

# A review of prospective Clinical Trials for neurogenic bladder: Pharmaceuticals

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## Article history

Submitted: Nov. 17, 2013

Accepted: May 31, 2014

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**Introduction** The neurogenic urinary bladder is defined as a dysfunctional bladder associated with a known neurological injury. We review the data from good quality clinical trials looking at drug therapy for the neurogenic bladder.

**Materials and methods** In order to identify as many prospective trials as possible, we performed Internet searches, using the same search string: Urinary Bladder, neurogenic (MESH). In each case, the search was limited to clinical trial, prospective trial, subjects were human and the language was English. There was no year limit for our search. The next step was duplicate removal, which led to a final number of 580 papers. We defined clear inclusion criteria for the papers.

**Results** A total of 82 full text papers were reviewed and analyzed according to the previously mentioned algorithm. The oldest two prospective clinical trials date back to 1976, with an obvious increase in number of trials each year, reaching more than five trials per year after 2001, which demonstrates increased interest toward the subject. The total number of patients included in the trials is 3904, 888 of which are children. The male: female ratio is close to 1, although there were 9 studies where no information regarding the sex of the patients was available.

**Conclusions** Our analysis stresses the acute need for good quality trials looking at the drugs used for the management of the patients with neurogenic bladders, with adequate statistical power to support the data they present.

**Key Words:** neurogenic bladder ◊ clinical trial ◊ drug therapy ◊ antimuscarinics ◊ botulinum toxin

## INTRODUCTION

The neurogenic urinary bladder is defined as a dysfunctional bladder associated with a known neurological injury, which can be spinal cord injury (SCI), multiple sclerosis (MS), spina-bifida, etc. Although the term has been known for at least 30 years now and the concepts behind it are continuously evolving, there is actually not much work that has been done to accumulate solid clinical evidence in this field [1].

There are many principles of treatment available for patients with a neurogenic bladder, including surgery, electrical stimulation, or physical exercise, many of them still being in an experimental phase.

However, drugs are the single most used element that is found, at least temporarily, in the therapeutic approach of all these patients, and a lot of research is being done in this direction. The main indications for drug therapy are towards lowering storage pressures and preventing detrusor overactivity or for treating or preventing urinary tract infections (UTI). Drugs are also used for improving urinary flow, lowering the post void residual volume (PVR), to fight vesico-ureteric reflux (VUR) or for reducing spasticity. Other possible indications for drug therapy are urinary incontinence, prevention of bladder tumor recurrences and the management of stone disease [2]. While it is widely accepted that antimuscarinics

are the safest and most effective class of drugs that works for neurogenic detrusor overactivity (NDO) and that antibiotics offer best results in the treatment and prevention of UTIs, it is not quite clear whether other drug classes that are sometimes used are really proficient or even safe to prescribe [3].

The main question that often arises when thinking about clinical evidence in the field of drug therapy used for patients with neurogenic bladders is about the actual number of good quality, prospective, randomized clinical trials and how do they really relate to the management of the urinary function of the patient [4, 5].

The aim of our work is to review the data on prospective clinical trials in relation to pharmaceutical agents used in the treatment of neurogenic bladder, to outline the general results of major agents used and to consider the principles of management that are most commonly used as reported in the literature.

## METHODS

In order to identify as many of the available prospective trials as possible, we performed searches on both PubMed and OVID databases, using the same search string: *Urinary Bladder, neurogenic (MESH)*. The option for the Medical Subject Heading (MESH) vocabulary was based on the idea of standardization of terminology and reporting, supported by the International Continence Society (ICS) and many other scientific organizations [6]. In each case, the search was limited to clinical trial, prospective trial, subjects were limited to human and the language of the paper had to be English. There was no year limit for our search, so even older papers were considered. The search on PubMed returned 478 results in total, while from OVID we were able to get only 425 papers. The results of the two searches were saved into two different files, containing title, abstract, authors, keywords, and the relevant data on the journal that published the paper. Data was then imported into the reference manager software and combined for easier processing.

The next step was duplicate removal, which led to a final number of 580 papers that needed to be considered for the purpose of our work. The entire reference was exported to a Microsoft Access database, which allowed for greater flexibility in sorting and indexing the data by different criteria.

