

ORIGINAL ARTICLE

An integrative review of standardized clinical evaluation tool utilization in anticholinergic drug trials for neurogenic lower urinary tract dysfunction

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Study design: To review prospective and randomized trials studying anticholinergic therapy for neurogenic bladder in SCI to identify whether trials included standardized clinical evaluation tools and reporting measures now recognized to enhance clinical trial data.

Methods: A systematic search via EMBASE, MEDLINE, CENTRAL, CINAHL (Cumulative Index to Nursing and Allied Health Literature), HTA (Health Technology Assessment), CMR (Comprehensive Microbial Resource), HAPI (Health and Psychosocial Instruments) and PsycINFO using the key term spinal cord injury crossed with oxybutynin, tolterodine, darifenacin, solifenacin, fesoterodine, trospium chloride, propiverine, propantheline and anticholinergic(s) for 1946–2015 inclusive. We then collated whether standardized clinical tools, measures and descriptors were used within each study identified: American Spine Injury Association (ASIA) impairment scale; symptom scores validated in SCI; technical methodology for urodynamics/video urodynamics; urinary diaries; and standardized urologic terminology.

Results: A total of 1225 entries with 610 unique articles were identified, 14 randomized and 16 prospective studies. In 6/30 the population comprised SCI patients with neurogenic bladder alone; the remainder included mixed neurogenic etiologies. Classification using the ASIA impairment scale was used in <10% of studies; none used symptom scores validated in SCI; <50% reported urodynamic test methodology fully, incorporated urinary diaries or used International Continence Society Standardization Subcommittee urinary tract terminology.

Conclusion: Integrative review of trials from 1946 to 2015 identified infrequent use of standardized clinical evaluation tools and reporting measures. Data from future trials evaluating therapies for neurogenic bladder would likely be more applicable to specific SCI patients if current standardized classification and descriptors now available were used consistently: for example, the ASIA scale, symptom scores validated in SCI, standardized urodynamic methodology, urinary diaries and urinary tract terminology. Studies recruiting SCI patients exclusively would also provide additional benefit.

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INTRODUCTION

An increasing number of people are living with spinal cord injury (SCI),^{1–3} and management of the bladder has been identified as a priority to prolong life,⁴ hence the importance of studies that define the efficacy of the treatment modalities available. Depending on the level and extent of SCI, bladder involvement includes loss of autonomic function and/or urinary sphincter mechanisms, leading to the symptom complex of neurogenic lower urinary tract dysfunction, and associated complications that include urinary incontinence, reflux, urinary tract infection, urosepsis, renal dysfunction and death.^{3,4}

Anticholinergic drugs remain central for lowering bladder pressure and preventing urinary incontinence via relaxation of the detrusor muscle.⁵ Although an increasing number of anticholinergic agents have become available to treat overactive bladder in the non-neurologically impaired population, their efficacy and safety in the SCI population are most often extrapolated from data obtained in

heterogeneous populations many of which do not include patients with SCI. This is obviously problematic as the idiopathic overactive bladder and neurogenic non-SCI populations differ in important ways from the SCI population, with the latter recognized to be at particular risk for vesicoureteric reflux, renal dysfunction, and comorbidities such as autonomic dysreflexia (AD). A recent meta-analysis of randomized controlled trials on the effectiveness of anticholinergic agents reported that 'compared with placebo, anticholinergic treatment in patients with NDO is associated with better patient-reported cure improvement', but 'there is still uncertainty about which anticholinergic drugs are most effective, at which dose, and by which route of administration', and 'a subgroup analysis based on different neurologic pathology was not possible'.⁵

To address this further, we have examined the methodologies in all studies that included SCI patients within a neurogenic bladder cohort to identify how external validity in the SCI population could be

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improved in future clinical trials. Using an integrative review of prospective and randomised controlled trials reporting the effectiveness of oral and intravesical anticholinergics that include data on patients with SCI, we have quantified the use of standardized clinical evaluation tools including the American Spine Injury Association (ASIA) scale,^{6,7} SCI-specific validated symptom scores⁸, use of a urinary diary,⁹ and recognition and utilization of methodology and standardized terminology for the urinary tract.^{10–12} These are all elements that when reported provide a more comprehensive description of study subjects and hence allow clinical trial data to be more comprehensively matched to the needs of an individual SCI patient.

