebo.[53] A dose-dependent effect on the proportion of patients with post-void residual urine volume (PVR) ≥200 mL was observed, and increases in CIC use and UTI rates were higher in those patients with PVR ≥200 mL.

Dr. Brin, who is the Chief Scientific Officer at Allergan, an AbbVie company: In the phase 2 study, the 100U dose had the most favorable benefit-risk profile. I asked one of our statisticians, Jihao Zhou, to explore a way to express the risk:benefit, or safety:efficacy relationship among the tested doses. Although I asked him to come back to me later in the week, I found the analysis in my inbox the next morning. This analysis was important, and we went with the 100U dose, anticipating statistical efficacy once we had greater power and additional design elements in place for the phase 3 protocol.

Thus, onabotulinumtoxinA 100U was chosen as the dose for the phase 3 studies for OAB. A number of experts were surprised that 100U worked so effectively since many had been using 200U off-label for OAB, highlighting the importance of randomized, controlled trials to the scientific community.

4. Efficacy and safety highlights

4.1. NDO

Beginning in 2011, onabotulinumtoxinA received regulatory approvals for UI due to NDO in adults who had an inadequate response to or are intolerant of an anticholinergic in the US; Canada; most major European, Middle Eastern, and South American countries; and many Asia-Pacific countries.[54] This indication was based on the results of the randomized, double-blind, placebo-controlled phase 3 trials, which showed significant decreases from baseline in the number of UI episodes/week as well as significantly higher proportions of patients who were responders for both onabotulinumtoxinA 200U and 300U versus placebo (Fig. 2).[55–57] Both onabotulinumtoxinA doses significantly increased maximum cystometric capacity versus placebo, with similar increases in patients with MS or SCI and in patients who were or were not using anticholinergics.[58] In patients who had an involuntary detrusor contraction (IDC), the maximum detrusor pressure during IDC also significantly decreased from baseline versus placebo, again regardless of etiology or anticholinergic use.

Ms. Jenkins, who was the Clinical Program Lead at Allergan during the registrational studies for onabotulinumtoxinA treatment of NDO and OAB: [At the meeting to review the topline data] I remember our statistician just being ecstatic and saying, "I have never seen data as good as this. I've never worked on a product that hit every single primary and secondary endpoint." There was just no question about the data.

In addition to the efficacy endpoints, large positive effects on QOL were observed, of particular importance since these patients had not been adequately treated with the available drug therapies. Patients treated with onabotulinumtoxinA 200U or 300U in either of the pivotal phase 3 trials showed significant improvements compared with placebo and exceeded the minimal important differences in several QOL and patient satisfaction outcome measures, including the Incontinence-QOL Questionnaire (I-QOL), the OAB Patient Satisfaction with Treatment Questionnaire, and the Patient Global Assessment.[59,60] A pooled analysis of the pivotal trials found that significantly more onabotulinumtoxinA-treated patients achieved their self-determined treatment goals compared with placebo regardless of etiology or use of CIC.[61]

The 200U dose of onabotulinumtoxinA was approved for NDO based on its similar efficacy to 300U but with an improved safety profile. For example, the proportion of patients who initiated CIC due to urinary retention was higher in those who received the 300U dose (44%) compared with the 200U dose (31%).[58] The most commonly reported AEs in the first 12 weeks following treatment with onabotulinumtoxinA 300U, 200U, or placebo in the NDO development program were UTI (30%, 24%, and 17%, respectively) and urinary retention (21%, 17%, and 3%).[54,62] The rate of urinary retention showed a dose-dependent increase in patients with MS who were not catheterizing at baseline (nearly all patients with SCI were using CIC at baseline). Of the patients with MS who received onabotulinumtoxinA 200U, 31% initiated CIC during the first treatment