The inclusion criteria a paper had to meet simultaneously to be evaluated by our research were:

Prospective clinical trial

Primarily looking at the management/treatment of neurogenic bladder (papers were not excluded if also

dealing with non neurogenic conditions)

Main paper (not abstract) in English

Use drugs as main therapy

Results clearly stated (numbers, statistics, etc)

If the abstract was not enough to clearly identify all the inclusion criteria, the full text paper was retrieved and analyzed. After applying these criteria, a total number of 86 papers were selected for in-depth analysis, but the full text paper could be found only for 84 of them.

Data was extracted from each paper into the database file, where we recorded the main subject of the paper, its objectives, the total number of subjects and the number of males and females that were enrolled. Other headers included results, conclusions, personal remarks, main drug used, source of funds for study and year of publication. Data was analyzed separately for adult and pediatric populations.

The final step of the analysis consisted in grouping together all studies looking at similar drugs (antimuscarinics, vaniloids, antibiotics, etc), pointing out the main neurological condition, then sorting them according to the source of funds used into four groups: *government, pharmaceutical industry, private sources or not stated*. We documented the adherence of each journal to the *Uniform Requirements for Manuscripts (UMS)* issued by the International Committee of Medical Journal Editors (ICMJE) in 2001 [7].

## RESULTS

A total of 84 full text papers were reviewed and analyzed according to the previously mentioned algorithm. The oldest two prospective clinical trials date back to 1976, with an obvious increase in number of trials each year, reaching more than five trials per year after 2001, which demonstrates increased interest toward the subject. The total number of patients included in the trials is 3904, 888 of which are children. The male:female ratio is close to 1, although there were 9 studies where no information regarding the sex of the patients was available.

There are a total number of 22 pediatric studies, which represents about 37.6% of the total number of trials, including those trials with mixed population, adult and pediatric. The male:female ratio in the pediatric studies is 0.83. The oldest prospective trial with a pediatric population dates back to 1976, the same as for the first prospective trial studying adults.

The largest population in one trial was 263 cases for adult trials and 255 cases for pediatric trials whilst the smallest series were of 5 and 7 patients respectively. The mean size for a series of patients is at

about 48 cases, and 40 cases for pediatric studies (Figure 1).

1. The main conditions being looked at are:
2. Spinal cord injury – 31 trials
3. Multiple sclerosis – 9 trials
4. Myelomeningocele – 9 trials
5. Spina bifida – 2 trials
6. Myelodysplasia – 2 trials
7. Behçet’s disease – 1 trial
8. Mixed conditions – 28 trials

In the pediatric trials, the main conditions are different, according to the pathologies that are more specific for this population. We note a significant number of trials on multiple sclerosis, a disease that occur more often in adults (Figures 2 and 3).

1. Myelomeningocele – 9 trials
2. Multiple sclerosis – 4 trials
3. Spina bifida – 2 trials
4. Myelodysplasia – 2 trials
5. Spinal cord injury – 2 trials
6. Mixed conditions – 3 trials

After sorting the trials according to the main source of funds, as declared by the authors, we noticed a significant increase in the number of papers sponsored by the pharmaceutical industry over the last years. The number of trials sponsored by government funds remained relatively constant at a low value over the period of time that we studied. There are also a significant number of trials sponsored by private organizations and also many papers where no source of funding was declared (Table 1).

There is a mean value of one prospective trial studying drug therapy for neurogenic bladder each year sponsored by the pharmaceutical industry, compared to about one such study every four years that is sponsored by the government.

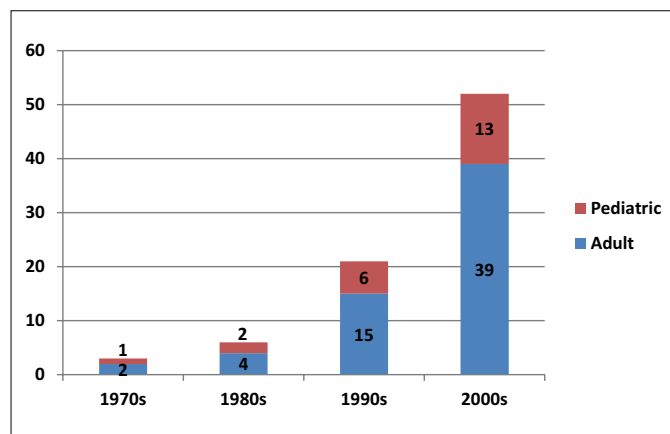


Figure 1. Number of trials for each ten year period.