MATERIALS AND METHODS

Integrative review search strategy

A literature search was conducted from the time period 1946 to the end of September 2015 inclusive of using the following databases: EMBASE, MEDLINE, CENTRAL, CINAHL (Cumulative Index to Nursing and Allied Health Literature), HTA (Health Technology Assessment), CMR (Comprehensive Microbial Resource), HAPI (Health and Psychosocial Instruments) and PsycINFO. The keyword search term 'spinal cord injury' was crossed with a title search and a keyword search for the following terms: oxybutynin, tolterodine, darifenacin, solifenacin, fesoterodine, trospium chloride, propiverine, anticholinergics and anticholinergic. A review of references within each article identified was conducted to locate additional articles.

Inclusion criteria

To be included the studies had to have been published, be available in English and contain at least one SCI adult subject in the study population. In addition, a full-text version of the paper was required for inclusion to allow review of tools used in the description of subjects and outcome measures.

Analytic process

The analytic summary process is provided in Supplementary Appendix A. In Table 1 of Supplementary Appendix A, SCI and the anticholinergic agent terms were crossed in a *keyword* search. The number of entries is listed below each database for the anticholinergic agent. The total number of entries is tallied below each column. A similar approach was used in the Table 2 of Supplementary Appendix A, with SCI and the anticholinergic agent terms crossed in a *title* search. The total number of entries has been tallied below each column. In Table 3 of Supplementary Appendix A, the terms SCI and anticholinergic were crossed in a keyword search. This was listed in a separate table because it was deemed an alternative search term. In total, the combined entries from all databases in keyword and title searches comprised 1225 articles.

Each paper identified was reviewed by the authors to extract the active drug, the control agent (if applicable), the number of subjects in the study and control group, the number of subjects included who had SCI, and hospitalizations and deaths if these data were reported.

We also identified whether standardized measures were or were not used and reported within each study, with a yes/no response for the following: (1) the ASIA impairment scale, (2) a symptom score validated in the SCI population, (3) technical methodology for urodynamics/video urodynamics, (4) urinary diaries and (5) standardized urologic terminology.

Pediatric studies, colonic studies, review articles, abstracts and posters were not included.

RESULTS

The integrative review process identified the articles shown in Figure 1. The search identified 30 citations, which were reviewed in detail.^{13–44} These studies constitute research published between the years 1972 and 2012, and 14/30 were randomized controlled trials (RCTs), the first of which was published in 1991. Table 1 summarizes the 14 randomized controlled trials reviewed. Within the RCTs, 6/14 recruited a SCI population exclusively. Seven studies included a placebo. The randomization strategy was reported in one study to

include the use of permuted blocks. Three were single center, nine multicenter and two were crossover in design.

Review for the use of standardized measures identified one study that classified patients using the ASIA scale²⁰ and one study²⁶ that predated the development of the ASIA scale. No studies reported using a validated symptoms score; four provided conventional detailed urodynamic studies (UDS) methodology and three indicated at least some portion of the population had video urodynamics;^{16,23,25} seven reported using a urinary diary; and nine referenced standardized terminology descriptors for the lower urinary tract. Table 2 summarizes the 16 prospective studies reviewed.

Within the prospective studies, 1/16 was a multicenter study. The ASIA scale was reported in three, whereas three predated the development of this scale; none reported the use of validated symptom scores; urodynamics methods were detailed in 8 of the 13 studies where UDS was part of the design, and 6 indicated that at least some of the population had video urodynamics; 5 used a urinary diary; and 3 made reference to standardized urinary tract terminology, with 3 predating their availability.

Both prospective and randomized trials commonly included patients with multiple forms of neurogenic bladder, such as those combining multiple sclerosis and SCI. Men and women were detailed as eligible in six RCTs, but in only three were the final number of men and women enrolled clearly defined.

