CLINICAL INVESTIGATION

New treatments for neurogenic detrusor overactivity

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Patients with neurogenic detrusor overactivity (NDO) are a heterogeneous group with different underlying neurologic conditions associated with several urinary symptoms and systemic complications. The first-line, mainstay treatment of NDO are antimuscarinic drugs, but unfortunately they show a low adherence over the years. Thus, in recent years new effective and less invasive strategies were developed. Aim of the present paper is to present available data about these therapies. In particular, data on botulinum toxin A, which is already a recognized alternative to antimuscarinics, will be presented; the role of percutaneous tibial nerve stimulation and sacral neuromodulation in NDO will be discussed and will be provided some data about Mirabegron, a new drug available on market for overactive bladder patients.

Keywords: botulinum toxin A • Mirabegron • neurogenic detrusor overactivity • percutaneous tibial nerve stimulation • sacral neuromodulation

The term 'neurogenic detrusor overactivity (NDO)' is used to describe a urodynamic finding which is characterized by involuntary detrusor (bladder) contractions during the filling phase, which may be spontaneous or provoked due to a relevant neurological condition [1].

NDO may be provoked by suprapontine or spinal cord lesions (above the sacral level). Cerebrovascular disease, Parkinson's disease (PD) and multiple sclerosis (MS) can be listed among the most frequent suprapontine pathologies causing NDO [1]. Spinal cord lesions may be traumatic, vascular, neoplastic or caused by MS [1]. NDO seems to arise from either increased afferent input from the bladder, abnormal central processing of afferent input leading to reduced suprapontine inhibition (with an important role of glutamatergic and dopaminergic pathways in both excitatory and inhibitory regulation of micturition [2]) or physical damage to the axonal paths integral to micturition reflex organized in spinal cord. Locally, there is a shift from the A-delta fibers, that dominate during the normal voiding, to abnormal C-fiber activity in the pathologic state. The ability of the nervous system to change transmitters, reflexes or synaptic transmission with disease, injury or changes in the environment involves neural plasticity [3].

It is important that individuals with NDO maintain a low bladder pressure during bladder storage and voiding with little to no involuntary bladder contractions because NDO may cause several complications (urinary tract infections, bladder stones, fibrosis, trabeculation and autonomic dysreflexia) [4].

A number of strategies have been developed to treat NDO. The most important populations that have been systematically studied are adults with MS, adults with spinal cord injury (SCI) and children and young adults with myelodysplasia. The mainstay of treatment for NDO, when pharmacological therapy is indicated, are anticholinergic (antimuscarinic) medications. One of the presumable functions of antimuscarinic medications is to suppress involuntary bladder contractions, facilitating the drainage from the upper tracts by lowering the pressure within the bladder wall [5].

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Despite their effectiveness, a major drawback of antimuscarinic medications is the presence of side effects, which include dry mouth, constipation, drowsiness and blurred vision. Another problem with antimuscarinic medications is that they need to be taken on a long term. An observational study from 2002 to 2007 noted that persistence with medication remained low [6]. The reason for the interruption in antimuscarinic medications is not exactly known, but may likely be due to side effects, cost, ineffectiveness or forgetting to take the medications [6].

Other traditional bladder management options may be a switch to reflex voiding with or without a sphincterotomy, bladder augmentation or urinary diversion [4]. These options are frequently not acceptable to many individuals with NDO because they involve surgery or wearing a urinary device.

The poor compliance of these strategies leads to find new effective and less invasive treatment options. Therefore in the last 15 years new strategies, some already existing and used in other fields, have been taken into account for the treatment of NDO.

The aim of this study is to carry out an overview of most up-to-date or under investigation of these therapies and provide the reader with clear and useful concepts.

Botulinum toxin

In recent years, botulinum neurotoxin type A (BoNT/A) treatment has been identified as an effective pharmacological therapy option in patients affected by NDO refractory to antimuscarinic.

BoNT/A is a neurotoxin produced by the Gram-positive anaerobic spore-producing organism *Clostridium botulinum*. It is the most lethal naturally occurring toxin known to mankind [7]. Seven distinct structural serotypes of botulinum toxin have been identified (A, B, C, D, E, F and G). Types A and B have been most widely used for medicinal purposes. All serotypes have a common basic structure with some variations in amino acid sequences. The functional core of the botulinum toxin molecule is a dichain complex composed of a light chain and a heavy chain. The light chain is the truly active moiety of the molecule. Once the botulinum toxin is intracellar, the light chain is translocated out of the endocytotic vesical into the cysoplasm. Here the light chain can disrupt the exocytosis of neurotransmitters such as Ach [8].