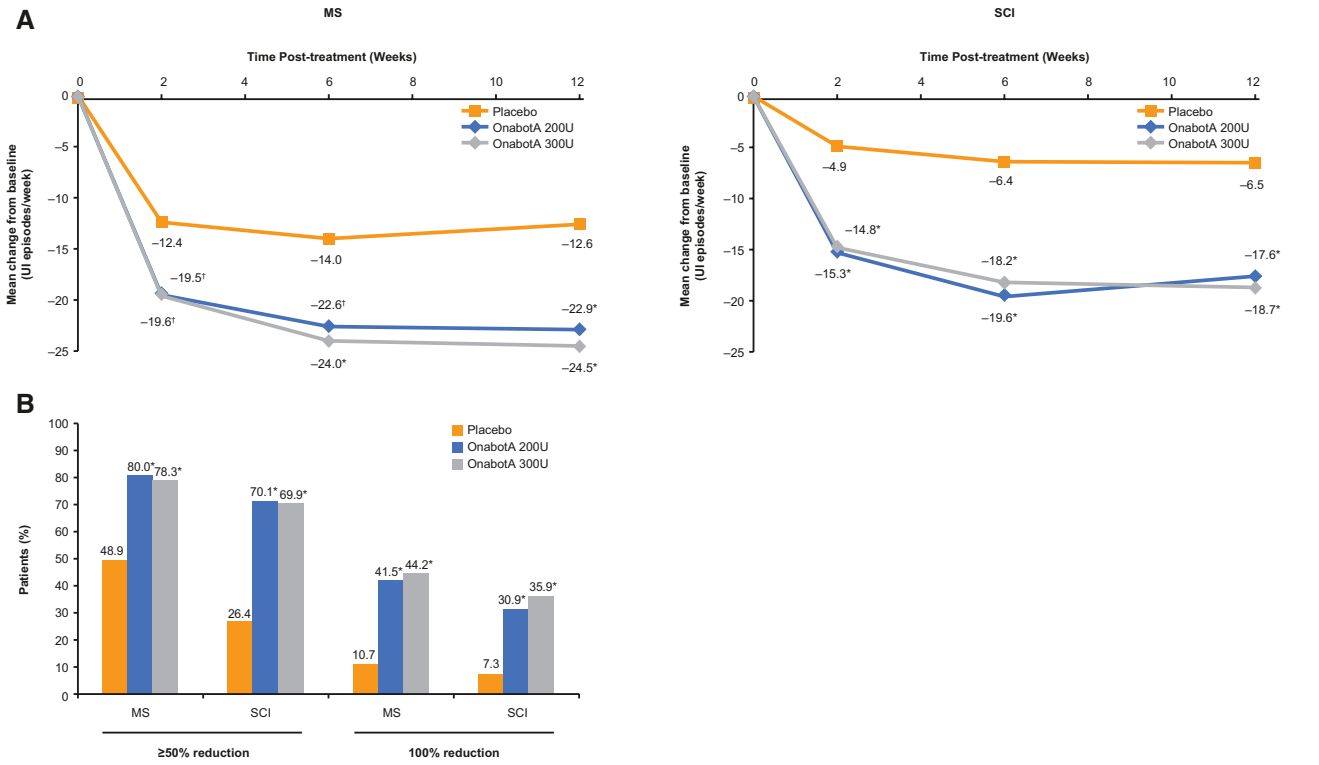

Figure 2. Pooled data from the two pivotal trials of onabotulinumtoxinA treatment of NDO. (A) Mean change from baseline in UI episodes/week (primary endpoint) in patients with MS or SCI. (B) Responder rates for ≥50% and 100% reductions in UI episodes at week 6 in the MS and SCI subpopulations. MS = multiple sclerosis; NDO = neurogenic detrusor overactivity; OnabotA = onabotulinumtoxinA; SCI = spinal cord injury; UI = urinary incontinence. *P <.001, †P <.05 vs placebo. Reprinted with permission from Ginsberg D, Cruz F, Herschorn S, et al. *Adv Ther.* 2013;30:819–33. https://doi.org/10.1007/s12325-013-0054-z.

cycle, and they showed the same satisfaction with treatment as those who did not need to initiate CIC.[57] In contrast, 47% of those with MS treated with onabotulinumtoxinA 300U initiated CIC during treatment cycle 1, and significant decreases in satisfaction with treatment were observed between those who initiated CIC and those who did not.

Since the 200U dose was the one submitted for and ultimately received regulatory approval for NDO, this was the dose received by patients who continued in the open-label, long-term extension study of the two pivotal NDO trials that followed patients for up to 4 years.[63,64] Results from this study showed that after repeat treatments with onabotulinumtoxinA, UI episodes were consistently decreased from baseline, with about half of patients achieving dryness.[63] Improvements in QOL were also sustained, and the median duration of effect for onabotulinumtoxinA 200U was 9.0 months. A post hoc analysis of this trial showed that long-term benefits continued in patients who achieved a ≥50% reduction in UI episodes after their first treatment with onabotulinumtoxinA, and that of the 17% of patients with <50% reduction in UI episodes after the first treatment, nearly 40% achieved ≥50% reductions in UI episodes in subsequent treatments.[65]

A post-approval, randomized, double-blind, placebo-controlled study tested onabotulinumtoxinA 100U in patients with MS whose NDO was inadequately managed with anticholinergics and were not using CIC at baseline.[66] With this lower dose, significant decreases from baseline in UI episodes relative to placebo were observed, as were improvements in urodynamics and QOL, exceeding the minimal important difference for the latter. In addition, significant improvements were seen in urinary urgency with onabotulinumtoxinA, an endpoint not measured in the earlier studies. Similar to the pivotal trials with 200U, the most common AEs were UTI (26% versus 6% for placebo), residual urine volume (17% versus 1% for placebo), and urinary retention (15% versus 1% for placebo). Notably, 15% of onabotulinumtoxinA 100U treated-patients initiated CIC in this study, lower than the 31% seen in the MS subpopulation of the pivotal trials who were treated with onabotulinumtoxinA 200U.[57]

Of note, dosing for onabotulinumtoxinA is not interchangeable with that of other botulinum toxin products due to differences in manufacturing, formulation, and assays used to determine activity.[54,67]

4.2. OAB

OnabotulinumtoxinA received regulatory approvals beginning in 2013 in the US; Canada; most major European, Middle Eastern, and South American countries; and many Asia-Pacific countries for the treatment of OAB in adults who had an inadequate response to or are intolerant of an anticholinergic medication.[54] The two pivotal, randomized, double-blind, placebo-controlled phase 3 trials each showed significant improvements from baseline with onabotulinumtoxinA 100U compared with placebo in the co-primary endpoints of change from baseline in UI episodes and positive response on the Treatment Benefit Scale at week 12 (Fig. 3).[68,69] A pooled analysis of the pivotal OAB studies showed that at week 12 following treatment, onabotulinumtoxinA conferred significant improvements in multiple efficacy endpoints versus placebo regardless of the number of prior anticholinergic treatments and whether patients discontinued anticholinergics due to insufficient efficacy or side effects.[70] In addition to the improvements in efficacy endpoints, recent papers indicate that among other treatments, including sacral nerve stimulation, percutaneous tibial nerve stimulation, anticholinergics, and mirabegron, intradetrusor onabotulinumtoxinA was the most cost-effective treatment for refractory OAB.[71,72]