DISCUSSION

This integrative review identified 30 prospective or randomized trials of anticholinergic agent use where at least one subject with SCI was included. Only six studies recruited SCI subjects exclusively, and in only three studies with a heterogeneous cohort was it possible to clearly identify the treatment arm to which the SCI subjects were assigned. This inability was due to the inclusion of subjects with neurogenic bladder because of multiple etiologies and failure of the methodology to allow distinction between them in the study results. In only four studies were the specifics of the SCI classified using the ASIA scale, and no studies used a symptom score validated in a SCI population. A urinary diary was absent in 63% (19 of 30); sufficient detail to repeat the methods used in urodynamic was lacking in the majority of studies, and video urodynamics was only used approximately in half of studies.

Considering the importance of anticholinergic medications in the management of neurogenic lower urinary tract dysfunction in patients with SCI and that there is now a choice of agents available, this represents a lack of information that compromises the ability of a clinician to match the needs of an individual SCI patient to a specific agent. This finding corroborates the conclusion of a 2012 meta-analysis of randomized trials in mixed populations with neurogenic bladder that trial data available do not allow differentiation between results in different neurogenic populations.⁵ From our review, we suggest that future clinical trials would more readily allow individualized matching of patients with SCI to specific therapeutic modalities if the following components were considered in their design:

Recruitment of the SCI population

Ideally, trials would be specifically tailored to the SCI population. Practically speaking, this is a challenge because this population is small compared with other neurogenic conditions, and hence multicenter studies are likely required. An advantage of a large multicenter study recruiting SCI patients alone would be the potential to stratify therapy based on the level and completeness of injury. Randomized crossover studies can be used in persisting disease states where the study drug modifies symptoms in a reversible way allowing for the subject to act as

Table 1 Randomized trials involving the use of anticholinergic drugs in spinal cord injury

Author, year	Active drug	Placebo	Active overall	Control overall	Active SCI n	Control SCI n	ASIA	UDS methodology	Video UDS	Standardized terminology	Bladder diary	Symptom score	Design
		n	n	n									
Nardulli, 2012	Group A: Oxybutynin 3x5.0 mg per day and Trospium chloride 4x20 mg per day Group B: Oxybutynin 3x5.0 mg per day and solifenacin 1x10 mg per day	X ^a	12	X	6	6	No	Not detailed	Not specified	Yes	Yes	No	Single center
Stöhrer, <i>et al.</i> ^{15, b}	Propiverine 15 mg Oxybutynin 3x5.0 mg	X	131 total, 70 (pro), 61 (oxy)	X	122	X	No	Not detailed	Not specified	Yes	No	No	Multicenter
Menarini <i>et al.</i> ¹⁷	Trospium chloride standard dose versus adjustable dose	X	80	X	80	X	No	Detailed	No	Yes	No	No	Multicenter
Horstmann <i>et al.</i> ^{16, b}	Tolterodine, 4 mg inc. to 8 mg OR trospium chloride, 45 mg inc. to 90 mg	X	21 total (toit), 11 (TCI)	X	17 total (10 tetra, 7 para)	X	No	Detailed	Yes	No	Yes	No	Single center
Ethans <i>et al.</i> ³³	+Tolterodine (SSD) ^b ; 4–12 mg per day Oxybutynin (SSD) ^b ; 10–15 mg per day Placebo	placebo	10	X	10	X	No	N/A	N/A	No	Yes	No	Crossover
Halaska <i>et al.</i> ¹⁸	Trospium chloride 2x20 mg per day Oxybutynin 2x5.0 mg per day	X	368 total, 267 (TCI), 90 (oxy)	X	X	X	No	Not detailed	Not specified	Yes	Yes	No	Multicenter
Lehteranta <i>et al.</i> ¹⁹	Intravesical oxybutynin	Placebo	9	X	1	1 (same patient crossover)	No	Not detailed	No	Yes	Yes	No	Double-blind crossover
Di Stasi <i>et al.</i> ²⁰	Oxybutynin 5 mg oral Intravesical passive diffusion oxybutynin 15 mg Intravesical electromotive administration Oxybutynin 15 mg	Placebo	12	X	All N=12 SCI	Yes	Not detailed	No	No	No	No	Single center	Multicenter
Birns <i>et al.</i> ²¹	Oxybutynin CR 1x10 mg Oxybutynin 2x5.0 mg	X	63 (62 final), 60	67 (66 final), 53	X	X	No	N/A	N/A	No	Yes	No	Multicenter
Stöhrer, <i>et al.</i> ¹⁰	Propiverine 15 mg	Placebo	71 total, 0.5 (20), 1.0 (16), 2.0 (18), 4.0 (17)	19	95 total (90 final)	No	Detailed	Yes/partial	Yes	Yes	No	Multicenter	Multicenter
van Kerrebrouck <i>et al.</i> ^{28, b}	Tolterodine 2x0.5, 1.0, 2.0 and 4.0 mg per day	Placebo	0.5 (20), 1.0 (16), 2.0 (18), 4.0 (17)	19	Of 52 group: Paraplegia – 20; Quadriplegia – 11; hemiplegia – 7; unspecified SCI – 8	53	No	Not detailed	Not specified	Yes	No	3-point rating scale	Multicenter
Madsbacher <i>et al.</i> ²⁴	Trospium chloride 2x20 mg per day	X	52 (TCI), 43 (oxy)	X	X	X	No	Not detailed	No	Yes	No	Non-validated well-being questionnaire	Multicenter
Stöhrer, <i>et al.</i> ²⁵	Oxybutynin 3x5.0 mg per day Trospium chloride 3x20 mg per day	Placebo	29	32	29	32	No	Detailed	Yes/partial	Yes	No	No	Multicenter
Throff, 1991	Oxybutynin 3x5 mg per day Propantheline 3x15 mg per day	Placebo	63 (oxy), 3x 54 (pro)	52 (plac)	X	X	No (pre-dates)	Some detail	No	No	No	Scored urologic history for female incontinence evaluation	Multicenter