Most of the effects of botulinum toxin are thought to result from the inhibition of Ach release from the presynaptic nerve terminal. When this occurs, Ach receptors in the muscle are not stimulated. Specifically it was supposed, but not yet confirmed, with intradetrusor injections, affected muscarinic receptors in the detrusor muscle cannot be stimulated and detrusor voluntary contractions are suppressed. It is clear that neurotransmitters other than Ach are also affected by botulinum toxin, including sensory/afferent neurotransmitters [9]. Although almost all urological literature involves BoNT/A, there are a few reports involving type B.

Two different BoNT/A formulations have been used in the bladder: onabotulinumtoxina (Botox®, Allergan, CA, USA) and abobotulinumtoxina (Dysport®, Ipsen, MA, USA). Although both are type A toxins, they are derived from different bacterial strains, have different molecular weights and are manufactured differently [8]. Only onabotulinumtoxina has been approved for use in NDO, on the basis of Phase III trials [10].

The effectiveness of BoNT/A injections into the detrusor smooth muscle to treat major NDO and neurogenic incontinence has been investigated in several studies [11–13]. Also, BoNT/A treatment of NDO reveals a significant improvement of lower urinary tract (LUT) function with regard to reduced urinary incontinence (UI), reduced detrusor pressure, increased bladder capacity and improved quality of life in NDO [9,14].

Intravesical BoNT/A injection can be performed using a rigid or flexible cystoscope under general, spinal, local or without any anesthesia. The injection should be gently given into the detrusor muscle. Penetration of the bladder wall and an injection into the perivesical tissues should be avoided. Dosage is the variable most frequently described; the range in adults is usually from 100 to 300 U [15]. Dosage in children should be determined by body weight, with caution regarding total dose if also being used for treatment of spasticity, and minimum age [9].

In 2000, Schurch and colleagues first published on the use of botulinum toxin injections into the detrusor for the treatment of NDO in patients with SCI [16]. In 2005, Schurch and associates randomized 59 patients with NDO to receive either 200 and 300 U of BoNT/A or placebo. In this 24-week study, significant improvements in key urodynamic parameters were seen at all time points in the BoNT/A-treated patients but not in the placebo-treated patients ($p < 0.05$), with significant decreases in incontinence episodes in the two BoNT/A groups compared with the placebo group ($p < 0.05$). In addition, quality-of-life scores were significantly better for BoNTA- versus placebo-treated patients at all time points ($p < 0.05$). The 200-U dose seemed to be equally as effective as the 300-U dose [17]. Since then, intradetrusor BoNT/A injections have become a well-established and widely accepted therapy for refractory neurogenic and non-neurogenic overactive bladder with or without urodynamically proven detrusor overactivity (DO) [17].

The first controlled study of BoNT/A in NDO was reported by Giannantoni and associates in 2004 [18]. They randomized patients with NDO to receive either 300 U BoNT/A (onabotulinumtoxina) or 0.6 µmol/l of intravesical resiniferotoxin in 50 ml normal saline (NS). Repeat injections or instillations were allowed. Both treatments resulted in improvement in continence and urodynamic parameters at 6, 12 and 18 months; however, the improvements were significantly better with BoNT/A for all variables at all time points. In addition, resiniferotoxin patients received a mean of 8.6 instillations whereas BoNT/A patients received a mean of 2.1 injections over an 18-month period.

In 2004, Reitz and coworkers reported on a 200 patient multicenter, open-label study on BoNT/A in NDO (e.g., due to SCI, MS or myelomeningocele). The investigators, after injected 300 U of BoNT/A (onabotulinumtoxina) at 30 sites excluding the trigone at a dilution of 100 U/10 ml, showed significant improvements in all urodynamic parameters; in addition, 73% of incontinent patients became continent at 12 weeks and in 72% of these, complete continence persisted at 36 weeks. Also of interest was the fact that at 12 weeks, antimuscarinic agents were discontinued in 28% and reduced in 72% of patients [19].

