Pharmacological Interventions for Bladder Dysfunction In Multiple Sclerosis: A Systematic Literature Review

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Abstract

Background: As many as 75% of multiple sclerosis (MS) patients experience urinary symptoms during the course of their disease, which can affect many aspects of their daily life.[28] Though effective pharmacological treatment for bladder dysfunction exists, effectiveness in the MS population has not been adequately reviewed.

Objective: To identify, appraise, and synthesize data to determine efficacy of current pharmacological treatments for bladder dysfunction, specifically overactive bladder in patients with MS.

Methods: We searched the Cochrane Database for related systemic reviews, in addition to searching the following databases for randomized controlled trials: PubMed, Medline [OVID], EMBASE [OVID], and Cochrane Central Register of Controlled Trials. Databases were searched from inception date to December 15th, 2015. We used comprehensive Cochrane review search terms for Medline, EMBASE, and the Cochrane central register. Two reviewers independently screened titles, abstracts, and full text articles to ensure all studies were randomized controlled trials, that results for MS patients were presented separately if the study had also included other patients with bladder dysfunction, and that the outcomes of interest were reported. We included studies meeting the following criteria: (1) prospective, and randomized controlled trials conducted in any setting; (2) published in English; (3) conducted on adult patients with a diagnosis of MS and experiencing bladder dysfunction, as defined by health professional or self reported symptoms; (4) Studies that examined any pharmacological therapy for treatment of bladder dysfunction in MS patients.

Results: Of 69 unique abstracts, 6 unique clinical trials met the final inclusion criteria. Oxybutynin was superior to Propatheline in the domains of mean cystometric capacity,

frequency, urgency, nocturia, and incontinence. There were no statistical differences between Atropine and Oxybutynin in similar domains. Further, Methantheline Bromide, was subjectively superior to Flavoxate Chloride, and Meladrazine tartrate. OnabotulinumtoxinA was found to be superior in all measures of bladder dysfunction in comparison with the placebo group. THC and Cannabinoid trials produced mixed results. A significant reduction in UIEs from baseline in both treatment groups was found in one trial. The other study did not find significant differences between treatment and placebo groups in terms of UIEs, however demonstrated significant improvement on other measures, such as daily voids, and nocturia episodes, and patients perception of the their bladder condition.

Conclusion: This review suggests that OnabotulinumtoxinA injections, and Anticholinergic Medications reduce urinary symptoms. Results of studies on Cannabinoids and THC products are inconsistent. Relative lack of current trials and poor study quality limit conclusions, and further researcher is warranted.

Table of Contents

Introduction

Background on Multiple Sclerosis

Multiple Sclerosis (MS) is amongst the world's most common disabling neurological diseases, and remains the leading cause of non-traumatic disability in younger adults.[1] MS is one of several demyelinating diseases that are immune- mediated. Specifically, MS is an autoimmune disease that affects the central nervous system (CNS), meaning the body attacks its own nervous system causing irreversible damage. The disease process in the CNS is characterized by chronic inflammation, demyelination, scarring or plaque formation, and neuronal loss.[2] The autoimmune process results in injury to both myelin and axons resulting in a wide range of symptoms, including motor weakness, gait ataxia, visual disturbance, sphincter dysfunction, and cognitive changes.[4] MS is a disease that involves dissemination in time and space, that is, MS manifests in multiple locations of the CNS, and new lesions develop over time. The disease course can be quite variable in different individuals, ranging from a relatively benign condition, to a devastating, incapacitating disease.[2]

Pathophysiology

The autoimmune process is predominantly mediated by mononuclear T cells and macrophages, which infiltrate white matter. The humoral immune system is also involved by sending B lymphocytes to infiltrate the nervous system, where myelin-specific autoantibodies are present. The hallmark of MS pathology is demyelination, which, explains many of the clinical and laboratory manifestations of the disease.[3] In a healthy CNS, there are myelinated, and unmyelinated axons. The myelinated axons are surrounded by a phospholipid bilayer, myelin. Nerve conduction through myelinated axons occurs through a process known as saltatory conduction. The nerve impulse travels down the axon by jumping from one node of Ranvier to

another without having to depolarize the length of the nerve between nodes. This process significantly increases the speed of conduction, conducting impulses at a velocity of approximately 70 m/s. In comparison, unmyelinated axons conduct nerve impulses by continuous propagation, a much less efficient process, conducting impulses at approximately 1 m/s. [2] Damage in MS is not confined to myelin, as neuronal pathology is also recognized as a major contributor to CNS dysfunction.[2]

Epidemiology and Etiology

The estimated number of people affected by MS worldwide is 2.3 million.[1] There appears to be an uneven distribution of the disease across the world, with an increase in disease prevalence, the further distance away from the equator. Notably, Canada has a prevalence amongst the highest in the world, of at least 200-250 per 100 000, with a particularly high prevalence in the prairie provinces.[4] The prevalence in North America, and Europe are 140 and 108 per 100 000 respectively. Australia is another world region with a high prevalence of MS, ranging from 60.01-100 per 100 000. In comparison, prevalence of MS is lower in Sub-Saharan Africa and East Asia, where the prevalence is estimated to be 2.1 and 2.2 per 100 000 respectively.[1,5] Variation in prevalence worldwide has suggested an important role for environmental factors.

The exact cause of MS is still unknown, however there seems to be a complex interplay between environment and genetics.[4] Environmental risk factors that have been proposed and for which there is strong biologic plausibility include, smoking, Epstein-Barr virus infection, and vitamin D insufficiency. In terms of genetic determinants of MS, there is a hereditary component. The risk of disease occurrence in a first-degree relative is 7-40 times that of the general population. To add further evidence for a hereditary component, monozygotic twin

concordance is 31%, where the dizygotic rate is 5%.[11] Hereditary is believed to be polygenic in nature. A haplotype termed, HLA-DRB1:1501 is highly prevalent and is the haplotype most strongly associated with MS.[7]

Onset of MS typically peaks around the third and fourth decade of life, but may occur in childhood or after age sixty.[1,5] MS affects more women, than it does men, and this ratio has remained significantly unchanged since 2008. The ratio of female to males affected seems to vary amongst geographic regions, ranging from 2.6 to 3.0.[1]

Diagnosis and Course of Disease

As MS can affect any part of the CNS (brain, spinal cord, or optic nerve) resulting symptoms are of a wide variety.[8] To establish a diagnosis of MS, there must be evidence that damage occurred in two separate areas in the CNS, at two separate points in time, and an alternative diagnosis has been sufficiently ruled out. These signify dissemination in space, and time, and MS is a diagnosis of exclusion.[12]

There are several diagnostic criteria and guidelines for MS. The 2010 McDonald criteria are currently considered the gold standard for diagnosis and follow the fundamental concept of dissemination in space and time. The McDonald diagnostic criteria emphasize clinically isolated syndromes (CIS). A CIS is a single neurological deficit that is consistent with MS. The most common syndromes appear to be optic neuritis, brainstem dysfunction in the form of ocular motor deficits, and transverse myelitis: a condition that evolves over hours to days manifesting as sensory and/or motor deficits. Many patients who present with a CIS, already have MS lesions on MRI, and 60-80% of those patients will go on to develop definite MS.[9]

To meet diagnostic criteria, individuals must have a minimum of two attacks that clinically affect more than one anatomical site. However, on initial presentation the second

lesion may not be clinically expressed, therefore, use of investigations plays a crucial role in diagnosis.[11] MRI is important to confirm dissemination of time and space. The MRI sequences used include sagittal, axial T2-weight scans, and axial T1 scans which are pre and post Gadolinium enhanced. The presence of Gadolinium enhanced lesions suggests sites of current inflammation, or active demyelinating lesions. Scans can then be repeated within months to show dissemination in time. MRI will also demonstrate the presence of multifocal lesions within the CNS.[3,9] In addition, evaluation of CSF allows for determination of intrathecal inflammation, and evoked potentials will demonstrate altered conduction patterns consistent with demyelination.[3]