Abbreviations: ASIA, American Spinal Injury Association Impairment Scale; N/A, not applicable; oxy, oxybutynin; plac, placebo; pro, propiverine; SCI, spinal cord injury; SSD, self-selected dose; TCI, trospium chloride; toit, tolterodine; UDS, urodynamic studies.
^aX = no information provided or could be obtained.
^bUnable to distinguish between active SCI and control SCI groups.

Table 2 Prospective trials of anticholinergic drugs in the management of neurogenic bladder related to SCI

Author, year	Active drugs compared	Active	Active SCI	ASIA	UDS methodology	Video UDS	Standardized terminology	Bladder diary	Symptom score	Multicenter
Kennelly <i>et al.</i> ²⁷	Transdermal oxybutynin initially 3.9 and 7.8 mg per day to oxybutynin final 7.8, 9.1 and 11.7 mg per day	24 Total 18 final	X ^a	Yes	Not detailed	No	Yes	Yes	No	Yes
Amend <i>et al.</i> ²⁸	Group A: Tolterodine and oxybutynin 15 or 30 mg Group B: Trospium chloride 90 mg and tolterodine 4–8 mg Group C: Oxybutynin 30 mg and trospium chloride 45 or 90 mg	27	21	No	Detailed	Yes	Yes	Yes	No	No
Zahariou <i>et al.</i> ³⁰	Oxybutynin 5 mg 1x3 daily DDAVP (intranasal)+oxybutynin 5 mg 1x3 daily	11	11	No	N/A	N/A	No	No	No	No
George <i>et al.</i> ³¹	Oxybutynin 5 mg Propantheline 15 mg	18	X	Yes	Not detailed	No	No	Yes	No	No
Bennett <i>et al.</i> ³²	Capsaicin 1 mm ³ in 30% ethanol in saline	39	10	No	N/A	N/A	No	No	No	No
O'Leary <i>et al.</i> ³⁴	Oxybutynin XL 10 mg, increasing to 15, 20, 25 and 30 mg Oxybutynin XL 10 mg, increasing to 30 mg (n = 5)	10 10	10 10	Yes	Detailed	Yes	No	Yes	No	No
Pannek <i>et al.</i> ³⁵	Oxybutynin (oral) 4x5 mg per day Oxybutynin (oral) 4x5 mg per day+oxybutynin (intravesical) 3x15 mg per day dissolved in 15 ml solution	25	25	No	Detailed	No	No	Yes	No	No
Haferkamp <i>et al.</i> ³⁶	Oxybutynin (intravesical) 0.3 mg/kg increasing to 0.9 mg/kg	32	17	No	Detailed	Yes	Yes	No	No	No
Vaidyanathan <i>et al.</i> ³⁷	Oxybutynin 1–3x5.0 mg per day	7	7	No	N/A	N/A	No	No	No	No
Szollar and Lee ³⁸	Ditropan 1–3x5.0 mg per day diluted in 30 ml saline solution	13	13	No	Detailed	Yes	No	No	No	No
Singh and Thomas ³⁹	Oxybutynin (intravesical) 1x10.0 mg per day diluted in 30 ml solution	6	6	No	Detailed	Yes	No	No	No	No
O'Flynn and Thomas ⁴⁰	Oxybutynin (intravesical) 1x5.0 mg diluted in distilled water	15	12	No	Detailed	No	No	No	No	No
Prasad and Vaidyanathan ⁴¹	Oxybutynin 3x5.0 mg per day dissolved in 10 ml boiled and cooled tap water	12	8	No	Detailed	No	No	No	No	No
Madersbacher <i>et al.</i> ⁴²	Intravesical oxybutynin 5 mg tab crushed into 30 cm ³ water	13	13	Predates	No	No	Predates	No	Predates	No
Diokno and Lapidés ^{44b}	Part 1: Oxybutynin 1x5.0 mg to Probanthine (oral) 1x15 mg OR probanthine (intravenous) 1x60 mg	8	5	Predates	No	No	No	No	No	No
Bodner <i>et al.</i> ⁴³	Part 2: Oxybutynin 2–3x5.0 mg per day to no medication Verapamil (alone) 24OSL Oxybutynin (alone) 5 mg Verapamil+oxybutynin ^b	8 14	8 14	Predates Predates	No No	No Yes	Predates Predates	No No	Predates Predates	No No