In 2005, Grosse and colleagues showed significant symptomatic and urodynamic improvement with repeat injections of BoNT/A in patients who received either 300 U of onabotulinumtoxina or 750 U of abobotulinumtoxina [20]. Two other smaller studies had similar results, with major improvements in urodynamic parameters and continence and reduction in antimuscarinic use [21,22]. In all these studies, there were no drug- or injection-related adverse events reported.

Ehren *et al.* in 2007 showed that intravesical injection of 500 U of BoNT/A in patients with neurogenic detrusor instability was an effective treatment which reduced use of oral medication, high detrusor pressure and frequency of urinary leakage [23]. Del Popolo *et al.* in 2008 evaluated the long-term effect of BoNTA (Dysport) for refractory NDO for possible reduction of BoNT/A efficacy after repeated injections. They used 1000, 750 and 500 U of BoNT/A at the beginning and thereafter they mainly used 750 U. No statistically significant differences were found in efficacy duration with the three Dysport doses ($p = 0.5274$) and with the intervals of injections ($p = 0.2659$), but there were a significant difference in patient satisfaction after each retreatment as expressed on the visual analogue scale (VAS) ($p < 0.001$) and a significant reduction in pads/condoms use in the first 4 weeks after each treatment ($p < 0.0001$) [24]. Deffontaines-Rufin and colleagues also confirmed in 2011 the effectiveness of BoNT in those with NDO [25].

Similarly, Cruz and colleagues reported successful results of BoNT/A for NDO of a multicenter, randomized, double-blind, placebo-controlled Phase III clinical trial. Patients with urge incontinence and NDO due to MS or SCI received intradetrusor injections of BoNT/A 200, 300 U or placebo. The injection of 200 and 300 U BoNT/A significantly reduced urge incontinence episodes ($p < 0.01$) compared with placebo at week 6. No differences in results were observed in MS and SCI populations. The effectiveness of the therapy was significantly longer (7 months) compared with placebo ($p < 0.001$). A significant increase in postvoid residual volume was observed in patients not using clean intermittent catheterization (CIC) prior to treatment, and 12, 30 and 42% of patients in the placebo, 200 and 300 U groups, respectively, initiated CIC post-treatment [26].

Patki and colleagues reported on 37 SCI patients their results. The researchers injected 1000 U of abobotulinumtoxina diluted in 30 ml NS at 30 sites sparing the trigone. At 3 months there were significant improvements in all urodynamic parameters. DO was abolished in 76% of patients, and 69% of incontinent patients became continent. Of the patients who were on antimuscarinic agents, 52% stopped and 32% reduced usage. The mean duration of symptomatic improvement was 9 months (2–21), and 32% of patients had a duration of response of 12 months or longer [27].

Two peer-reviewed studies investigated BoNT/A (abobotulinumtoxina) for NDO. Another randomized, double-blind, multicenter trial detailed the efficacy of BoNT/A injection for NDO and UI in 57 patients with SCI and MS [28]. Despite current antimuscarinic treatment, patients were randomized to BoNT/A 300 U or saline placebo. At week 36, all patients were offered open-label BoNT/A 300 U. A significantly lower mean daily frequency of UI was observed in the BoNT/A group compared with the placebo group at weeks 6 ($p < 0.0001$), 24 ($p = 0.0007$) and 36 ($p = 0.0112$). In addition, urodynamic parameters showed significant differences between BoNT/A and placebo ($p \leq 0.05$). No systematic side effects were observed.

Another recent multicenter, double-blind, randomized, placebo-controlled Phase III clinical trial by Ginsberg and colleagues reported the significant benefit of BoNT/A (200 and 300 U) compared with placebo in patients with NDO and UI due to MS and SCI [29]. The risk of CIC due to urinary retention ascended with high doses of BoNT/A. However, CIC should always be considered in neurogenic patients treated with BoNT/A, especially when high doses are used [30].

One other study suggested that BoNT/A was not as effective in DO caused by cerebrovascular accident as it was in DO caused by spinal cord lesions. They

found that suburothelial botulinum A toxin at a dose of 200 U increased bladder capacity and improved the incontinence grade for only 50% of the patients with cerebrovascular accident (CVA) [31].

Two case reports described the successful use of botulinum toxin type B in patients who became resistant to BoNT/A [32,33].