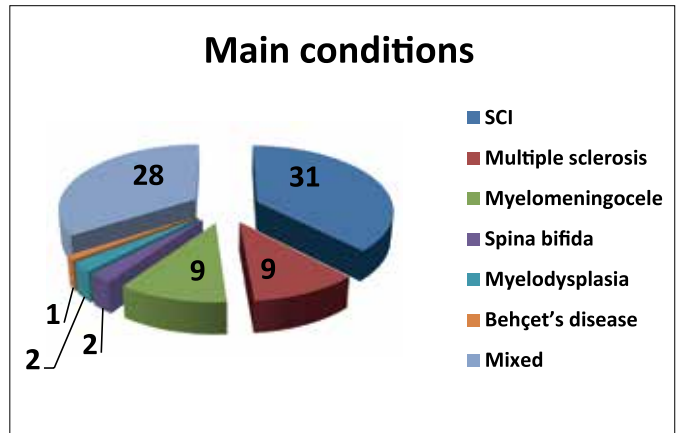


Figure 2. Main conditions behind the neurogenic bladder.

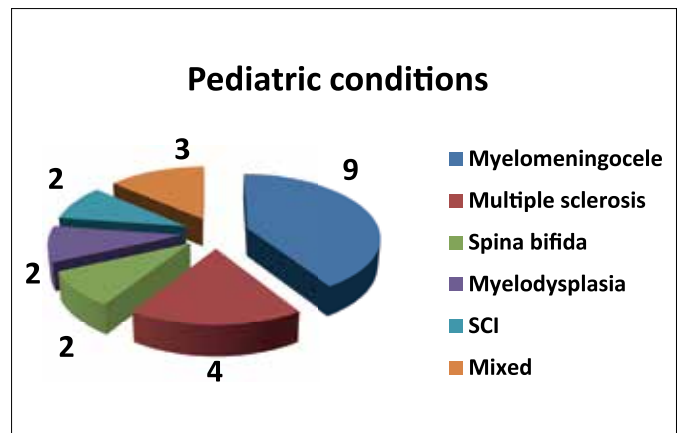


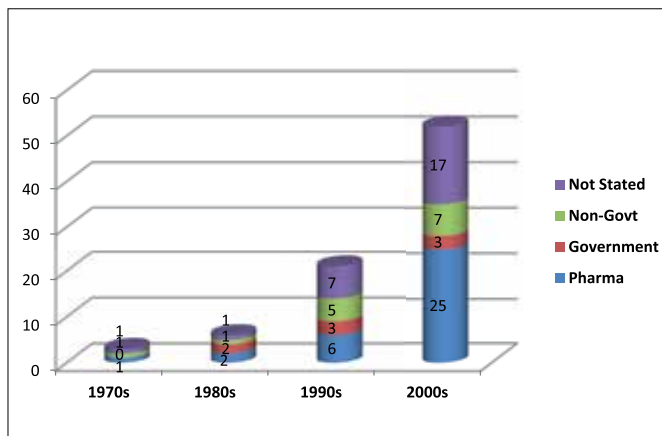
Figure 3. Pediatric conditions behind the neurogenic bladder.

Considering the high costs of care associated with neurogenic bladder patients, one could expect more implication by governmental institutions in research projects that could, in the end, reduce those costs (Figure 4).

After sorting our data by the main drug used during the trial, we identified 21 trials for antimuscarinics, 21 trials using botulinum toxin, 12 papers evaluating vaniloids for NDO, 13 trials looking at antibiotics aiming to treat or prevent UTIs, 5 studies with  $\alpha$  blockers aiming to improve flow and reduce PVR and

Table 1. Trial declared source of funding

Sponsor	N
1 Pharmaceutical company	34 (41.6%)
2 Government organization	8 (9.7%)
3 Non-government / private	14 (17%)
4 Not stated	26 (31.7%)



**Figure 4.** Number of trials for each ten year period sorted by source of funding.

10 trials with different other drugs (desmopresin, cisapride, etc). Vanilloids and  $\alpha$  blockers were not used for pediatric populations in any study.