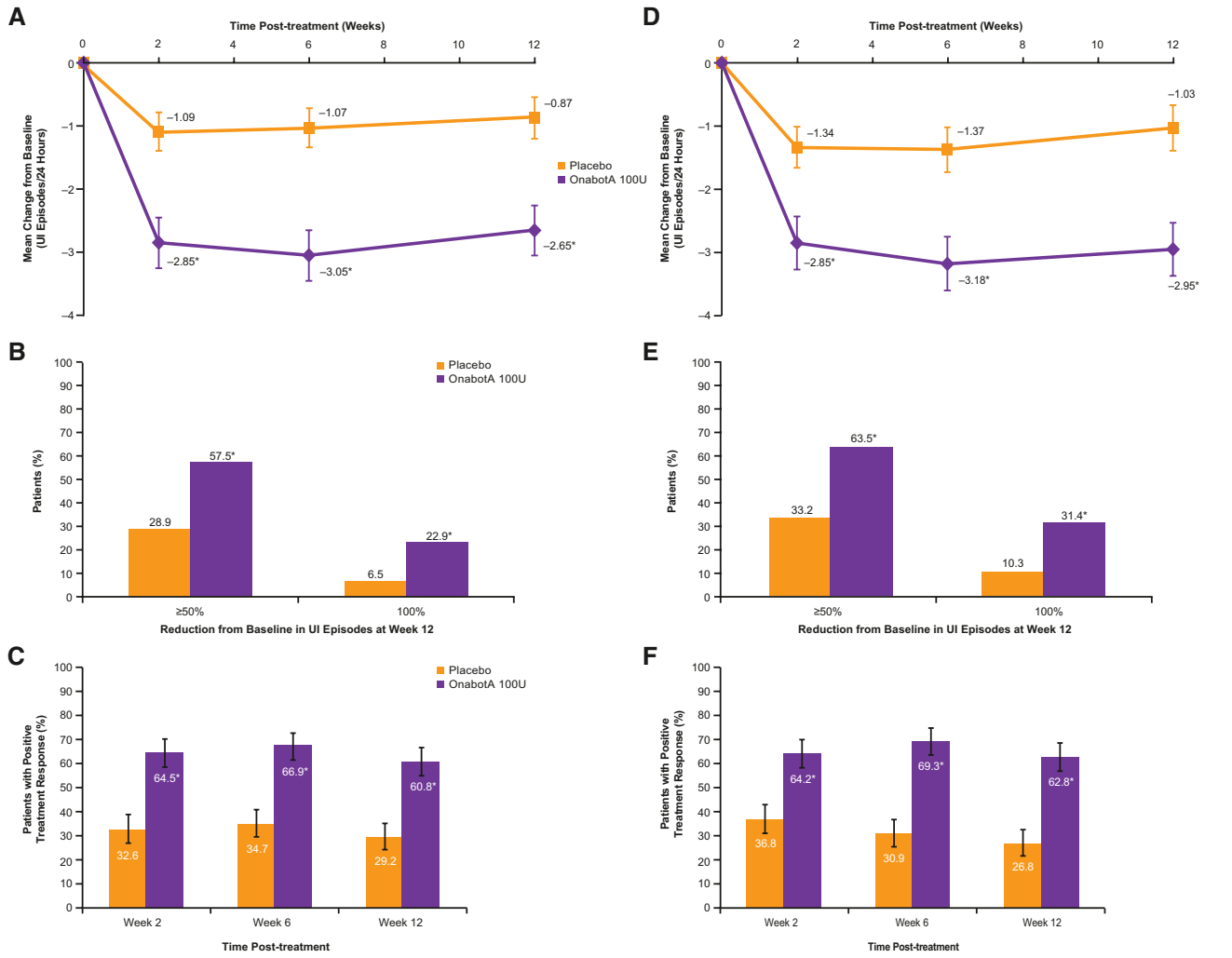

Figure 3. Data from the pivotal trials of onabotulinumtoxinA for the treatment of OAB. (A, D) Change from baseline in mean urinary incontinence episodes/day (co-primary endpoint), (B, E) responder rates for ≥50% and 100% reductions in UI episodes at week 12, and (C, F) proportion of patients with a positive response on the Treatment Benefit Scale (co-primary endpoint) at week 12 following treatment with onabotulinumtoxinA 100U or placebo. OAB = overactive bladder; OnabotA = onabotulinumtoxinA; UI = urinary incontinence. *P <.001 vs placebo. Panels A, B, and C are reprinted with permission from Nitti VW, Dmochowski R, Herschorn S, et al. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. *J Urol.* 2013;189: 2186–93. Official Journal of the American Urological Association: https://www.auajournals.org/. Panels D and F are reprinted from *Eur Urol*, Vol 64, Chapple C, Sievert K D, MacDiarmid S, et al., OnabotulinumtoxinA 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: a randomised, double-blind, placebo-controlled trial, Pages 249–56, Copyright 2013, with permission from Elsevier. Official journal of the European Association of Urology: https://www.europeanurology.com/.

Significant improvements in multiple measures of QOL were observed with onabotulinumtoxinA treatment, including exceeding the minimal important differences by several fold on both the I-QOL and King's Health Questionnaire.[68,69] These results were noteworthy because these patients had not been satisfactorily treated with prior drug therapies. A pooled analysis of the pivotal OAB trials showed that these improvements in QOL persisted whether patients were using CIC or had a UTI.[73]

An open-label extension of the pivotal OAB trials showed that improvements in both efficacy and QOL endpoints were sustained over multiple treatments spanning 3.5 years, with a median duration of effect of 7.6 months of onabotulinumtoxinA 100U.[74,75] This extension trial initially allowed a dose increase to 150U beginning at treatment 3, but only the 100U dose was allowed after a planned interim statistical analysis showed no additional efficacy with the higher dose.