Abbreviations: ASIA, American Spinal Injury Association Impairment Scale; N/A, not applicable; SCI, spinal cord injury; TCI, trospium chloride; tolt, tolterodine; UDS, urodynamic studies.
^aX = No information provided or could be obtained.
^bOnly parts 1 and 2 included patients with neurogenic bladder.

their own control, exposes the subject to both treatments and reduces the sample size needed. Examples of crossover design are the studies by Lehtoranta *et al.*¹⁹ and Ethans *et al.*³³ Alternatively, N of 1 designs defined as 'where an individual is exposed to a random sequence of control or treatment many times' may be possible in conditions where the event of interest occurs frequently in an individual. In the context of reduction in neurogenic bladder symptoms in SCI, this may be hampered because of the small effect size of drugs used, including anticholinergics.

Conduct of mixed cohort trials

When recruitment of a SCI population alone is not possible, mixed neurogenic population cohorts can be used. We found this to be common in neurogenic bladder-related studies. However, data related to individual neurologic conditions can be difficult or impossible to identify from such reports. Use of stratified randomization in neurogenic bladder whether based on disease etiology, level of function (paraplegia versus quadriplegia) or urodynamic parameters was virtually absent in the studies examined. This limited the ability to tract SCI patient's from within the overall cohort. Provision of a randomization diagram within mixed cohort studies aids readers in the interpretation of results related to SCI patients.

Incorporation of validated tools and standardized terminology

Standardized and/or validated tools exist that should be used; many of these have been validated for use in patients with SCI. These include descriptors that are specific to SCI and to urologic conditions. It is currently possible to accurately describe patients with SCI by using (1) a scale of physical impairment (ASIA scale), (2) validated history/symptom scores for neurogenic bladder or those that are specific to SCI and bladder function, (3) urinary diaries, (4) standardized urodynamic testing methodology and (5) the use of standardized lower urinary tract terminology.

(1) *The ASIA impairment scale.* The ASIA Impairment scale is an internationally accepted clinical tool to standardize reporting of the level, extent and degree of completeness of SCI.⁷ The benefits of incorporating an ASIA assessment into clinical trials have been outlined by the International Campaign for Cures of SCI Paralysis Clinical Guidelines Panel, including the ability to compare sub-populations of SCI between centers.⁶

Even though the majority of RCTs were reported after the current ASIA scale was developed in our review, only Di Stasi *et al.*²⁰ included ASIA classification of subjects. The level of cord lesion was described in some studies as quadriplegia or paraplegia. Pannek *et al.*³⁵ distinguished between subjects who had a cervical spinal cord lesion and those in whom the injury was at a thoracic level. In future, this limitation can be avoided by incorporation of ASIA classification, which is inexpensive and does not require specialized equipment to complete.⁶

(2) *Validated symptom scores.* Validated questionnaires to document history related to urinary tract function in SCI patients now exist.⁸ None were used in any of the 30 studies we reviewed; this may be due to the timing of development of these scores in relation to the conduct of the studies reported, or to slow adoption. However, other validated instruments that quantify quality of life in the neurogenic population in general or use validated questionnaires to document their bladder symptoms were not identified.