There are three identified courses of disease in patients with MS. Classification is based on initial and current clinical disease, as previously mentioned, disease course has great variability among individuals affected by MS. At initial diagnosis, most patients (85%) are classified as having relapsing-remitting MS (RRMS). During a relapse, acute symptoms develop over days to weeks, and gradually resolve over weeks to months. Residual symptoms may or may not persist after a relapse and they occur at random intervals.[9,10,12] Of those with an initial diagnosis of with RRMS, approximately 50% will go onto develop secondary progressive MS (SPMS) within 10 years, and 90% within 20 years.[12] SPMS is characterized by a gradual worsening of neurological symptoms, with clear relapses and remissions becoming less evident.[9,10] Primary progressive MS (PPMS), is characterized by gradually progressive neurological disability from diagnosis. The primary progressive course makes up 15% of MS patients, and a later age of onset, in the fourth and fifth decades of life is often seen.[9,10]

Symptoms and Complications

As it has been previously alluded to, damage to CNS is variable amongst individuals with MS, therefore producing different symptoms and course of disease. Symptoms affecting an individual can also fluctuate over time.[12,13]

Sensory deficits are among the most common presenting symptom, ranging from absence of sensation (numbness), to increased/abnormal sensation in the form of paresthesias (numbness and tingling). Sensory symptoms can be severe enough to cause functional impairment of the affected site. In addition, motor symptoms typically manifest as weakness, often accompanied by spasticity.[8] Spasticity manifests as stiffness, involuntary muscle spasms, and loss of muscle function resulting from disequilibrium in ascending and descending excitatory and inhibitory pathways within the brain and spinal cord. The onset of spasticity may follow a period of exacerbation.[13,14] Coordination abnormalities can also be seen with difficulties in hand dexterity and/or gait. Visual disturbances are also common presenting symptoms of MS. Optic neuritis refers to inflammation of the optic nerve, which can manifest as subtle visual impairment, to complete visual loss, along with retro-orbital soreness with eye movements. If the brainstem is affected, eye movement abnormalities, such as an internuclear opthalmoplegia may cause diplopia.[8]

Among the less visible symptoms are fatigue, cognitive deficits, depression, sexual dysfunction, pain, and bowel and bladder dysfunction. Fatigue affects almost all patients with MS, and can be severely debilitating. MS-related fatigue manifests as an overwhelming tiredness after little or no activity independent of mood disturbance.[13] Cognitive deficits include impairment of working memory, concentration, information processing speed, word-finding, and executive functions. In addition, more than 50% of MS patients will experience a major

depressive episode in their lifetime.[12] More than 50% of MS patients will also experience neuropathic pain. The pain is often burning in character and may be difficult to localize and treat.[13]

Bladder Dysfunction

Bladder dysfunction, and related pharmacological treatments are the main focus of this systematic review. Bladder dysfunction is an important issue to address, as it affects up to 90% of MS patients and can have a significant impact on quality of life. Complications from bladder dysfunction such as infection can also exacerbate disease.[14] A normally functioning urinary system is well-controlled. Simply, urine accumulates in the bladder causing it to expand. Once a minimum amount of urine is present in the bladder, nerve endings in the bladder transmit signals to the spinal cord, and consequently to the brain to signify voiding needs to occur. As preparation for urination occurs, the brain relays a return signal to the spinal cord to commence the voiding reflex. The voiding reflex consists of simultaneous detrusor muscle contraction to expel urine from the bladder, and external sphincter relaxation to allow urine to pass into urethra to be expelled.[15]

MS causes bladder dysfunction when areas of demyelination in the brain and spinal cord disrupt normal signal transmission between the brain and urinary system, and voiding reflex no longer works in such a coordinated fashion. Three primary types of bladder dysfunction can arise. Storage dysfunction refers to failure to store urine due to an over-active detrusor muscle that begins to contract as soon as a small amount of urine is present in the bladder. Repeated contraction signals the need to void even when the bladder has not reached normal capacity. With demyelination in the spinal cord, the signal does not reach the brain and the process of urination becomes less controlled. The process of urination becomes more of a reflex response

and results in urgency, frequency, nocturia, and incontinence. Emptying dysfunction can result from demyelination of the area that signals the voiding reflex. This creates a scenario of bladder filling, without appropriate communication to the brain or to external sphincter. This results in an over filled, overly relaxed bladder, causing urgency, dribbling, hesitancy, and incontinence. The third form of bladder dysfunction affecting MS patients is a combination of storage and emptying failure, or detrusor-external sphincter dyssynergia. As the name implies, the detrusor and external sphincter no longer work in coordination. Instead, both contract simultaneously, resulting in residual, or trapped urine in the bladder.

Methods of Assessing Bladder Dysfunction

There are several methods of assessing bladder dysfunction. Of the studies included in this systematic review, urinary diaries, where the patient keeps track of specified bladder dysfunction symptoms and/or criteria, and Urodynamic studies. A Urodynamic study is a test in which the bladder is filled with sterile fluid to assess the pressure within the bladder and the function of the external sphincter.[15] (Table 2).

Current Pharmacological Treatments for Bladder Dysfunction

Current pharmacological treatments are of wide variety and can be tailored to the type of bladder dysfunction. Pharmacological treatment of storage dysfunction includes medications of the anticholinergic class to relax the detrusor muscle. Examples include Oxybutynin, tolterodine, and fesoterodine. In addition, treatment with Onabotulinum toxin A (BOTOX) has also been used to relax the overactive detrusor muscle. It is delivered by injection into the bladder under cystoscopy. Furthermore, antispasticity agents, such as baclofen, can be used to relax the external sphincter, and alpha-adrenergic blocking agents such as tamsulosin (Flomax) can be used to promote urine flow through the sphincter for those with combined dysfunction.[15]

Specific pharmacologic agents in the studies included in this review include: Anticholinergic class, Onabotulinumtoxin A, Cannabinoid and THC products. Anticholinergic medications work to relax the detrusor muscle in the bladder, increasing capacity, as well as block basal acetylcholine release during filling to decrease urgency.[26] Neurotoxins, such a Onabotulinumtoxin A, work to temporarily relax an overactive bladder muscle.[15] Cannabis agonists work predominately through a CB1 receptors which are present within the bladder, and CNS regions of bladder control. Theoretically Cannabis agonists have been shown to increase the micturition threshold.[21]

Objectives

The objective of this systematic review is to identify, appraise, and synthesize data to determine efficacy of current pharmacological treatments for bladder dysfunction, specifically overactive bladder in patients with MS. Since MS is an incurable progressive neurological disease, it is important that symptomatic treatments are carefully considered. This review was conducted with an aim to determine which pharmacological treatments provide the best symptomatic relief for bladder dysfunction in MS patients. The goal is to give healthcare providers accurate information that will allow for appropriate prescribing, and enable them to provide adequate education to their patients.

Previous research pertaining to this topic includes a Cochrane review conducted by Nicholas et al. in 2009, which evaluated the efficacy, tolerability and safety of anticholinergic medications in the context of MS. They limited evaluation to research pertaining to anticholinergic medication and its role in managing bladder dysfunction in MS patients. Furthermore, the research evaluated in their systematic review was deemed to be of low quality,

and showed little support for the use of anticholinergic medication.[16]

By expanding the scope of the review the current systematic review aims to capture a larger body of clinical trials on pharmacological treatment for bladder dysfunction in MS patients, and will include trials investigating all forms of pharmacologic intervention.

Methods

Study Inclusion Criteria and Characteristics

The primary research question for this systematic review was "what is the efficacy of current pharmacological treatment for bladder dysfunction in patients with Multiple Sclerosis?" We included studies meeting the following criteria: (1) prospective, and randomized controlled trials conducted in any setting; (2) published in English; (3) conducted on adult patients with a diagnosis of MS and experiencing bladder dysfunction, as defined by health professional or self reported symptoms; (4) Studies that examined any pharmacological therapy for treatment of bladder dysfunction in MS patients. For example, there was no preference for only oral therapies, or a specific class of drug. Studies were excluded if they did not specifically investigate bladder dysfunction in MS patients, or display results for MS patients separately if the study population included more than one disease group.

Outcome Measures, Interventions and Comparators

The primary outcome measure is a decrease or improvement in symptoms of bladder dysfunction (urinary frequency, urgency, number of leakage episodes, incontinence, etc.) measured by any means from baseline to follow-up. The main intervention of interest was any pharmacological therapy for bladder dysfunction. Secondary outcomes of interest were adherence with intervention, cost of interventions, adverse effects of interventions, and quality of

life after receiving the intervention. Comparators in all studies included were to be placebo, or a prior therapy/treatment.