Unlike in the NDO trials, in which initiation of CIC was based on investigator assessment, patients in the OAB trials were to initiate CIC if the PVR was ≥200 to <350 mL with associated symptoms that the investigator deemed as requiring CIC, or if PVR was ≥350 mL regardless of symptoms. In the combined pivotal trial population, 36/552 (6.5%) of those treated with onabotulinumtoxinA initiated CIC based on these criteria for a median of 63 days, compared with 2/542 (0.4%) for placebo.[54]

The most common AEs in the combined onabotulinumtoxinA groups in the first 12 weeks of both pivotal OAB trials were UTI (18%), dysuria (9%), and urinary retention (6%).[54] Region-specific information regarding safety and efficacy can be found in local labeling.

A post-approval, double-blind, randomized study compared the efficacy and safety of onabotulinumtoxinA 100U, the anticholinergic solifenacin (5 mg but could be titrated to 10 mg), and placebo.[76] Although both onabotulinumtoxinA 100U and solifenacin 5/10 mg significantly reduced the number of daily UI episodes at week 12 (co-primary endpoint) compared with placebo, a post hoc analysis showed that the reduction of UI episodes was significantly greater for onabotulinumtoxinA versus solifenacin. Significantly higher proportions of patients achieved 100% reduction in daily UI episodes at week 12 (co-primary endpoint) with onabotulinumtoxinA

(33.8%) or solifenacin (24.5%) treatment compared with placebo (11.7%). The rates of UTI in the first 12 weeks were similar to those in the pivotal trials, with 19%, 6%, and 10% for onabotulinumtoxinA, solifenacin, and placebo, respectively.

4.3. Onset, duration, and immunogenicity

Onset of efficacy has not been specifically explored in controlled clinical trials of onabotulinumtoxinA for NDO or OAB. However, a recent trial showed significant reductions from baseline in UI episodes in the onabotulinumtoxinA group versus placebo as early as one week following treatment.[77]

The duration of onabotulinumtoxinA noted in the long-term NDO (median 9.0 months)[63] and OAB (median 7.6 months)[74] trials is substantially longer than the 3.5- to 4-month duration usually reported following skeletal muscle injections for indications such as cervical dystonia and glabellar lines.[78–80] The duration differences seen in these indications may result from the tendency of neurons innervating skeletal muscles to sprout;[81] axonal sprouting in the smooth muscle of the bladder of patients treated for NDO does not differ before first treatment or after treatment with onabotulinumtoxinA.[82]

Dr. Brin: The long duration in overactive bladder confirmed that the pharmacology of Botox is very much dependent on the target tissue. This is similar to the 7-month duration reported in axillary hyperhidrosis,[83,84] and in addition, some hyperhidrosis patients experience benefit for at least a year following a single injection cycle.[84]

Since onabotulinumtoxinA is a protein complex repeatedly administered to patients over time, immunogenicity is a potential concern. However, the rates of neutralizing antibody development were low in patients in the pivotal and open-label extension studies, in 3/300 (1%) of patients who received onabotulinumtoxinA 200U for NDO and in 0/954 (0%) of those who received onabotulinumtoxinA 100U for OAB.[54] Two of the three patients who seroconverted still experienced improvements in UI episodes, and no post-seroconversion data were available for the third patient.

5. Impact of onabotulinumtoxinA on the broader biomedical community

OnabotulinumtoxinA is now widely used in the urological and urogynecological communities.

Dr. Chancellor: For years I did a course at the American Urological Association annual meeting on how and why to use onabotulinumtoxinA. I don't need to do my AUA course any more on the technique of toxin because urologists are trained in it and residents are being trained in it. It's [Botox has] become a standard of care.

Perhaps the largest scientific impact of the use of onabotulinumtoxinA in the bladder is that it led to a greater understanding of the mechanisms of action of onabotulinumtoxinA. Prior to injection of onabotulinumtoxinA into the smooth muscle of the bladder, it had primarily been injected into striated muscle for other indications. The ability of botulinum toxin to inhibit acetylcholine release in neurons and reduce muscle contraction had been well documented. However, the observed reduction in urgency following onabotulinumtoxinA treatment suggested an additional sensory/afferent mechanism.

Sensory mechanisms in the bladder have been documented in both laboratory and clinical studies. Botulinum toxin type A reduced mechanoreceptor-stimulated ATP release from sensory afferents in a laboratory model of spinal cord injury[85] and reduced pain and release of calcitonin gene-related peptide from sensory neurons in a model of bladder pain.[86] In suburothelial tissue from patients with detrusor overactivity, onabotulinumtoxinA reduced transient receptor potential vanilloid cation channel (TRPV1)- and purinoceptor 3 (P2X3)-positive fibers, returning them to levels that were comparable to those of control patients.[87] The decreases in P2X3 receptors after onabotulinumtoxinA treatment were significantly correlated with improvements in sensations of urgency. These findings led to further studies investigating ion channel receptors in nerve membranes, finding that insertion of these channels is inhibited by onabotulinumtoxinA.[88]

Dr. Brin: The translational work showing the importance of TRPV1 and P2X3 channels was critical in understanding the mechanism of action of Botox in the bladder.[87] *Dr. Fowler, who was subsequently honored as a Commander of the British Empire by the Queen of England for establishing the new subspecialty uro-neurology, was instrumental in this study, which was conducted at the Imperial College London.*

6. Impact of treatment with onabotulinumtoxinA on patients

In addition to the positive effects on QOL observed in the clinical trials, patients have related their satisfaction with onabotulinumtoxinA treatment.