So far there have been only a few studies evaluating the long-term effects of repeated BoNT/A injection on bladder function. The effect of BoNT/A treatment on clinical outcome and urodynamic parameters and quality of life was studied regarding repeated BoNT/A injections (at least five, injection interval ranging from 6.6 to 14.9 months) [34,35].

Pannek and colleagues reported long-term efficacy, with 74% avoiding major surgical procedures and suggestions of a decreased detrusor strength due to repeated BoNT/A injections [36]. Sengoku *et al.* confirmed the efficacy and tolerability of onabotulinumtoxinA injection for the treatment of NDO in Japanese SCI patients [37].

Concerning long-term efficacy and safety of repeat BoNT/A injections in patients with UI due to NDO (MS and SCI), recently Kennelly and colleagues presented an interim analysis of 387 patients (SCI: 200 U, n = 83; 300 U, n = 74; MS: 200 U, n = 119; 300 U, n =111) focusing on the results of repeated treatment for up to five treatment cycles. Of these patients, 387, 336, 241, 113 and 46 patients received one, two, three, four and five BoNT/A treatments, respectively. Patients received repeat treatment if the treatment criteria (minimum of 12 weeks since the previous injection, ≥1 UI episode within 3 days) had been fulfilled. Episodes of UI/week were significantly decreased at week 6. The proportion of dry (100% reduction) patients ranged from 36 to 55%. The time to patients' request for repeat treatment over cycles 1 and 2 remained consistent (~36 weeks). Because the long-term study is ongoing, several patients in treatment cycles 3–5 had not yet requested or received their next treatment. However, a trend toward a slight reduction in time to patients' request for repeat treatment was observed [38].

Kim *et al.* considering urodynamic parameters found a good results from intradetrusor botulinum toxin A injection in children with NDO [39].

Nearly all studies reported an excellent safety profile of BoNT/A intradetrusor injection. The main reported adverse events were either transient or easily manageable (i.e., mild hematuria, injection site pain, urinary tract infection) or, especially in NDO, anticipated and intended (i.e., urinary retention) [9,14].

All published series support the use of botulinum toxin for the treatment of NDO. Several open-label studies, three randomized controlled study and two randomized placebo-controlled study all have shown good efficacy with respect to symptoms and urodynamic findings. There have been no negative open-label or randomized-controlled studies.

Despite the fact that more than 80% of the patients were satisfied or very satisfied with the BoNT/A effect [11], the individual indication and the temporally limited effectiveness of BoNT/A should be considered carefully. However, nuances on dosage, interval between injection, injection technique, injection localization, as well as different impact between gender and diseases are still not completely understood. Further investigations are warranted in larger placebo-controlled, randomized studies.

Percutaneous tibial nerve stimulation

Percutaneous tibial nerve stimulation (PTNS) is a LUT neuromodulation technique performed by percutaneous electrical stimulation of the posterior tibial nerve.

This technique was described by Stoller in the late 1990s for the treatment of overactive bladder syndrome [40]. The technique consists of stimulating the nerve by means of a 34 gauge needle electrode inserted 4–5 cm cephalad to the medial malleolus. Once the current is applied, the flexion of the big toe or the movement of the other toes confirms the correct positioning of the needle electrode. The current intensity is determined by the highest level tolerated by the patient. The stimulation sessions last for 30 min and are performed once a week for 10–12 weeks in the majority of published papers [41]. The advantage of more frequent sessions is to obtain effects in 4 weeks instead of 12: results seemed to be dependent upon the number of stimulations performed and not the time elapsed from the beginning of the stimulation program [42].

Few reports have been published on the effects of PTNS in patients with neurogenic bladder. Acute urodynamic effects of PTNS were observed in a mixed population of OAB patients, most of whom neurologically impaired (MS, SCI, PD). During stimulation, an increase of first involuntary detrusor contraction volume and cystometric capacity was found [43]. Similar results were observed by Kabay [44] in PD patients with DO. On the other hand, Fjorback [45] failed to obtain acute urodynamic reductions of DO in MS patients.