Search Strategy

We searched the Cochrane Database for related systemic reviews, in addition to the following databases for randomized controlled trials: PubMed, Medline [OVID], EMBASE [OVID], and Cochrane Central Register of Controlled Trials. Databases were searched from inception date to December 15th, 2015. We used comprehensive Cochrane review search terms for Medline, EMBASE, and the Cochrane central register. We used keyword search terms including "MS" AND "Overactive Bladder" AND "Treatments" for PubMed database preliminary searches (see Appendix A for detailed search strategy).

Study Selection

Two reviewers independently screened titles and abstracts after they were imported into an Excel spreadsheet. The first screen was done to ensure studies were conducted on a population with MS and bladder dysfunction. After selection of appropriate abstracts, full text articles were obtained. Two reviewers then independently screened full text articles to ensure all studies were randomized controlled trials, that results for MS patients were presented separately, had the study also included other patients with bladder dysfunction, and that the outcomes of interest were reported.

Data Abstraction

The following data elements were extracted: study design, inclusion criteria, identification/classification of MS disease state when applicable, method of identifying bladder dysfunction, interventions used (including dosage, route of administration), any efficacy or

safety outcomes, and outcome measures (as listed above). (Tables 3.1-3.6).

Risk of Bias Assessment

Risk of Bias was evaluated using the Cochrane Collaboration's Risk of Bias tool (adapted by Higgins and Altman).[17] Risk of bias was graded as low, high, or unclear on the domains of: sequence generation, allocation concealment, masking/blinding of participants, incomplete outcome data, selective outcome reporting, and other sources of bias determined. (Table 5).

Results

Results of the Search

We screened 69 unique abstracts, excluding 45 based on predetermined criteria: 10/45 abstracts were not a randomized controlled trial, 26/45 abstracts were duplicates, and 9/45 did not meet one or more of the following criteria: were not conducted on MS patients, or primary outcomes did not include bladder dysfunction. We reviewed 24 full-text articles. Of these, 6 unique clinical trials met the final inclusion criteria (Figure 1). 13 abstracts that were considered potentially relevant did not exist as full-text, shown in table 4.

Description of Studies

The 6 randomized controlled trials were published from 1977-2013, and conducted in the United States (n =1, 16.7%)[20], United Kingdom (n=2, 33.3%)[18,19], Halifax, Canada (n =1, 16.7%)[23], Denmark (n=1, 16.7%)[22], and one was a multicenter study including UK, Belgium, Romania, Denmark (n=1, 16.7%)[21](Table 1). The number of MS patients enrolled ranged from 34-630. The primary outcome for all 6 trials was the effect of a pharmacological therapy on some form of bladder dysfunction in MS patients. The 6 clinical trials included a variety of pharmacological treatments, and routes of administration. One study, conducted by Fader et al. compared efficacy of Atropine injections, to oral Oxybutynin.[18] Another, by Ginsberg et al.

focused specifically on intradetrusor injections of onabotulinumtoxinA.[20] Two trials conducted by Kavia et al, and Freeman et al. focused on cannabinoids administered both in oral pill form and oral mucosal spray.[19,21] Another trial, by Gajewski and Awad compared oral oxybutynin, and propantheline.[23] The final trial, by Hebjorn et al., examined efficacy of Methantheline bromide, Flavoxate chloride, and Meladrazine tartrate medications.[22] Inclusion criteria for the trials were varied, with some studies requiring a certain number of bladder dysfunction episodes a week. Most trials excluded patients with a current urinary tract infection (UTI).

Inclusion Criteria

Specific inclusion criteria for each study are summarized in (tables 3.1-3.6). Age range of participants across studies appeared to be 18-80 years. All studies required patients to have a clinical diagnosis of MS, and symptoms of bladder dysfunction. Two of the six studies required participants to has previously, or currently used an anticholinergic medication. One study required patients to remain on previous anticholinergic medication to compare outcomes. Two of six studies made reference to characterizing disability status, using mobility characteristics, and expanded disability score. One study made reference to a disability assessment but provided no details.

Assessments and Interventions

Methods of assessing bladder dysfunction in all trials are described in detail in table 2. Bladder dysfunction was identified in the four of the six trials by self-report in the form of a bladder diary. The trials using bladder diaries to assess baseline condition included varying parameters. For example, Fader et al. asked participants to include frequency and volumes. Freeman et al, used a three day record of UI episodes, Ginsberg et al. asked for a report of number of UI episodes a week. Kavia et al. asked for more specific parameters of number of

doses of study medication used, and other urinary dysfunction parameters. More advanced diagnostic tests, such as a urodynamic study were used either in conjunction with a bladder diary, or as a sole form of bladder dysfunction assessment (Gajewski & Awad, and Hebjorn). In addition, two of the six trials used additional methods of assessment, Freeman et al. used the United Kingdom Neurological Disability Score (UKNDS) and King's Health Questionnaire to better assess outcome measures on incontinence, and Kavia made use of an Incontinence Quality of life (I-QOL) scale.

Interventions varied amongst studies, with different classes of agents, and routes of administration, however, all were pharmacological in nature. Pharmacological agents used in the 6 studies analyzed in the review included: Anticholinergics, Neurotoxins (Botulinum), and Cannabis agonists.

The aim of the Gajewski and Awad study was to compare two anticholinergic oral treatments. The intervention consisted of oral administration of Oxybutynin or Propatheline. They used two treatment groups: a total of 19 patients received 5mg of Oxybutynin 3 times a day, and the other 15 patients received 15 mg of Propatheline three times a day for a total of 6 to 8 weeks.[23] Similarly, Hebjorn also compared efficacy of different anticholinergic oral treatments. The intervention included: 50 mg of Methantheline bromide (Banthine) administered once a day, or 200 mg of Flavoxate Chloride (Urispas) four times a day, or 150 mg of Meladrazine (Lisidonil) four times a day. Patients were assessed on their assigned treatment for fourteen days.[22] In contrast, Fader et al. compared two anticholinergic treatments with different routes of administration: injected Atropine solution, versus Oral Oxybutynin. Patients in the study randomly received either Atropine injection with a placebo oral pill, or a placebo injection and Oral Oxybutynin to make it a true blind double cross-over trial.[18] Ginsberg et al. used a double-

blind placebo control trial to determine the efficacy of Onabotulinum A neurotoxin injections. Their intervention included a dose of 200 units, or 300 units, or a placebo injection for 52 weeks, with assessments at 2, 6, 12 weeks, and every 12 weeks thereafter.[20] Two studies: Freeman et al., and Kavia et al. assessed the efficacy of cannabinoid, or THC related therapy. Freeman et al. administered 2.5 mg of THC equivalent or 1.25 mg of cannabidiol to patients in treatment groups, with control groups receiving a placebo pill.[19] The intervention used in the Kavia et al. study was Sativex (Naboximols), a cannabinoid combination oral mucosal spray. Comparator placebo group received an oral mucosal spray not containing cannabinoid extracts.[21]

Primary Outcomes

Assessment of outcomes were variable amongst studies, with all 6 studies relying on reporting of bladder dysfunction symptoms, and measurements of voids via a bladder diary pre and post treatment. Most studies included more quantitative measures, such as Urodynamic measurements based off baseline data, and pad weight tests (n=5).[19,20,21,22,23]

Bladder Dysfunction

For the purposes of this review, any symptoms of bladder dysfunction, measured by any means from baseline to follow up was considered a primary outcome. Of the 6 studies reviewed: bladder capacity(1), number of voids (4), number of incontinence events (4), maximum cystometric capacity (3), incidence of nocturia (2), incidence of urgency(3), height of contraction (1) and bladder volume at first contraction (1) were amongst primary outcomes. A detailed summary of primary outcomes is found in Table 1.