Dr. Schurch: The first patient I treated called me after three or four days [following treatment with onabotulinumtoxinA] and she told me, "I am reborn!"

Ms. Jenkins: On several occasions, emails were forwarded to me from patients that were in the [NDO] trial that had reached out to Allergan to thank the company for conducting the study. The patients wrote that once they received Botox in the study, their lives were so much better. And that really motivated me, and it really has stuck with me throughout all of the time that I've been working with Botox. The fact that these patients worked so hard to get this message to us really says a lot.

One of the most notable effects of the use of onabotulinumtoxinA for the treatment of NDO has been the decrease in the number of augmentation cystoplasty surgeries.[89]

Dr. Nitti: There is no question that the approval of Botox in the NDO patients has saved a lot of patients major surgery.

Dr. Schurch: We saw a parallel decrease of the number of enterocystoplasties concomitant to the increase of the number of patients we injected with Botox.

Dr. Kennelly: I typically was doing between 25 and 30 augmentation cystoplasties, appendicovesicostomies a year... Nowadays, I probably do one to two per year.

Dr. Chancellor: For the 10 years before 1998– before I used toxin– I was doing at least one bladder augmentation a month. For that period of time, I would have done 150 of them. For the 10 years after, I did a total of three.

Other advantages of onabotulinumtoxinA treatment for NDO include removing some of the burden of patients' underlying disease by improving their UI.

Dr. Chancellor: [There] is a patient I saw last week. This is her 18th year of receiving onabotulinumtoxinA injections from me... Her husband is a retired urologist now, so he must have heard about what I was doing. His wife has MS, so he asked me, "Can you go ahead and do it?" It's obviously gone well enough, now they're in their late 70s... She had her 36th injection. She has them religiously, every 6 months, same dose, 18 years. If he hadn't [contacted Dr. Chancellor], I can't imagine that she would have the quality of life, being able to spend time with her grandchildren, great-grandchildren.

For OAB, onabotulinumtoxinA has had a large impact on patients' QOL as documented not only via patient-reported measures in clinical trials[68,69,73–75] but also observed in the clinic.

Dr. Nitti: In the overactive bladder population, I think it [onabotulinumtoxinA] has had a profound effect on those who have been exposed to it. I think it's been a real life-changer for

a lot of people that have elected to use Botox when other things haven't worked for them… I'm grateful that I have it in my armamentarium and still use it regularly and will continue to do so.

Acknowledgments

Writing and editorial assistance was provided to the authors by Jennifer L. Giel, PhD, on behalf of Evidence Scientific Solutions, Inc, and was funded by Allergan, an AbbVie company. Mitchell F. Brin, MD, of AbbVie, reviewed the manuscript. All authors met the ICMJE authorship criteria. Neither honoraria nor other form of payments were made for authorship.

Author contributions

Conceptualization: Brenda Jenkins.
Funding acquisition: Brenda Jenkins.
Supervision: Brenda Jenkins.
Writing – review & editing: Victor Nitti, Cornelia Haag-Molkenteller, Michael Kennelly, Michael Chancellor, Brenda Jenkins, Brigitte Schurch.