The antimuscarinics trials total a number of 1057 cases, with more than 570 of them being children. In fact, the largest pediatric trial looks at antimuscarinic treatment for various neurological conditions in children. Overall, efficacy rate ranges from 67% to 96%, with no trial showing poor results after therapy. Antimuscarinics are proven to increase bladder capacity, decrease intravesical pressure and, for up to 75% of the cases, resolve VUR. Autonomic dysreflexia does not occur or its symptoms are milder in up to 67% of cases. Incontinence rate decreases significantly, although the exact cause of incontinence is not identified by most of the trials. The results of the therapy do not seem to be affected by age, sex or time since the diagnosis of the neurological condition. Transdermal or intravesical administration do not lead to improved efficacy but associate a much higher rate of side effects, and an increase by 25% in the number of patients that stop the therapy due to poor tolerability, compared to oral administration. Higher doses of the same agent usually offer better outcomes, with a significantly increased rate of adverse effects. There seems to be a good indication for antimuscarinics in patients that perform clean intermittent catheterization (CIC) and who accuse leakage between voidings.

Botulinum toxin of type A seems to be one of the most investigated substances of the last decade, with 21 trials available for the neurogenic bladder, the oldest one dating back to 1998. The vast majority of the investigators injected the toxin into the bladder wall, in adult patients. There are a total number of 597 patients treated, of which 133 are children. The overall success rate goes up to 97% (lowest re-

ported is 47%) with no significant adverse reactions reported. The effects last from one month to more than two years, with the majority of reports ranging from three to nine months [8]. When injected into the external sphincter, botulinum toxin is able to offer results that are similar to sphincterotomy, and far superior to the use of anesthetics or other substances that try to paralyze the muscle, while keeping the same safety profile and duration of action. In about 87% of cases, botulinum toxin improves the health related quality of life as early as one week after treatment. Repeated doses of toxin offer same efficacy and tolerability, leading to long lasting results.

There are reports of up to 66% improvement in the bowel function of neurological patients, without a clear understanding of the action pathways, if any, and not just a placebo effect. Some investigators report a decrease in the number of symptomatic UTIs after the treatment with botulinum toxin but consider this as the effect of improving bladder health. There also seems to be a significant nerve growth factor deprivation, lasting for three months, but the mechanisms and clinical implications behind this process are unclear for the moment. It is proved that all histological changes are reversible with time. Associating antimuscarinic treatment does not improve in any manner the results obtained after injecting the toxin. Injecting a double dose of toxin at one time makes the results last longer but there were reports of systemic reactions, which were not life threatening in any case [9].

The main concern for authorities and many practitioners is not only about efficacy but also about the safety of willingly injecting the most powerful neurotoxin known of into patients [10]. However, there seems to be enough data to support a good safety profile of botulinum toxin, for both adult and pediatric populations with neurogenic bladders.

The two vanilloids used for neurogenic detrusor overactivity, capsaicin and resiniferatoxin (RTX) seem to have completely different clinical profiles. There are a total number of 266 patients, all adults, treated with vanilloids in 12 prospective trials. Resiniferatoxin leads to better outcomes than capsaicin, while both associate a relatively high rate of side effects, which is considered by some authors to be due to the dose possibly being higher than necessary. The overall response rate to RTX is around 60%, while there are two papers reporting no improvement after the treatment with capsaicin. When compared to botulinum toxin, the efficacy of vanilloids was always inferior.

Since capsaicin is usually diluted in an ethanol vehicle, it is considered that many of the side effects may be due to the alcohol being injected and not by the



toxin itself. Current data suggest that capsaicin does not increase the risk of malignancy and that a new formulation that replaces ethanol with a glucidic solvent may reduce the side effects, but not enough to make the change significant.