Anticholinergic Agents

As previously mentioned, three of six trials investigated the effect of anticholinergic medications on bladder dysfunction. Two of the three trials did not make use of a control placebo group. The trial conducted by Fader et al. used bladder capacity, number of voiding frequency events, and number of incontinence events as primary measures, and found no statistical differences between the two treatments. An increase in bladder capacity was found to be greater in the Atropine treatment group, in comparison to the Oxybutynin group, with mean capacity changes of 79.6 ml, and 55.5 ml, respectively, ($p = 0.053$). Number of voiding frequency episodes in 24 hours was found to be decreased by 1.5 voids in the Atropine treatment group, and only 1 void in the Oxybutynin group (95% CI -0.9, 0,2). In addition, the number of incontinence events decreased by 1 event in both Oxybutynin and Atropine groups.[18]

In the trial conducted by Gajewski and Awad, change in maximum cystometric capacity, change in height of contraction, frequency, nocturia, urgency, and incontinence were used as primary outcome measures. Oxybutynin was found to be significantly superior to Propatheline on two of three outcome measures. Mean maximum cystometric capacity was found to be larger in the Oxybutynin group than in the Propatheline group, 283.5, and 198.3 respectively ($p<0.05$). Decrease in mean severity of symptoms (frequency, nocturia, urgency, and incontinence) graded by patients was greater in the Oxybutynin group, $p<0.05$. There was no statistically significant change reported between Oxybutynin and Propatheline groups for height of contraction of detrusor muscle.[23]

The final trial, conducted by Hebjorn used patient opinion of improvement, residual volume measurements, incontinence, and bladder volume at first contraction as primary outcome measures. Of the three medications (Methantheline bromide, Flavoxate chloride, and Meladrazine tartrate), Methantheline bromide was reported as superior, with 18/27 ($p<0.001$)

patients preferring the treatment. This result had a 60% concordance between evaluations of cystometric pattern. Effective volume at first bladder contraction was found to be significant in the Methanetheline bromide group, with a median volume of 110 ml, in comparison to Flavoxate chloride, 25 ml, and Meladrazine tartrate, 20 ml, however when corrected for residual urine, none of the medications significantly increased the volume at first bladder contraction. Additionally, none of the three therapies significantly reduced the number of incontinence episodes. [22]

In summary, Oxybutynin was significantly superior to Propatheline in the domains of mean cystometric capacity, frequency, urgency, nocturia, and incontinence. There were no statistical differences between Atropine and Oxybutynin in similar domains. Further, Methantheline Bromide, was more subjectively superior to Flavoxate Chloride, and Meladrazine tartrate.

Neurotoxin

As previously discussed, one trial, conducted by Ginsberg et al. studied the efficacy of OnabotulinumtoxinA. They used number of urinary incontinence episodes (IE) a week, number of voluntary voids a week, maximum cytometric capacity (MCC), and involuntary detrusor contraction (IDC), as outcome measures. At the 6 week follow up, patients receiving Onabotulinumtoxin injections were found to have improvement in all outcomes. Number of weekly UI episodes, reported in mean weekly changes from baseline were -22.6, and -24.0 in the 200U injection, and 300U injection group respectively, in comparison with -14.0 in the placebo group ($p<0.05$). The number of voluntary voids per week were: -15.0 with 200U injection, and -25.0 with 300U injection, compared to -4.0 in the placebo group ($p<0.05$). In addition, MCC increased from compared with placebo $p<0.001$, and IDC occurrence decreased by 68.0%, and

70.9% in the 200U dose group, and 300U dose group respectively compared to the 18.5% in the placebo group, $p<0.001$ after six weeks. All outcomes did not reach statistical significance for clinically relevant difference between doses. They also added an important finding, which offered greater support for efficacy of OnabotulinumtoxinA. They reported on patients that had been using Anticholinergic medication for bladder dysfunction symptoms, prior to and for the duration of the study. Bladder dysfunction was inadequately managed in 76.1% of these patients on Anticholinergic medications. At follow up, those patients showed significant improvement in their symptoms in comparison to the placebo group ($p< 0.05$). There was also no difference in outcomes amongst those using and not using Anticholinergic medication prior to the study.[20]

Cannabinoids and THC Equivalents

Two of six trials in this review examined the efficacy of Cannabinoid and THC equivalents. In the trial conducted by Freeman et al. urinary incontinence episodes (UIE), judged by a 3-day diary, pad tests, and urodynamic measures were used to evaluate bladder dysfunction outcomes. Both treatments consisting of 2.5 mg of THC equivalent, and 1.25 mg of cannabidiol were found to have a significant effect over placebo. Reductions in UIEs were 25%, $p < 0.005$ and 19% $p < 0.039$ in the cannabidiol and THC groups respectively. Reductions in pad test weight were greater in both treatment groups when compared with the placebo group. Mean reductions were 44.7 ml, and 43.2 ml for cannabidiol, and THC groups respectively with a mean increase of 8.3 ml for placebo. There were no reported significant differences in urodynamic parameters amongst treatment and placebo groups.[19]

Bladder dysfunction was evaluated by number of UIE, incidence of nocturia, urgency, overall bladder condition, daily use of incontinence pads and pad weight in the trial conducted by Kavia et al. There was not a statistically significant difference between treatment and placebo

groups in terms of change in number of UIEs from baseline. At follow-up, UIE mean change from baseline was -1.08, in the Sativex treatment group, and-0.98 in the placebo group $p = 0.569$. The number of daytime voids, total 24 hour voids, and nocturia episodes were significantly reduced in the Sativex treatment group, adjusted means: -1.23 (p =0.044), -1.75 (p=0.007), -0.52 (p=0.01) respectively. Patient's opinion of severity of symptoms (overall bladder condition) showed a significant difference in favor of Sativex with a decrease in mean from baseline of 2.21, in comparison to a decrease of 1.05 in placebo group (p=0.001). Daily use of incontinence pads, and pad weight did not show statistically significant differences between Sativex and placebo groups.[21]

Secondary Outcomes

Tolerability and Side effects

All trials included in this review reported side effects and tolerability of pharmacological interventions.

Anticholinergic Agents

Of the 3 trials that administered anticholinergic agents, dry mouth was amongst one of the main side effects. In the Fader et al. study, Atropine was shown to cause less dry mouth than Oxybutynin after administration of treatment (p<0.0001) (Figure 2.2).[18] Dry mouth was also a reported side effect in the Hebjorn trial, amongst the methantheline bromide treatment group.[22] Gajewski and Awad also reported dry mouth in a list of side effects in both Oxybutynin and Propatheline groups, but did not quantify the occurrence of dry mouth specifically.[23]

Other side effects reported amongst the trials administering anticholinergic agents, were: nausea, anorexia, abdominal pain, constipation, dizziness, blurred vision, and headache. Gajewski and Awad indicated 68% of patients treated with Oxybutynin, and 53% of patients

treated with Propatheline experienced such side effects.[23] Fader et al. also added, that 1 participant experienced dizziness, and 6 reported urinary retention after receiving atropine. In the Oxybutynin group a small amount of patients reported experiencing night sweats, depression, and abdominal pain.[18] Hebjorn noted participants in all treatment groups also reported nausea, vomiting, headache, vertigo, and depression, fatigue, and dizziness, with Meladrazine tartrate causing side effects severe enough to discontinue treatment, however, did not quantify proportion of participants experiencing each side effect.[22]

Onabotulinumtoxin

Urinary tract infection (UTI) was the most common side effect in the trial administering OnabotulinumtoxinA by Ginsberg et al. UTI occurred 69% of the time in both the 200U and 300U OnabotulinumtoxinA treatment groups ($p<0.001$) (Figure 2.1). They also reported that one patient receiving 300U developed pyelonephritis. Other side effects with an incidence of 5% or greater, included: urinary retention, hematuria, diarrhea, fatigue, constipation, nasopharyngitis, pyrexia, muscular weakness, and dysuria. Ginsberg et al. further examined urinary retention, which appeared to show a dose-dependent increase in patients who were not catheterizing at baseline. The rate of initiation of clean intermittent catheterization (CIC), due to urinary retention in treatment groups was 31.4% and 47.1% in the OnabotulinumtoxinA 200U, and 300U groups respectively, compared with 4.5% in the placebo group. [20]