References

[1] Ruffion A, Castro-Diaz D, Patel H, et al. Systematic review of the epidemiology of urinary incontinence and detrusor overactivity among patients with neurogenic overactive bladder. Neuroepidemiology. 2013;41:146–55.
[2] Jeong SJ, Cho SY, Oh SJ. Spinal cord/brain injury and the neurogenic bladder. Urol Clin North Am. 2010;37:537–46.
[3] Ginsberg D. The epidemiology and pathophysiology of neurogenic bladder. Am J Manag Care. 2013;19(10 Suppl):s191–6.
[4] Manack A, Motsko SP, Haag-Molkenteller C, et al. Epidemiology and healthcare utilization of neurogenic bladder patients in a US claims database. Neurourol Urodyn. 2011;30:395–401.
[5] de Sèze M, Ruffion A, Denys P, et al. GENULF. The neurogenic bladder in multiple sclerosis: review of the literature and proposal of management guidelines. Mult Scler. 2007;13:915–28.
[6] Haylen BT, de Ridder D, Freeman RM, et al. International Urogynecological Association. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn. 2010;29:4–20.
[7] Irwin DE, Kopp ZS, Agatep B, et al. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. BJU Int. 2011;108:1132–8.
[8] Plata M, Bravo-Balado A, Robledo D, et al. Prevalence of lower urinary tract symptoms and overactive bladder in men and women over 18 years old: the Colombian overactive bladder and lower urinary tract symptoms (COBaLT) study. Neurourol Urodyn. 2019;38:200–7.
[9] Chuang YC, Liu SP, Lee KS, et al. Prevalence of overactive bladder in China, Taiwan and South Korea: results from a cross-sectional, population-based study. Low Urin Tract Symptoms. 2019;11:48–55.
[10] Wang JY, Liao L, Liu M, et al. Epidemiology of lower urinary tract symptoms in a cross-sectional, population-based study: the status in China. Med Baltimore. 2018;97:e11554.
[11] Coyne KS, Sexton CC, Bell JA, et al. The prevalence of lower urinary tract symptoms (LUTS) and overactive bladder (OAB) by racial/ethnic group and age: results from OAB-POLL. Neurourol Urodyn. 2013;32:230–7.
[12] Milsom I, Abrams P, Cardozo L, et al. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int. 2001;87:760–6.
[13] Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. World J Urol. 2003;20:327–36.
[14] Tang DH, Colayco D, Piercy J, et al. Impact of urinary incontinence on health-related quality of life, daily activities, and healthcare resource utilization in patients with neurogenic detrusor overactivity. BMC Neurol. 2014;14:74.
[15] Tapia CI, Khalaf K, Berenson K, et al. Health-related quality of life and economic impact of urinary incontinence due to detrusor overactivity associated with a neurologic condition: a systematic review. Health Qual Life Outcomes. 2013;11:13.
[16] Tang DH, Colayco DC, Khalaf KM, et al. Impact of urinary incontinence on healthcare resource utilization, health-related quality of life and productivity in patients with overactive bladder. BJU Int. 2014;113:484–91.
[17] Milsom I, Kaplan SA, Coyne KS, et al. Effect of bothersome overactive bladder symptoms on health-related quality of life, anxiety, depression, and treatment seeking in the United States: results from EpiLUTS. Urology. 2012;80:90–6.
[18] Yehoshua A, Chancellor M, Vasavada S, et al. Health resource utilization and cost for patients with incontinent overactive bladder treated with anticholinergics. J Manag Care Spec Pharm. 2016;22:406–13.
[19] Bartoli S, Aguzzi G, Tarricone R. Impact on quality of life of urinary incontinence and overactive bladder: a systematic literature review. Urology. 2010;75:491–500.
[20] Lai H, Gardner V, Vetter J, et al. Correlation between psychological stress levels and the severity of overactive bladder symptoms. BMC Urol. 2015;15:14.
[21] Coyne KS, Sexton CC, Kopp ZS, et al. The impact of overactive bladder on mental health, work productivity and health-related quality of life in the UK and Sweden: results from EpiLUTS. BJU Int. 2011;108:1459–71.
[22] Ganz ML, Smalarz AM, Krupski TL, et al. Economic costs of overactive bladder in the United States. Urology. 2010;75:e1–18.
[23] Coyne KS, Wein A, Nicholson S, et al. Economic burden of urgency urinary incontinence in the United States: a systematic review. J Manag Care Pharm. 2014;20:130–40.
[24] Blok B, Pannek J, Castro-Diaz D, et al. EAU guidelines on neuro-urology. 2016. Available at: https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Neuro-Urology-2022.pdf [access date March 10, 2020].
[25] Çetinel B, Kocjancic E, Demirdağ C. Augmentation cystoplasty in neurogenic bladder. Investig Clin Urol. 2016;57:316–23.
[26] Wiart L, Joseph PA, Petit H, et al. The effects of capsaicin on the neurogenic hyperreflexic detrusor. A double blind placebo controlled study in patients with spinal cord disease. Preliminary results. Spinal Cord. 1998;36:95–9.
[27] de Sèze M, Wiart L, Joseph PA, et al. Capsaicin and neurogenic detrusor hyperreflexia: a double-blind placebo-controlled study in 20 patients with spinal cord lesions. Neurourol Urodyn. 1998;17:513–23.
[28] Kim JH, Rivas DA, Shenot PJ, et al. Intravesical resiniferatoxin for refractory detrusor hyperreflexia: a multicenter, blinded, randomized, placebo-controlled trial. J Spinal Cord Med. 2003;26:358–63.
[29] Silva C, Silva J, Ribeiro MJ, et al. Urodynamic effect of intravesical resiniferatoxin in patients with neurogenic detrusor overactivity of spinal origin: results of a double-blind randomized placebo-controlled trial. Eur Urol. 2005;48:650–5.
[30] Kuo HC, Liu HT, Yang WC. Therapeutic effect of multiple resiniferatoxin intravesical instillations in patients with refractory detrusor overactivity: a randomized, double-blind, placebo controlled study. J Urol. 2006;176:641–5.
[31] Reitz A, Schurch B. Intravesical therapy options for neurogenic detrusor overactivity. Spinal Cord. 2004;42:267–72.
[32] Dasgupta P. Capsaicin, resiniferatoxin and botulinum toxin-A - a trip down memory lane. BJU Int. 2015;115:675.
[33] Madersbacher H, Jilg G. Control of detrusor hyperreflexia by the intravesical instillation of oxybutynine hydrochloride. Spinal Cord. 1991;29:84–90.
[34] Gormley EA, Lightner DJ, Burgio KL, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. 2019. Available at: https://d56bochluxqnz.cloudfront.net/media/EAU-Guidelines-on-Urinary-Incontinence_2018-V3.pdf [access date March 9, 2020].
[35] Burkhard FC, Bosch JLHR, Cruz F, et al. EAU guidelines on urinary incontinence in adults. 2018. Available at: https://d56bochluxqnz.cloudfront.net/media/EAU-Guidelines-on-Urinary-Incontinence_2018-V3.pdf [access date March 9, 2020].
[36] Fox C, Richardson K, Maidment ID, et al. Anticholinergic medication use and cognitive impairment in the older population: the Medical Research Council Cognitive Function and Ageing Study. J Am Geriatr Soc. 2011;59:1477–83.
[37] Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. JAMA Intern Med. 2015;175:401–7.
[38] Szabo SM, Gooch K, Schermer C, et al. Association between cumulative anticholinergic burden and falls and fractures in patients with overactive bladder: US-based retrospective cohort study. BMJ Open. 2019;9:e026391.
[39] Schurch B, Schmid DM, Stöhrer M. Treatment of neurogenic incontinence with botulinum toxin A. N Engl J Med. 2000;342:665.