An example of a questionnaire recently validated in the SCI population is the Rick Hansen SCI Registry questionnaire.⁴⁵ Scores validated for use in both the SCI and MS populations include the SF-Qualiveen (Short Form Qualiveen),⁴⁶ the Qualiveen⁴⁷ and the IQOL

questionnaire.^{48,49} The Qualiveen includes questions regarding urinary incontinence and storage symptoms such as urgency. The SF-Qualiveen contains only eight questions. A more broadly used single question tool is the Patient Perception of Bladder Condition Questionnaire.⁵⁰ The IQOL is longer, validated in neurogenic bladder (not disease specific to SCI) and contains 28 items measured on a Likert scale for ease of subject use. Visual analog scales can also be used to assess treatment satisfaction. Where possible instruments developed and validated by expert panels should be used. The International Consultation of Incontinence Modular Questionnaire is an example and has been used in a recent study, which included subjects with neurogenic bladder.^{51,52}

(3) *Urodynamic methodology.* Trials examining the effectiveness of treatment related to the bladder include the evaluation of physiologic measures related to bladder function; the gold standard evaluation is urodynamics (UDS),⁹ which is fundamental in the decision regarding the need for anticholinergic therapy and assessing response to treatment. UDS measures a number of variables; UDS results can be influenced by elements of the methodology including the size of catheters used, the type of fluid infused and the use of EMG and hardware parameters including the bladder filling rate. Specifically reporting these variables allows other researchers to reproduce the methodology and facilitates translation of the findings to patients with similar physiologic function. Reports of UDS measurements should itemize methodological elements listed above or cite a methodology reference. It is important to highlight the fact that lower urinary tract function can vary from individual to individual with the same level of SCI, and hence the importance of using objective UDS data combined with the ASIA score to provide a comprehensive description of the subject.

International guidelines on the management of neurogenic bladder such as those from the European Urologic Association include the relevance of video urodynamic studies,⁹ but we found that they were only used occasionally. This limits the ability to speak to the effectiveness of reducing or eliminating reflux in the setting of a high-pressure neurogenic bladder.

A further consideration related to the SCI population is the potential onset of AD during UDS. Also, AD is relevant in patients with high-pressure neurogenic bladder where treatment given is intended to lower bladder pressure and the potential for AD therefore exists, but we did not find the topic of AD management discussed within any of the 30 extant articles.

(4) *Urinary diaries.* A patient-completed standardized urinary diary is commonly used to quantify symptoms, as evidenced in RCTs evaluating idiopathic overactive bladder. These diaries should be used as they document times of micturition and voided volumes, incontinence episodes, pad usage and other relevant information.⁹

(5) *Standardized urologic terminology.* The International Continence Society Standardization of Terminology group has provided a set of definitions that relate to patient symptoms, signs and urodynamic findings.¹⁰⁻¹² These definitions have evolved over time, as the understanding of lower urinary tract dysfunction has increased and the technical methods for measuring bladder function have improved.

We found that more than half of studies made reference to the current terminology of the lower urinary tract definitions of the International Continence Society.