Cannabinoids and THC Equivalents

Cannabinoids or THC products seemed to be well tolerated in both trails administering such medication. Freeman et al. reported subjects in both treatment and placebo groups developed UTIs. The number of UTIs that occurred: 33, 35, and 42 in the cannabinoid, THC, and placebo groups respectively (Figure 2.1). Urinary retention was also reported in the THC group,

and placebo group, suggesting these adverse effects can't be explained by administration of treatment alone. Side effects found to be more prevalent in active treatment groups included: dizziness, dry mouth, gastrointestinal effects, and increased appetite. They expanded on GI side effects to say, constipation was reported to more frequently in the Cannabidiol group (26 events), than in the THC group (9 events), where as diarrhea episodes were common amongst both treatment groups with 38 events, and 36 events in the Cannabinoid, and THC groups respectively, compared with 15 events in placebo. Increased appetite was also slightly more prevalent in the treatment groups, with 4, 6, and 1 events in the Cannabinoid, THC, and placebo groups respectively. [19,25] In the study by Kavia et al. most adverse events were considered mild or moderate in severity. These events included dizziness, headache, disorientation, and impaired balance. UTI was a common event, that had a similar prevalence amongst both the treatment Sativex group, and placebo group, 6%, and 10% respectively (Figure 2.1). They added that, ten subjects stopped the medication due to treatment related events, 7 on the active treatment medication, Sativex, and 3 on placebo.[21]

Quality of Life

Four of the six trials used for this review reported quality of life (QOL) as a secondary outcome, with all but one of those trials demonstrating improvement. Fader et al. reported quality of life favoring the Atropine treatment group in the emotion and sleep domains, -5.7, and -5.4 respectively ($p = 0.05$).[18] Ginsberg et al. reported a mean change from baseline in the incontinence-QOL total score of greater than 11 points (minimally important difference).[20] Kavia et al. also reported an increase in mean incontinence-QOL total scores in the treatment group, however, it did not reach statistical significance.[21] Freeman et al. did not see an improvement in

quality of life based of the King's Health Questionnaire despite significant reduction in urinary symptoms (UIEs).[19]

Ease of Use

Only one study, Fader et al. commented on ease of use, as it required an intravesical injection of Atropine. Participants in the study reported the procedure required more time when compared to catheterization, however, overall, 63% of users found the procedure easy.[18]

Discussion

The current systematic review provides a synthesis of RCTs and prospective randomized trials of current pharmacological treatments for bladder dysfunction in MS patients. The objectives of this review were to identify, appraise, and synthesize data to determine the efficacy, tolerability, and safety of different pharmacological medications used to manage bladder symptoms in patients with MS. Of 69 citations reviewed, 6 met the final inclusion criteria. The studies reviewed were heterogeneous in terms of treatments used.

Summary of Findings

As previously mentioned, three studies examined the efficacy of different anticholinergic medications. It is difficult to draw conclusions in terms of efficacy of treatment on bladder dysfunction, as none of the three studies compared treatment to a placebo group. However, as previously mentioned, Oxybutynin was significantly superior to Propatheline in the domains of mean cystometric capacity, frequency, urgency, nocturia, and incontinence. There were no statistical differences between Atropine and Oxybutynin in similar domains. Further, Methantheline Bromide, was subjectively superior to Flavoxate Chloride, and Meladrazine tartrate.

OnabotulinumtoxinA was found to be significantly superior in all measures of bladder dysfunction in comparison with the placebo group, with no differences between treatment doses. They also reported and compared those patients who were on at least one anticholinergic medication for bladder dysfunction prior to and for the duration of the study, finding similar improvement as those not currently taking anticholinergic medications. These results suggest superiority of OnabotulinumtoxinA over anticholinergic medications in treatment of bladder dysfunction in MS patients.

THC and Cannabinoid trials produced mixed results. Both studies had differing outcome measures, also making them harder to compare. The oral medications given in the study by Freeman et al. demonstrated a significant reduction in UIEs from baseline in both treatment groups, however urodynamic measures did not improve. On the other hand, the study by Kavia et al, which administered the oral mucosal spray did not find significant differences between treatment and placebo groups in terms of UIEs, however demonstrated significant improvement on other measures, such as daily voids, and nocturia episodes, and patients perception of the their bladder condition. In both studies, the pharmacological therapy appeared to be well tolerated.

In terms of side effects and tolerability, THC and Cannabinoid products appear to be tolerated best, with lower incidence of UTIs, than with neurotoxin treatment, and a lower incidence of other side effects experienced with anticholinergic medications, such as dry mouth, GI symptoms, and dizziness.

Risk of Bias and Quality Assessment

Risk of Bias was evaluated using the Cochrane Collaboration's Risk of Bias tool (adapted by Higgins and Altman)[17] Two of the included studies conducted by Gajewski and Awad, and Hebjorn, were determined to have a high risk of bias, and had major flaws in the design. The

blinding method was unclear in both studies. In the study by Gajewski and Awad, blinding is not mentioned, and Hebjorn alludes to a double blind, however, provides no details on how it was achieved. The remaining 4 studies reviewed were rated as low risk for bias. The study by Fader et al. was conducted at a high standard, in terms of giving details of blinding and randomization, however, it was only two weeks in duration, and did not use a placebo control group. Ginsberg et al. scored low risk of bias on all domains, as sequence generation, allocation concealment, and the blinding processes were all thoroughly outlined. A lengthy follow-up period, with 3 points of evaluation also added to the quality of the study. The studies by Freeman et al. and Kavia et al. were also determined to be a low bias risk on multiple domains. Appropriate methodological details were given, and studies were carried out for 10-15 weeks duration.

Previous Studies

Limited systematic reviews investigating the efficacy of pharmacological agents for bladder dysfunction exist. One Cochrane review published in 2009 by Nicholas et al. looked at the use of anticholinergic medications for urinary symptoms in MS patients. They reviewed the same 3 studies conducted by Hebjorn, Gajewski and Awad, and Fader et al. Their interpretations were much the same as the current review, in that not much evidence can be obtained given that two of the studies are of poor quality, and the study by Fader et al. was of very short duration, and did not involve a placebo control group. They highlighted that the poor quality of the studies shows little support for the use of anticholinergic medications for bladder symptoms in MS patients, and none of the studies attempted to address long-term outcomes.[16]

Another systematic literature review conducted by Karsenty et al. in 2007 looked at efficacy of Intradetrusor Botulinum ToxinA in patients with overactive bladder. This review included any type of patient with known bladder dysfunction due to various causes, majority

being spinal cord injury. From the results of their review, Karsenty et al. concluded that treatment with Botulinum ToxinA injections provides a clinically significant improvement in bladder symptoms in those patients who were not effectively managed on anticholinergic/antimuscarinic medications. They also concluded that treatment with botulinum A toxin was well tolerated, with minimal side effects.[27] The results of this review are consistent with, and reinforce the findings in the study by Ginsberg et al. (included in the current review) which showed an improvement in bladder symptoms in those patients inadequately managed on Anticholinergic medications prior to receiving onabotulinumtoxinA injections.

There were no prior systematic literature reviews looking specifically at the efficacy of Cannabinoids and THC agents on bladder dysfunction.

Strengths, Weaknesses and Future Research

The strengths of this review include the use of a rigorous study protocol including a comprehensive search strategy that was adopted from the Cochrane review. Search terms were comprehensive to ensure no relevant studies were missed. In addition, the current systematic review is unique in that we considered all pharmacological treatments for bladder dysfunction in MS patients, whereas the prior reviews focused only on one class of medications. These strengths are limited by several factors. First, given the heterogeneity of the studies, and broad outcome measures included in this review, comparison of results between studies was difficult. Future reviews may wish to reduce heterogeneity by focus on a specific outcome measure, such as only including studies that used quantitative reports of UIEs. In addition, a meta-analysis was not performed, which could have enhanced interpretation. Another weakness of this review is the studies that were included. Two of the six studies were determined to be of low quality, limiting the level of inference possible.

Conclusion

The main objectives of this systematic review were to identify, appraise and synthesize trials investigating the efficacy of current pharmacological treatments for bladder dysfunction. This review met those objectives, however clear conclusions are lacking due to the heterogeneity of the studies assessed, and poor quality of two of the six studies. This review suggests that OnabotulinumtoxinA injections, Cannabinoids and THC products are superior to Anticholinergic medications in managing bladder dysfunction in MS patients, with respect to efficacy, and adverse effect profiles. As many as 75% of MS patients experience bladder problems during their course of disease, which can affect many aspects of their daily life.[28] It is clear from the low number of trials found, specifically testing the efficacy of pharmacological agents for urinary dysfunction in MS patients that more high quality trials need to be conducted.