[40] Kerner J. Das Fettgift oder die Fettsäure und ihre Wirkung auf den tierischen Organismus. Tuebingen, Germany: Cotta; 1822.
[41] Dykstra DD, Sidi AA, Scott AB, et al. Effects of botulinum A toxin on detrusor-sphincter dyssynergia in spinal cord injury patients. J Urol. 1988;139:919–22.
[42] Naumann M, Flachenecker P, Bröcker EB, et al. Botulinum toxin for palmar hyperhidrosis. Lancet. 1997;349:252.
[43] Stöhrer M, Schurch B, Kramer G, et al. Botulinum A-toxin in the treatment of detrusor hyperreflexia in spinal cord injured patients: a new alternative to medical and surgical procedures? Joint Meeting of the International Continence Society, the International Urogynecological Association, and the International Children's Continence Society. Denver, CO: ICS, IUGA, ICCS; 1999.
[44] Schurch B, Stöhrer M, Kramer G, et al. Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. J Urol. 2000;164(3 Pt 1):692–7.
[45] Schurch B, de Sèze M, Denys P, et al. Botox Detrusor Hyperreflexia Study Team. Botulinum toxin type a is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. J Urol. 2005;174:196–200.
[46] Kennelly MJ, Kang J. Botulinum-A toxin injections as a treatment for refractory detrusor hyperreflexia. Top Spinal Cord Inj Rehabil. 2003;8:46–53.
[47] Smith CP, Boone TB, de Groat WC, et al. Effect of stimulation intensity and botulinum toxin isoform on rat bladder strip contractions. Brain Res Bull. 2003;61:165–71.
[48] Smith CP, Franks ME, McNeil BK, et al. Effect of botulinum toxin A on the autonomic nervous system of the rat lower urinary tract. J Urol. 2003;169:1896–900.
[49] Schmid DM, Sauermann P, Werner M, et al. Experience with 100 cases treated with botulinum-A toxin injections in the detrusor muscle for idiopathic overactive bladder syndrome refractory to anticholinergics. J Urol. 2006;176:177–85.
[50] Dmochowski R, Chapple C, Nitti VW, et al. Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial. J Urol. 2010;184:2416–22.
[51] Rovner E, Kennelly M, Schulte-Baukloh H, et al. Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinumtoxinA in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder. Neurourol Urodyn. 2011;30:556–62.
[52] Fowler CJ, Auerbach S, Ginsberg D, et al. OnabotulinumtoxinA improves health-related quality of life in patients with urinary incontinence due to idiopathic overactive bladder: a 36-week, double-blind, placebo-controlled, randomized, dose-ranging trial. Eur Urol. 2012;62:148–57.
[53] Brubaker L, Gousse A, Sand P, et al. Treatment satisfaction and goal attainment with onabotulinumtoxinA in patients with incontinence due to idiopathic OAB. Int Urogynecol J. 2012;23:1017–25.
[54] Botox (onabotulinumtoxinA) [prescribing information]. Irvine, CA: Allergan Pharmaceuticals Ireland, a subsidiary of Allergan, Inc.; 2020.
[55] Ginsberg D, Gousse A, Keppenne V, et al. Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. J Urol. 2012;187:2131–9.
[56] Cruz F, Herschorn S, Aliotta P, et al. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. Eur Urol. 2011;60:742–50.
[57] Ginsberg D, Cruz F, Herschorn S, et al. OnabotulinumtoxinA is effective in patients with urinary incontinence due to neurogenic detrusor overactivity regardless of concomitant anticholinergic use or neurologic etiology. Adv Ther. 2013;30:819–33.
[58] Rovner E, Dmochowski R, Chapple C, et al. OnabotulinumtoxinA improves urodynamic outcomes in patients with neurogenic detrusor overactivity. Neurourol Urodyn. 2013;32:1109–15.
[59] Chancellor MB, Patel V, Leng WW, et al. OnabotulinumtoxinA improves quality of life in patients with neurogenic detrusor overactivity. Neurology. 2013;81:841–8.
[60] Sussman D, Patel V, Del Popolo G, et al. Treatment satisfaction and improvement in health-related quality of life with onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity. Neurourol Urodyn. 2013;32:242–9.
[61] Chartier-Kastler E, Rovner E, Hepp Z, et al. Patient-reported goal achievement following onabotulinumtoxinA treatment in patients with neurogenic detrusor overactivity. Neurourol Urodyn. 2016;35:595–600.
[62] Allergan, an AbbVie company. Data on file.
[63] Kennelly M, Dmochowski R, Schulte-Baukloh H, et al. 191622-094 Investigators. Efficacy and safety of onabotulinumtoxinA therapy are sustained over 4 years of treatment in patients with neurogenic detrusor overactivity: final results of a long-term extension study. Neurourol Urodyn. 2017;36:368–75.
[64] Rovner E, Kohan A, Chartier-Kastler E, et al. Long-term efficacy and safety of onabotulinumtoxinA in patients with neurogenic detrusor overactivity who completed 4 years of treatment. J Urol. 2016;196:801–8.
[65] Denys P, Dmochowski R, Aliotta P, et al. Positive outcomes with first onabotulinumtoxinA treatment persist in the long term with repeat treatments in patients with neurogenic detrusor overactivity. BJU Int. 2017;119:926–32.
[66] Tullman M, Chartier-Kastler E, Kohan A, et al. Low-dose onabotulinumtoxinA improves urinary symptoms in noncatheterizing patients with MS. Neurology. 2018;91:e657–65.
[67] Brin MF, James C, Maltman J. Botulinum toxin type A products are not interchangeable: a review of the evidence. Biologics. 2014;8:227–41.
[68] Nitti VW, Dmochowski R, Herschorn S, et al. EMBARK Study Group. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. J Urol. 2013;189:2186–93.
[69] Chapple C, Sievert KD, MacDiarmid S, et al. OnabotulinumtoxinA 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: a randomised, double-blind, placebo-controlled trial. Eur Urol. 2013;64:249–56.
[70] Sievert KD, Chapple C, Herschorn S, et al. OnabotulinumtoxinA 100U provides significant improvements in overactive bladder symptoms in patients with urinary incontinence regardless of the number of anticholinergic therapies used or reason for inadequate management of overactive bladder. Int J Clin Pract. 2014;68:1246–56.
[71] Murray B, Hessami SH, Gultyaev D, et al. Cost-effectiveness of overactive bladder treatments: from the US payer perspective. J Comp Eff Res. 2019;8:61–71.
[72] Shepherd JP, Carter-Brooks CM, Chermanksy C. A cost-effectiveness analysis of Onabotulinumtoxin A as first-line treatment for overactive bladder. Int Urogynecol J. 2018;29:1213–9.
[73] Everaert K, Gruenenfelder J, Schulte-Baukloh H, et al. Impact of onabotulinumtoxinA on quality of life and practical aspects of daily living: a pooled analysis of two randomized controlled trials. Int J Urol. 2015;22:1131–7.
[74] Nitti VW, Ginsberg D, Sievert KD, et al. 191622-096 Investigators. Durable efficacy and safety of long-term onabotulinumtoxinA treatment in patients with overactive bladder syndrome: final results of a 3.5 year study. J Urol. 2016;196:791–800.
[75] Ginsberg DA, Drake MJ, Kaufmann A, et al. 191622-096 Investigators. Long-term treatment with onabotulinumtoxinA results in consistent, durable improvements in health related quality of life in patients with overactive bladder. J Urol. 2017;198:897–904.
[76] Herschorn S, Kohan A, Aliotta P, et al. The efficacy and safety of onabotulinumtoxinA or solifenacin compared with placebo in solifenacin naïve patients with refractory overactive bladder: results from a multicenter, randomized, double-blind phase 3b trial. J Urol. 2017;198:167–75.
[77] McCammon K, Gousse A, Kohan A, et al. Early and consistent improvements in urinary symptoms and quality of life with onabotulinumtoxinA in patients with overactive bladder and urinary incontinence: results from a randomized, placebo-controlled, phase IV clinical trial. Female Pelvic Med Reconstr Surg. 2021;27:450–6.
[78] Brashear A, Watts MW, Marchetti A, et al. Duration of effect of botulinum toxin type A in adult patients with cervical dystonia: a retrospective chart review. Clin Ther. 2000;22:1516–24.
[79] Comella CL, Jankovic J, Shannon KM, et al. Dystonia Study Group. Comparison of botulinum toxin serotypes A and B for the treatment of cervical dystonia. Neurology. 2005;65:1423–9.
[80] Glogau R, Kane M, Beddingfield F, et al. OnabotulinumtoxinA: a meta-analysis of duration of effect in the treatment of glabellar lines. Dermatol Surg. 2012;38:1794–803.
[81] Holds JB, Alderson K, Fogg SG, et al. Motor nerve sprouting in human orbicularis muscle after botulinum A injection. Invest Ophthalmol Vis Sci. 1990;31:964–7.
[82] Haferkamp A, Schurch B, Reitz A, et al. Lack of ultrastructural detrusor changes following endoscopic injection of botulinum toxin type A in overactive neurogenic bladder. Eur Urol. 2004;46:784–91.
[83] Lowe NJ, Glaser DA, Eadie N, et al. North American Botox in Primary Axillary Hyperhidrosis Clinical Study Group. Botulinum