Kabay *et al.* in 2008 analyzed the urodynamic effects of 29 patients with MS. The improvements in the first involuntary detrusor contraction and maximum cystometric capacity were statistically significant during stimulation ($p < 0.001$). The difference of mean first involuntary detrusor contraction volume and mean maximum cystometric capacity at baseline and after PTNS was statistically significant ($p < 0.001$) [43]. The

year after the same group analyzed the urodynamic effect of PTNS in 32 patients with PD confirming that PTNS is acutely effective to suppress DO in these patients [44]. In 2011, Gobbi and colleagues investigated the effect of PTNS on the LUT symptoms in MS patients and found there was a significant reduction of daytime frequency (from 9 to 6, p = 0.04), nocturia (from 3 to 1, p = 0.002) and mean postmicturition residual (from 98 ± 124 to 43 ± 45 ml, p = 0.02); the mean voided volume increased from 182 ± 50 to 225 ± 50 ml (p = 0.003); 89% of patients reported a treatment satisfaction of 70% [46].

No randomized controlled trial is available for PTNS as treatment for NDO; only prospective nonrandomized trials are available (level of evidence 2–3).

No major complications are reported in the literature, following PTNS treatment. Only mild to moderate pain in the site of the puncture was reported by some authors; the majority of patients, with the inclusion of children [47,48], seem to tolerate perfectly the positioning of the needle and the subsequent stimulation.

The only available long-term study on results of PTNS on the treatment of overactive bladder showed sustained improvement from 12 weeks at 6 and 12 months, with 94 and 96% of responders, respectively [49].

PTNS is an effective treatment for patients with NDO not responding to conservative and conventional therapies. Further studies are needed to assess the exact role of PTNS in these indications and to evaluate the long-term durability of the treatment. Further research is needed as well to assess several still unanswered questions about PTNS [50].

Sacral neuromodulation

Sacral neuromodulation (SNM) offers an alternative treatment for patients with LUT dysfunction with symptoms refractory to conservative treatment including pharmacotherapy, pelvic floor re-education and clean intermittent self-catheterization [51–53].

SNM is based on the application of electrical currents to the sacral nerves in order to modulate reflexes involved in LUT control. Directly after implantation, the implantable neurostimulator (INS) is activated, and optimal stimulation settings are chosen. The stimulation setting (uni- or bipolar) that gives the best sensory response (anal, vaginal or perineal) at the lowest amplitude is considered optimal. Patient follow-up after implantation of the neurostimulator is scheduled at 6 weeks, 6 months and yearly thereafter.

Originally, SNM was not considered an option for neurogenic bladder dysfunction because it has been assumed that the efficacy of SNM relies on the integrity of the spinal and supraspinal reflex arcs [54]. Nevertheless, several studies have demonstrated that SNM can be used successfully in patients with voiding symptoms due to neurological disorders [55–57].

In a recent review and meta-analysis, the efficacy of SNM for neurogenic voiding dysfunction was evaluated [58]. Overall, 224 patients in 22 studies underwent implantation of the permanent neuromodulator, with a mean follow-up of 26 months. Of those, 87% (194 of 224) used unilateral and 13% (30 of 224) used bilateral SNM. The pooled success rate of permanent SNM was 92%, with a 99% probability that the success rate was >75%. Overall, six patients reported an adverse event (lead migration: n = 5; pain: n = 1) during SNM testing, and none underwent surgery because of an adverse event. For permanent SNM, 69 patients reported an adverse event, and 45 underwent surgery because of an adverse event. The pooled adverse event rate of permanent SNM was 24%. The most frequent adverse events were lead migration (15 patients) and pain at the site of the permanent neuromodulator (12 patients). Regarding surgical intervention as a result of adverse events, explanation of the lead or permanent neuromodulator was most often required (33 patients).

Hohenfeller *et al.* illustrate that while SNM may be effective for neurogenic bladder dysfunction, the results may be temporary. In 8 of 27 patients, the symptoms of LUT dysfunction were significantly attenuated (50% or more) for 54 months (range 11–96). After this period, all implants became ineffective, except one, which was still in use at the last follow-up visit [59]. Sievert *et al.* declared in 2010 that early SNM implantation in SCI patients may prevent DO and urinary incontinence, ensure normal bladder capacity, reduce UTI rates, and improve bowel and erectile functionality without nerve damage [60].