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Tables

Table 1: Summary of Primary Outcomes

First Author	No. of Patients	Study Design	Intervention	Comparator	Result
Anticholinergic					
Fader	n =57	Blind double cross-over trial	Atropine injection OR oral Oxybutynin	Effect of each treatment	**Average bladder capacity(ml):** Oxybutynin/Atropine Baseline: 221.9 +/- 106.9 55.5 +/- 67.2, 79.6 +/- 89.6 (95% CI -0.4, 49.7) Not significant difference **No. Voiding frequency** Oxybutynin/Atropine Baseline: 8.8 +/- 2.9 -1.2 +/- 1.8, -1.6 +/- 2.0 (95% CI -0.9,0.2) between treatment differences not significant. **No. Incontinence events** Oxybutynin/Atropine Baseline: 1.7 +/= 2.1 -0.9+/-1.6, -0.9+/-1.7 (95% CI -0.3, 0.3) Difference is not significant
Gajewski & Awad	n = 34	Prospective Randomized study	5 mg Oxybutynin orally (n=19) 15 mg Propanthelin e orally (n=15)	Effect of each treatment	**Mean Decrease in grades of symptoms**: Oxybutynin-Propatheline Frequency: 1.3, 0.6 Nocturia: 1.0, 0.6 Urgency: 0.8, 0.5 Urge incontinence: 1.0, 0.5 All 4 differences significant p<0.05 for Oxybutynin group only compared to pre-treatment scores **Changes in cystometrography:** Oxybutynin-Propatheline Maximum cystometic capacity (ml): 138.3 before

					vs. 282.5 after, 163.3 before vs. 198.3 after Change significant p<0.5 for Oxybutynin group **Height of contraction:** Not significant for either group.
Hebjorn	n = 34	Double blind randomized crossover study of three oral treatments	50 mg Methanthelin e bromide (Banthine) 200 mg Flavoxate chloride (Urispas) 150 mg Meladrazine Tartrate (Lisidonil)	Effect of each treatment	**Median volume of first bladder contraction:** No treatment: n=32, 110 ml (95% CI 40, 190) Methantheline Bromide: n=32, 130 ml (95% CI 100, 250) Meladrazine Tartrate n = 20, 115 ml (95% CI 20,190) Flavoxate Chloride n = 31, 60 ml (95% CI 30, 250) Difference of Methantheline bromide to no treatment was only significant finding p <0.05 **Median amplitudes for first bladder contraction [cm H20]** No treatment: n=32, 47 (95% CI 30, 57) Methantheline Bromide n =32, 27 (95% CI 22,52) Meladrazine Tartrate n =20, 45 (95% CI 38,56) Flavoxate Chloride n =31, 53 (95% CI 27, 64). No significant difference between treatment groups and no treatment group p<0.05. **Incontinence Episodes:** No significant differences amongst therapies.
Neurotoxin					
Ginsberg	n = 381 MS	International Multicenter,	OnabotulinumtoxinA	Placebo	**Change from baseline UI episodes at 6 week follow**

	patients	Randomized double-blind, placebo-controlled trials (pooled data)	200U, 300U	**up:** Placebo (n = 131) = -14.0, OnabotA 200U (n=130) = -22.6, OnabotA 300U (n = 120) **=** -24.0 (P < 0.05). **Reduction in weekly UI episodes (dry rates) at 6 week follow up:** Placebo (n = 131) = 10.7%, OnabotA 200U (n=130) = 41.5%, OnabotA 300U (n = 120) **=** 44.2% (p<0.001) No differences between dosages. **Mean change from baseline voluntary voids/week:** Placebo (n = 131) = -3.0 OnabotA 200U (n=130) = -15.0 OnabotA 300U (n = 120) **=** -25.0 p<0.05 compared to placebo **Maximum Cystometric Capacity change from baseline at 6 week followup:** Placebo (n = 131) = 6.8 ± 120.2 OnabotA 200U (n=130) = 149.3 ± 169.2 OnabotA 300U (n = 120) **=** 165.1 ± 174.0 (p<0.001) **Patients who had an IDC, decreases from baseline in PdetmaxIDC:** Placebo (n = 131) = 10.7 ± 41.2, OnabotA 200U (n=130) = –22.1 ± 34.1, OnabotA 300U (n = 120) **=** –24.1 ± 27.8 (p<0.001)

THC/Cannabinoid					
Freeman	n = 630	Randomized placebo control trial (2 treatment groups, 1 placebo)	2.5 mg of THC equivalent or 1.25 mg of cannabidiol	Placebo	**Change in UI episodes from baseline:** Placebo (n = 81) = 0.822 (18%) THC (n = 86) = 0.666 (33%) Cannabis extract (n = 88) = 0.616 (38%) **Pad Test:** Mean difference combined cannabis groups vs placebo = 52.1 ml, (95% CI = 13.4-90.0 ml, p = 0.001) **Urodynamic Measures:** Trend to increasing voided volume for treatment groups, not statistically significant
Kavia	n = 135	Double blind randomized controlled trial, parallel group	Oral mucosal spray containing 2.7 mg THC, 2.5 mg CBD (Sativex)	Placebo oral mucosal spray	**Daily UIEs:** Placebo (n= 64) adjusted mean = -0.98 Sativex (n = 60) adjusted mean = -1.08 (p = 0.569) **Total Number of voids per 24 hour:** Placebo (n= 64) adjusted mean = -0.9 Sativex (n = 60) adjusted mean = -1.75 (p = 0.007) **Number of daytime voids:** Placebo (n= 64) adjusted mean = -0.66 Sativex (n = 60) adjusted mean = -1.23 (p = 0.044) **Nocturia episodes:** Placebo (n= 64) adjusted mean = -0.24 Sativex (n = 60) adjusted mean = -0.52 (p = 0.01)

	Void Urgency Episodes: Placebo (n= 64) adjusted mean = -1.12 Sativex (n = 60) adjusted mean = -1.88 (p = 0.07) **Bladder symptom severity:** Placebo (n= 66) adjusted mean = -1.05 Sativex (n = 61) adjusted mean = -2.21 (p = 0.001) **Incontinence QOL:** Placebo (n= 61) adjusted mean = 10.4 Sativex (n = 59) adjusted mean = 14.3 (p = 0.166) **Patient Global Impression of Change:** Placebo (n= 67) 58% improved Sativex (n = 61) 84% improved (p = 0.005)

Table 2: Methods of Assessment of Bladder Dysfunction

Study	Method of Assessment of Bladder Dysfunction
Fader	**Bladder diary**: frequency and volumes to determine baseline bladder dysfunction
Freeman	**Bladder diary**: 3 day diary recording number of UI episodes **United Kingdom Neurological Disability score (UKNDS) and Kings Health questionnaire** **Urodynamic Study**
Gajewski & Awad	**Urodynamic Study**: spontaneous, uninhibited contraction more than 15 cm of water with maximum cystometric capacity less than 300 ml
Ginsberg	**Bladder Diary/Self report**: 14 or more UIEs per week **Urodynamic Study**: Measurements of maximum cystometric capacity and maximum detrusor pression
Kavia	**Bladder Diary:** Time and number of doses of study medication, frequency of UIEs, micturition, feelings of urgency, nocturia, number of incontinence pads used **Pad Weight and daily voided volume**: collected for 3 days per week during baseline and weeks 7 and 8. **Incontinence Quality of life (I-QOL)**: 0-10 NSR of their overall bladder condition Patient Global Impression of Change (PGIC) **Urodynmaic Study**: Cystometry measuring post-mucturition residual volumes
Hebjorn	**Urodynamic Measurements**: Residual urine, volume at first contraction, effective volume at first bladder contraction, amplitude at first bladder contraction

Table (s) 3: All Study Characteristics

3.1

Fader 2007	
Methods/Study information	**Recruitment/Context**: MS Society user publications and via clinical continence/MS specialists. **Design:** Blind double cross-over trial
Patients/ Participants	**n** = 57 (51 Female) **Age**: 31-72