toxin type A in the treatment of primary axillary hyperhidrosis: a 52-week multicenter double-blind, randomized, placebo-controlled study of efficacy and safety. J Am Acad Dermatol. 2007;56: 604–11.
[84] Naumann M, Lowe NJ, Kumar CR, et al. Hyperhidrosis Clinical Investigators Group. Botulinum toxin type A is a safe and effective treatment for axillary hyperhidrosis over 16 months: a prospective study. Arch Dermatol. 2003;139:731–6.
[85] Khera M, Somogyi GT, Kiss S, et al. Botulinum toxin A inhibits ATP release from bladder urothelium after chronic spinal cord injury. Neurochem Int. 2004;45:987–93.
[86] Chuang YC, Yoshimura N, Huang CC, et al. Intravesical botulinum toxin A administration produces analgesia against acetic acid induced bladder pain responses in rats. J Urol. 2004;172(4 Pt 1):1529–32.
[87] Apostolidis A, Popat R, Yiangou Y, et al. Decreased sensory receptors $P2X_3$ and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. J Urol. 2005;174:977–82; discussion 982.
[88] Ferrandiz-Huertas C, Mathivanan S, Wolf CJ, et al. Trafficking of thermoTRP channels. Membranes (Basel). 2014;4:525–64.
[89] Shreck E, Gioia K, Lucioni A. Indications for augmentation cystoplasty in the era of onabotulinumtoxinA. Curr Urol Rep. 2016;17:27.