About the complications, pain after implantation is not uncommon, occurring in 24–34% after long-term follow-up [61]. Pain can be located at the site of the INS or at the site where the stimulation sensation is perceived. Two important improvements were the introduction of tined leads (leads with hooks) and the gluteal placement of the INS instead of abdominal, which reduced the incidence of adverse events [62]. The physician can attempt to relieve pain symptoms by altering the stimulation settings. If no pain relief occurs, repositioning of the INS or lead can be necessary. Other adverse events reported lead migration (7%), pain at lead site (1%), infection at lead site (2%), lead fracture (1%), migration of permanent neuromodulator (1%), pain at site of permanent neuromodulator (5%), infection at site of permanent neuromodulator (5%), hypersensitivity to stimulation (4%) and neuromodulator malfunction (1%).

The majority of adverse events do not require surgical intervention [58,63].

SNM is not the first-line treatment for NDO. If pharmacotherapy fails to relax the hyper-reflexic detrusor, SNM may be optional in patients with NDO. Although the setup for conditional, event-driven electrical stimulation is not suitable in a clinical setting, the treatment modality is promising and it warrants further investigation.

Mirabegron

Mirabegron is an agonist of the human beta-3 adrenergic receptor (AR) which stimulates the intracellular cAMP accumulation by acting with full agonistic activity and high efficacy on human beta-3 ARs, with a low activity on beta-1 and beta-2 ARs [64]. Mirabegron relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle by activation of beta-3 AR which increases bladder capacity. In animal studies, β3-AR agonists directly cause dose-dependent detrusor relaxation during the storage phase of the micturition cycle and inhibited NDO [65]. It has been shown that, compared with other agents (including antimuscarinics), β3-AR agonists increase bladder capacity with no change in micturition pressure and residual volume, supporting the principle of β3-AR agonism as a new therapeutic approach to overactive bladder [65]. Although β3-ARs on detrusor muscle cells were believed to be the main site of action of β3-AR agonists, the main *in vivo* effect of these compounds could be on the afferent side of the micturition reflex by a direct inhibition of afferent nerves or of the myogenic/urotheliogenic mechanisms involved in the promotion of afferent activity [66].

Mirabegron has been extensively studied in more than 10,000 individuals and about 40 clinical studies have been performed. This drug reached the final stages of pharmacological development and has been recently granted marketing approval in several countries [67].

The drug product is available in two different dosages: 50 mg (recommended dose, orally once daily) and 25mg (for patients with renal or hepatic impairment).

The approval of Mirabegron was based on three placebo-controlled Phase III studies in which 12 weeks treatment from 25 and 50 mg dose resulted in statistically significant improvement in coprimary efficacy end points. Mirabegron demonstrated good safety and tolerability in the reported studies. The most commonly reported side effects were gastrointestinal disorders, headache and hypertension. No episodes of acute urinary retention were reported [68–71].

There are no data available for β3-AR agonists in the neurogenic population. Although the tolerability of Mirabegron offers the potential to improve adherence to NDO treatment, this optimal efficacy–tolerability balance is still to be demonstrated in clinical practice [65]. Therefore could not be excluded a possible role of Mirabegron for NDO patients in the future but further research is necessary.

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a noninvasive technique for cortical stimulation that uses electromagnetic induction to generate a strong fluctuating magnetic field which induces intracranial currents [72]. Repetitive TMS (rTMS) applies repeated TMS pulses at set frequencies or patterns to induce changes in cortical excitability which last longer than the period of stimulus administration [73].

rTMS has been investigated as a potential therapy for numerous conditions, including depression, epilepsy, migraine and PD [74–76].

In a study of 2009, Brusa *et al.* evaluated the possible impact of a 2-week course of low frequency 1 Hz rTMS on LUT behavior in eight advanced PD patients complaining of urinary disturbances. rTMS was able to improve temporarily LUT behavior in PD patients, increasing bladder capacity and the first sensation of filling phase, lasting for up to 2 weeks after the end of the stimulation. No complications were reported [77].

A recent study was carried out by Vasquez *et al.* in 2014 on a cohort of 23 incomplete SCI subjects with a neurogenic bladder, showing that cortical TMS was effective in facilitating the pudendo-anal reflex in some incomplete SCI subjects. The presence of cortical facilitation of the pudendo-anal reflex was not related to the degree of urinary continence. No complication were reported [78]. Depending on the target, cortical stimulation might improve motor performance or other symptoms associated with PD. Unfortunately, clinical application of rTMS to treat PD patients is limited by the short duration of the effects beyond the time of stimulation, even if long-lasting improvements have been observed after repeated rTMS sessions [79].