Urinary tract infection was studied in 498 patients, of which 133 were children. The antibiotics show good overall safety and efficacy, and the optimal period of treatment seems to be around 14 days from the point of view of long-term results. Reinfection rate is not correlated with the total period of treatment. When prophylaxis was the main objective, there are no proven treatments that can prevent UTIs. One trial demonstrates very good results, with no recolonizations and dramatically reduced rate of symptomatic UTIs, using a once-per-week scheme, for two years, using the antibiotic selected according to the sensitivity test. There were no effective measures to decrease the incidence of bacteriuria in patients on CIC. There is no clearly demonstrated change in sensitivity or type of bacteria after longer treatment periods. Inoculating the bladder with non-pathogenic *E. Coli* reduces the infection rate dramatically, but the inoculation seems to be successful in only about half of the cases.

Data from the trials investigating the use of  $\alpha$  blockers for improving flow in adults show poor overall efficacy. There are 814 patients treated, 209 being women. Some results suggest that a treatment course over one year may improve flow and reduce PVR in patients that have detrusor overactivity but no changes are seen in those with an acontractile detrusor. Maximum detrusor pressure at the moment of maximum flow is also reduced, but not to a value that could be considered as safe. There are no significant differences related to the sex of the patients. All studies demonstrate a good safety profile of  $\alpha$  blockers in patients with neurogenic bladder.

There are many trials looking at various substances that aim to replace antimuscarinics, but none show better results, despite a generally lower rate of side effects. There is one study suggesting that intravesical atropine works better than oral antimuscarinics in children with MS, and with a lower rate of side effects, on a series of 57 patients.

## DISCUSSION

The total number of prospective studies that could be identified seems rather small, considering the period of over 30 years and the increased incidence of neurological conditions that lead to urinary dysfunction. Lots of trials included both adult and pediatric populations, which might affect the results from the point of view of safety and effectiveness [11].

Many of the trials are not specifically geared towards the main principles of care of the neurogenic bladder, looking only at one particular aspect, which is, in fact, part of a bigger puzzle, where a slight change in one parameter triggers changes to all the others [12].

Since the patients with neurological conditions and consecutive urinary disorders tend to be among the most expensive cases to treat [13], the direct implication of medical insurance companies, or other organizations that have to pay for healthcare would have been expected. However, this is not the case for the majority of the papers we reviewed; in fact the number of those papers was the lowest in our analysis [14]. More than one third of the trials are sponsored by the pharmaceutical industry; mostly companies that seek support data to get their substances approved. In the vast majority of cases, these trials extend over a short period of time, so the long-term benefit for the patient is unknown and this is yet another issue that needs to be addressed by larger scale studies [15].

Our in-depth review of the papers revealed that many of the trials, although well designed and performed in a prospective manner, do not have the statistical power required to actually support their conclusions, mainly due to the small series of patients they analyze. In other cases, there is no power calculation at all, and conclusions are based only on a global assessment of results [16].

Although antimuscarinics are widely used and accepted as the only effective treatment for NDO, there are actually a relatively small number of prospective trials documenting the effects that can be expected for each particular condition or population [17].

The use of botulinum toxin A proved both safe and effective in virtually all the trials and thus has been approved for use in the neurogenic detrusor overactivity, as an option for the patients who fail after trying antimuscarinics. The use of vanilloids still needs to be researched, as there is inconclusive data regarding their use in adults and there is no data about pediatric populations [18].

There does not seem to be an effective way of preventing UTIs in neurogenic bladder patients using drug therapy, but recent data show promising results with the use of modified treatment schemes [19].

## CONCLUSIONS

Our analysis stresses the acute need for good quality trials looking at the drugs used for the management of patients with neurogenic bladders, with adequate statistical power to support the data they present. The global issues associated with the neurogenic bladder, such as renal function, stones and tumors,

need to be addressed to complete this puzzle of data. Many of the available trials are sponsored by the pharmaceutical industry, which needs the data in order to request approval for the drugs they are producing. Large scale studies, with financing from governmental institutions are needed in order to obtain a more comprehensive image of the treatments over long periods of time, in different indications and

subpopulations. The cooperation of several dedicated centers is also vital in order to acquire the needed knowledge.

There is still a great amount of work required in order to obtain clear and useful clinical data that could eventually serve as a base for future, more comprehensive guidelines for the treatment of the main conditions associated with the neurogenic bladder.

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