	Years with MS diagnosis: 1-21+ **Mobility characteristics**: Walks independently-Wheelchair always **Inclusion Criteria:** 1.Adults with a diagnosis of MS 2. Previous benefit from or were using oral antimuscarinic treatment 3. Performing intermittent catheterization **Exclusion Criteria:** 1. Symptomatic UTI 2. Inability to tolerate oxybutynin IR 3. potential or actual pregnancy
Interventions **Comparator** **Duration**	Intervention: Up to 4 syringe solutions of atropine every 24 hours OR Oral Oxybutynin Patients randomly received: 1. Atropine injection and placebo oral medication OR 2. Placebo injection and oral Oxybutynin Comparator: Injection of Atropine Solution to Oral Oxybutynin Duration: 2 weeks
Primary Outcome Measures	Bladder Capacity No. of voiding frequency No. incontinence events
Secondary Outcome Measures	Side Effects Quality of Life
Results/Conclusions	**Bladder Capcity (mL) reported in Mean +/-SD**: Oxybutynin = 55.5 (67.2) Atropine = 79.6 (89.6) Atropine increase is greater however not significant p= 0.053 **No. of voiding frequency** Oxybutynin = -1.2(1.8) Atropine = -1.6 (2.0) **No. of Incontinence events** Oxybutynin = - 0.9 (1.6) Atropine = -0.9(1.7) **Side Effects**: Main side effect = dry mouth. Mean change in side effect score (better) Statistically significant for Atropine treatment group **QOL:** Differences in sleep and emotions between treatments

	significantly better for Atropine group

3.2

Ginsberg (2013),(2011), Cruz (2011)	
Methods/Study information	International Multicenter, Randomized double-blind, placebo-controlled trials (pooled data)
Patients/ Participants	**n** = 691 (n=381 MS) (n=310 SCI) Age: 18-80 MS (clinically stable for _3 mo before screening and an Expanded Disability Status Score _6.5) **Inclusion Criteria:** 1. >/= to 14 UI episodes per week 2. Managed with inadequate response with anticholinergic for their UI
Interventions Comparator Duration	Intervention: Randomized 1:1:1 to receive 1-mL intradetrusor injections of placebo, onabotulinumtoxin A: 200U, 300U Comparator: placebo Duration: followed for 52 weeks. Evaluated at weeks 2,6, 12
Primary Outcome Measures	UI episodes/week No. of voluntary voids/week MCC IDC
Secondary Outcome Measures	QOL AEs
Results/Conclusions	**UI episodes**: 6 week follow-up = mean weekly decreases in treatment groups with Onabotulinumtoxin A (no significant difference between dose) Placebo = -14.0, 200U = -22.6, 300u = -24.0. (P <.05) **No. of voluntary voids/week**: at 6 week follow up treatment group (non-catheterizing) decreased non-dose dependent (p<.05) **MCC**: Increase from baseline at 6 weeks p<.001 **IDC**: decrease in occurrence at 6 weeks: placebo = 18.5%, 200U = 68.0%, 300U = 70.9% p <0.001 QOL: Considerably greater than 11 points (mean change) which is minimally important difference AEs Most common was UTI- was higher in OnabotulinumA- treated

	compared to placebo p<0.001 Urinary retention- 37.4% in 200U, 47.1% in 300U, 4.5% in placebo – if resulted in clean intermittent catherization satisfaction was no affected.

UI = Urinary Incontinence
QOL = Quality of life
AEs = adverse effects
IDC = involuntary detrusor contraction
MCC = maximum cytometric capacity

3.3

Freeman 2006	
Methods/Study information	**Recruitment/Context**: Patients recruited from 33 neurology and rehabilitation centers in the UK. **Design:** Randomized placebo control trial **(2 treatment groups, 1 placebo)**
Patients/ Participants	**n** = 630 **Age**: 18–64 years, means from 3 groups: 50.6, 49.9, 50.2 **Forms of MS**: relapsing/remitting, Primary progressive, secondary progressive (2.3,9.3, 4.9), (22.7, 20.9, 28.4), (75.0, 69.8, 66.7) for 3 groups respectively with clinically definite or laboratory-supported multiple sclerosis who, in the opinion of the treating doctor, had had stable disease **Inclusion Criteria:** 1.Adults with a diagnosis of MS 2. Urge incontinence episodes 3. Permanent catheter patients **Assessment of Incontinence** - 3 day urinary diary – number of UIEs - Kingdom Neurological Disability score - Urodynamic studies
Interventions Comparator Duration	**Intervention:** 2.5 mg of THC equivalent or 1.25 mg of cannabidiol **Comparator:** Placebo **Duration:** 15 weeks
Primary Outcome	UIEs- judged by 3 day diary

Measures	
Secondary Outcome Measures	Side Effects Quality of Life
Results/Conclusions	**UIEs**: Cannabis extract group: adjusted change from baseline 38% THC group: adjusted change from baseline = 33% Placebo: 18% p<.01 Significant treatment effect over placebo: Cannabis extract = 25% reduction p=0.005, THC 19% reduction p=0.039 Treatment benefit at 15 weeks (improvement in bladder function) = Cannabis extract = 44%, THC = 40%, placebo = 33% **Quality of life** Assessed by King's Health Questionnaire- unclear results **AEs** UTI Others not reported

3.4

Kavia, 2009	
Methods/Study information	**Recruitment/Context**: Patients recruited from 15 centres (9 in UK, 3 in Belgium, 3 in Romania) **Design:** Double blind randomized controlled trial, parallel group trial
Patients/ Participants	**n** = 135 **Age**: Mean 47.7 **Inclusion Criteria:** 1.Adults with a diagnosis of MS and OAB 2. On a stable dose of anticholinergic medication for at least 14 days prior to study entry and remained unchanged during study 3. at least 3 incontinence episodes over 5 consecutive days during the baseline period **Exclusion Criteria**

	1. Presence of symptomatic UTI 2. Performing intermittent self-catheterization 3. History of use of cannabis or cannabis derived medicines within 7 days of study 4. Hypersensitivity to cannabinoids 5. History of major psychiatric disorder 6. Severe personality disorder or history of substance abuse 7. Severe cardiovascular disorder, history of epilepsy, or significant renal or hepatic impairment 8. Concomitant use of fentanyl, levodopa, sildenafil citrate **Assessment of Incontinence** - Self reporting voiding diary
Interventions **Comparator** **Duration**	**Intervention:** Sativex (Naboximols)- endocannabinoid system modulator derived from strains of Cannabis sativa L. plants- extraction produces principle cannabinoids (THC, CBD) mixed and formulated with other products such as terpenes. Administered as pump-action oromucosal spray, 2.7 mg THC, 2.5 mg CBD Max 8 sprays in 3-h period, and 48 in any 2 day periods- subjects self titrated to their optimal dose **Comparator:** Placebo oral mucosal spray not containing cannabinoid extracts **Duration:** 10 weeks
Primary Outcome Measures	Reduction in number of UI episodes from baseline to end of treatment Incidence of nocturia and urgency, overall bladder condition
Secondary Outcome Measures	QOL Tolerability PGIC
Results/Conclusions	**UI episodes reported in mean change from baseline**: Sativex group = -1.08 Placebo = -0.98 P = 0.569- not statistically significant **Total number of voids per 24 hours:** Sativex group = -1.75 Placebo = 0.9 P= 0.007 **Void urgency episodes:** Sativex group = -1.88 Placebo = -1.12 P = 0.07

	***Overall bladder condition** Sativex group = -2.21 Placebo = -1.05 P =0.001 QOL: Sativex = 14.3 Placebo = 10.4 P=0.166 PGIC: Sativex = 84% improved Placebo = 58% improved P = 0.005 Tolerability: well tolerated Most common AEs= Dizziness UTI Headache

PGIC = patients global impression of change

3.5

Gajewski_Awad, 1985	
Methods/Study information	**Design:** Prospective randomized study
Patients/ Participants	**n** = 34 **Inclusion Criteria:** 1.Adults with a diagnosis of MS 2. Patients with detrusor hyperreflexia (spontaneous, uninhibited contraction more than 15 cm) Assessed by Modified Kurtzke scale- specifics not provided **Exclusion Criteria:** 1. presence of UTI **Assessment of hyperreflexia**