The application of repetitive forms of TMS to obtain functional benefits by inducing favorable plastic changes in patients with NDO following diseases such as SCI or PD has received poor attention over the years. Therefore, new clinical and neurophysiological studies are necessary to better define the role of TMS in the treatment of NDO.

Other therapies

The evidence for efficacy of desmopressin in MS for treatment of nocturia and daytime frequency is level 1, based on the results of a meta-analysis published in 2005. However, desmopressin does carry the risk of hyponatremia, particularly in older patients [80].

Two studies have looked at the efficacy of cannabinoids on urinary problems in patients with NDO but evidence of limited efficacy was found. Freeman *et al.* test whether cannabinoids reduce urge incontinence episodes without affecting voiding in patients with MS. Patients treated with cannabis extract showed significant effects over placebo (p = 0.005) [81]. Kavia *et al.* undertook a 10-week, double-blind, randomized, placebo-controlled, parallel-group trial in 135 subjects with MS and overactive bladder to assess the efficacy, tolerability and safety of nabiximols (cannabinoid drug) as an add-on therapy in alleviating bladder symptoms. They provided evidence of improvement in some of the symptoms analyzed, such as nocturia (p = 0.010), overall bladder condition (p 0.001), number of voids/day (p = 0.001), number of daytime voids (p = 0.044) and Patient's Global Impression of Change (p = 0.005). No statistically significant results were found regarding daily number of urinary incontinence episodes and improvement in I-QOL [82].

Conclusion

Antimuscarinics are the first-line therapy for NDO. Botulinum toxin A is already a valid alternative to antimuscarinics for NDO. PTNS and, in particular, SNM showed positive effects. Mirabegron could be a potentially useful treatment but evidence of its efficacy in NDO is still missing. Other therapies have still few data in the literature to be considered useful strategies for NDO. For this purpose further studies are warranted.

Future perspective

It is our opinion that in the nest years all the strategies discussed in this manuscript could find a wide consensus and validation for the treatment of NDO. This consensus already exists or it is well advanced in some cases (e.g., botulinum toxin, PTNS and SNM) and should be still confirmed for others (e.g., Cannabinoids, TMS and Mirabegron). For this purpose, further investigations in larger placebo-controlled, randomized studies are warranted.

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Executive summary

The therapy of neurogenic detrusor overactivity (NDO) was based on the antimuscarinic drugs for a long time, and once they were inefficient, the invasive surgery was performed. During the 21st century, new therapeutic strategies have been applied in this field.

- Botulinum neurotoxin treatment has been identified as an effective pharmacological therapy option in patients affected by NDO refractory to antimuscarinic. All published series support the use of botulinum toxin for the treatment of NDO.
- Percutaneous tibial nerve stimulation (PTNS) is a lower urinary tract neuromodulation technique performed by percutaneous electrical stimulation of the posterior tibial nerve. PTNS is an effective treatment for patients with NDO not responding to conservative and conventional therapies, but further studies are needed to assess the exact role of PTNS in these indications and to evaluate the long-term durability of the treatment.
- Sacral neuromodulation (SNM) offers an alternative treatment for patients with lower urinary tract dysfunction with symptoms refractory to conservative treatment. SNM is not the first-line treatment for NDO. If pharmacotherapy fails to relax the hyper-reflexic detrusor, SNM may be optional in these patients. Although the setup for conditional, event-driven electrical stimulation is not suitable in a clinical setting, the treatment modality is promising and it warrants further investigation.
- Mirabegron is an agonist of the human beta-3 adrenergic receptor. Although the tolerability of Mirabegron offers the potential to improve adherence to NDO treatment, this optimal efficacy–tolerability balance is still to be demonstrated in clinical practice for patients with NDO.
- Transcranial magnetic stimulation is a noninvasive technique for cortical stimulation that uses electromagnetic induction to generate a strong fluctuating magnetic field which induces intracranial currents. Currently the data in the literature regarding the use of transcranial magnetic stimulation in patients with NDO are still scarce, so new studies are needed to define the role of this therapy for NDO.
- Other therapies suggested and under investigation for NDO include not antimuscarinics drugs, such as desmopressin and cannabinoids.

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