Adverse events reporting

Standardized definitions are available for the reporting of adverse events, as well as the criteria for their use. The presence or absence of certain events such as AD occurring in SCI should be reported in

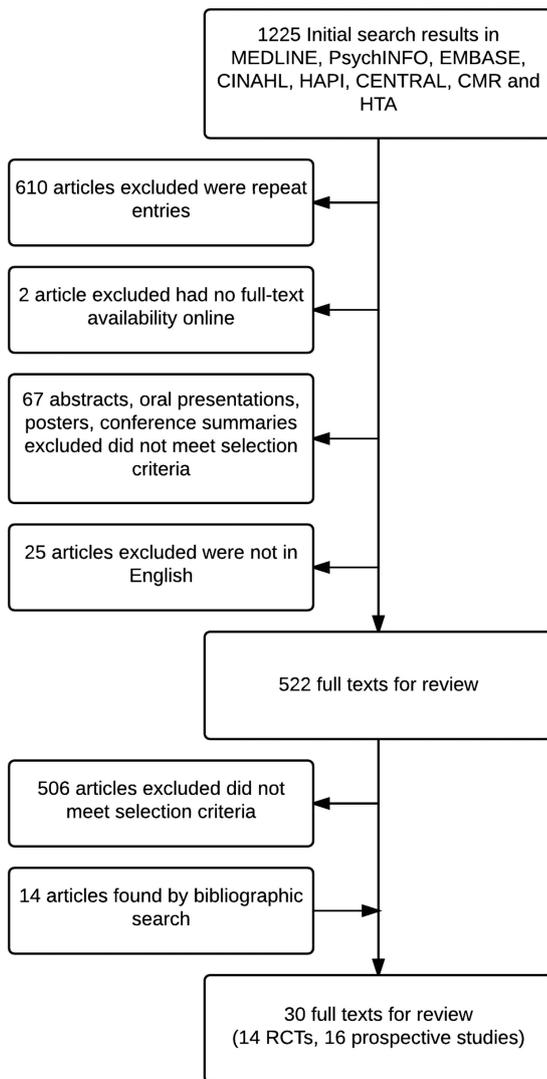


Figure 1 Search flow strategy CINAHL, Cumulative Index to Nursing and Allied Health Literature; CMR, Comprehensive Microbial Resource; HAPI, Health and Psychosocial Instruments.

mixed cohort trials even where patients with other neurologic conditions are not at risk. Adverse events related to pharmacotherapy with anticholinergics such as cognitive impairment have particular relevance in SCI as coexisting traumatic brain injury may be present. However, in the context of AEs reported in the trials reviewed for this study, it was only reported that these were similar in type and frequency to those seen in the idiopathic overactive bladder population and included dry mouth, constipation, vision abnormality, headache and urinary retention.^{13–44} However, a meta-analysis concluded that side effects were more common in the neurogenic population.⁵ This underscores the need to document the frequency and severity of AEs in future trials with SCI subjects to examine for differences that may be apparent based on the ASIA scale.

Female/male-specific considerations

Reporting the number of males and females enrolled within a SCI cohort is relevant for a number of reasons. Bladder management

options vary between men and women such as the ability to use condom drainage in men. Also, there are implications of bladder management during pregnancy; some anticholinergic drugs are contraindicated and others have not been studied sufficiently for their use to be recommended. This is important as the number of women with SCI becoming pregnant is increasing.⁵³

We recognize limitations in this study; article omission may have occurred because of the inherent methodological risks of an integrated review. Every effort was made to find articles through bibliographic search and the use of a librarian. Our search strategy was also limited to articles published in English; some articles of relevance may have been published in other languages. Our review is limited to prospective and randomized trials, due to the increased levels of evidence that can be obtained in the hierarchy of their study design. Also, as these studies are designed before data collection, researchers have the ability to include measurements and outcomes such as the ones we have recommended in advance.

CONCLUSIONS

Despite the importance of management of neurogenic bladder in the SCI population, this integrative review of 30 trials evaluating the effects of anticholinergic drug therapy in the management of neurogenic bladder indicates that the information provided is too limited for clinicians to be able to match trial data to the needs of individual patients with SCI. This is principally because the cohorts enrolled were predominantly heterogeneous, and the number of SCI patients studied was small. However, the classification of those patients who were included was also very limited. Most studies lacked inclusion of standardized clinical evaluation tools—in particular, the ASIA scale and validated symptom scores. Many also did not incorporate a urinary diary, although most did use current standardized terminology for the urinary tract. In future, trials evaluating drug efficacy will ideally include more that are SCI patient specific, but all can use these standardized clinical evaluation tools to provide a more comprehensive classification. This will add to the applicability of trial data and the ability of clinicians to understand the acute and chronic effects of treatment modalities required by a patient population that is growing annually and where many are dependent on therapy for their lifetime.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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