	- Urodynamic studies- cystometrography, videocystography, electromyography
Interventions Comparator Duration	**Intervention:** 19 patients received oxybutynin 5mg orally 3 times a day, 15 received propantheline 15 mg orally 3 times a day Clinical response categorized as good, fair and poor **Duration:** 6-8 weeks
Primary Outcome Measures	Change in maximum cystimetric capacity Change in height of contraction after treatment Grade of symptoms: frequency, nocturia, urgency, urge incontinence Comparing the two treatments
Secondary Outcome Measures	Side Effects (Dry mouth, nausea, anorexia, abdominal distention, constipation, dizziness, blurred vision , headache)
Results/Conclusions	Clinical response: Oxybutynin: Good = 10/15(67%) Fair = 2/15 (13%) Poor = 3/15 (20%) Propatheline: Good = 4/11 (26%) Fair = 1/11 (9%) Poor = 6/11 (55%) Decrease in severity of symptoms more pronounced in Oxybutynin group (Frequency, Nocturia, Urgency, Urge incontinence) $p<0.05$ Mean maximum cystometric capacity larger in Oxybutynin group (282.5 +/117.9 $p<0.05$ vs 198.3 +/129 $p>0.05$) No statistically significant change in height of contractions in either group Side effects in 13 patients in Oxybutynin group (68%) vs 8 (53%) in Propatheline Overall- Oxybutynin is more effective than Propatheline

3.6

Hebjorn (1977)	
Methods/Study information	**Recruitment/Context**: Surgical Department, Gentolfte Hosptial, Hellerup **Design:** double blind crossover clinical trial
Patients/ Participants	**n** = 34 (26 Female, 8 males) **Age**: median age 46.6 **Duration of urological symptoms:** Median=8.2 **Inclusion Criteria:** Patients with MS and urological symptoms (urgency and urge incontinence due to detrusor hyperreflexia) **Exclusion Criteria** Patients with severe heart failure, glaucoma, respiratory insufficiency, or marked intravesical obstruction Patients catheterized four times during the trial Initial cystometric recording
Interventions Comparator Duration	**Intervention:** 1. Methantheline bromide, 50 mg, (Banthine) 2. Flavoxate chloride, 200 mg QID (Urispas) 3. Meladrazine tartrate, 150 mg QID (Lisidonil) **Comparator:** Above mentioned treatments **Duration:** 14 days
Primary Outcome Measures	Patients opinion of effect of compounds, residual volume measurement (ml) Urgency, Urge incontinence Bladder volume at first contraction
Secondary Outcome Measures	Side Effects
Results/Conclusions	Primary: 1. Patients opinion: - 18/27 patients preferred Methantheline bromide - 60% concordance between evaluation of cystometric pattern and patients opinion 2. Number of micturitions: - Methantheline bromide and Meladrazine tartrate lowered number, statistically significant

	3. None of therapies significantly reduced number of incontinence episodes 4. None of therapies changed residual volume 5. Bladder volume at first contraction- MEthatheline Bromide increased (significant) - when corrected for residual urine, none resulted in significant increase in bladder volume at first contraction Secondary: SEs: All drugs caused various SEs Meladrazine Tartrate was only agent causing severe SEs- discontinued Main SEs: Methantheline bromide- dry mouth, Headache, nausea Meladrazine Tartrate: Nausea, vomiting, headache, vertigo, depression Flavoxate chloride: Nausea, vomiting, headache, fatigue, dizziness Final conclusions: - Detrusor hyperreflexia treated better with Methantheline bromide than flavoxate chloride and meladrazine tartrate

Table 4: Characteristics of Excluded Studies

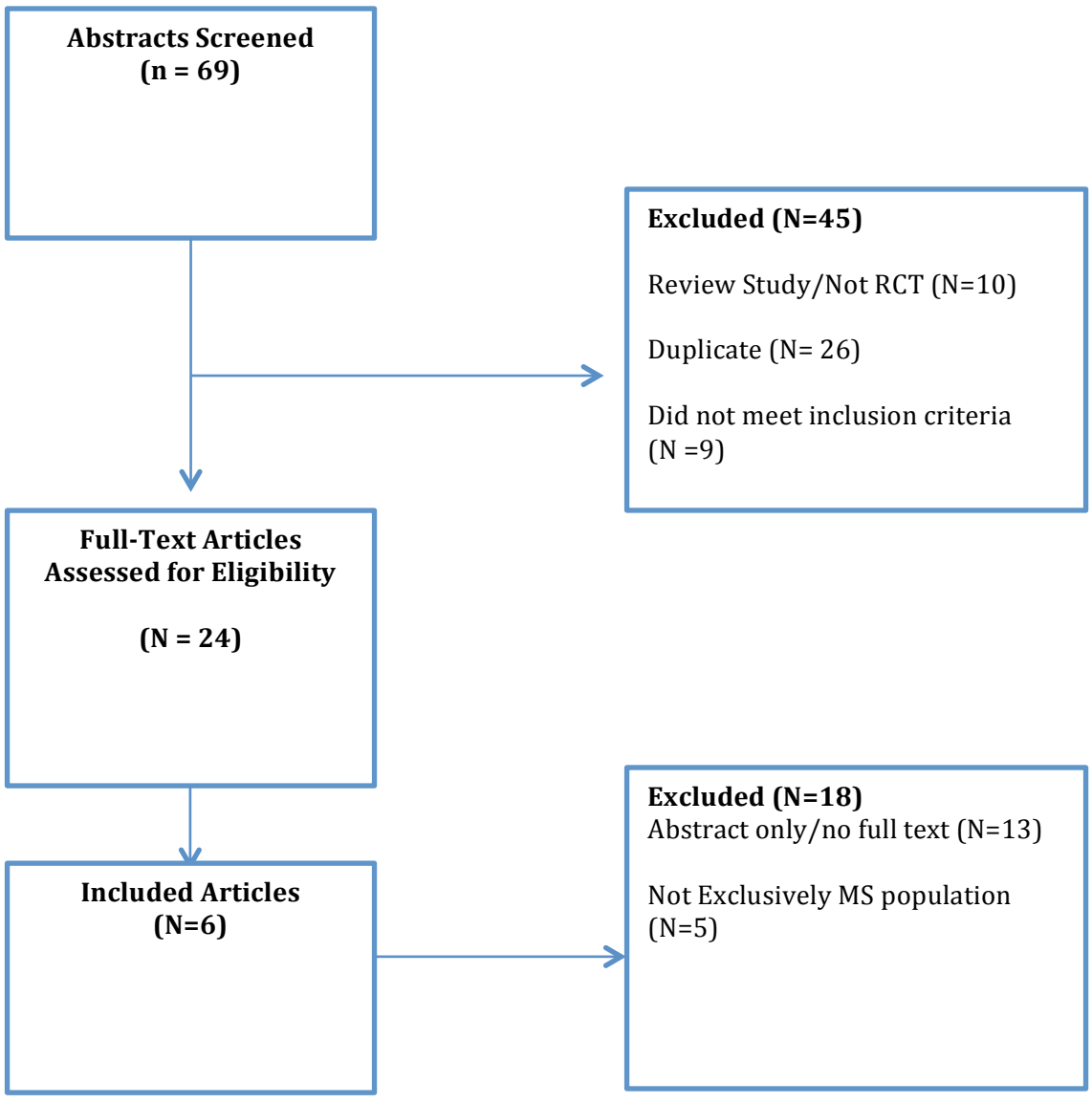
Study	Reason for Exclusion
Panicker (2014)	Abstract only
Denys (2014)	Abstract only
Chartier-Kastler (2013)	Abstract only
Dmochowski (2013)	Abstract only
Lucio (2013)	Abstract only
Sievert (2011)	Abstract only
Chancellor (2011)	Abstract only
Herschorn (2011)	Not exclusively MS patients (results not presented separately)
Ethans (2003)	Not exclusively MS patients (results not presented separately)
Grise (2010)	Not exclusively MS patients (results not presented separately), and no comparator
Ehren (2007)	Not exclusively MS patients (results not presented separately)
Schurch (2007)	Not exclusively MS patients (results not presented separately)
Kim (2003)	Not exclusively MS patients (results not presented separately)
Gobbi (2011)	Not a RCT
Amend (2008)	Not exclusively MS patients (results not presented separately)
Rovner (2013)	Not exclusively MS patients (results not presented separately)

Table 5: Bias Risk Assessment

Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Reporting	Selective Outcome Reporting	Other Sources of Bias	Overall Risk of Bias
Fader (2007)	Low	Low	Low	Low	Unclear	Low	Low
Ginsberg (2013), (2011), Cruz	Low	Low	Low	Low	Low	Low	Low
Freeman (2006)	Low	Low	Low	Low	Low	Unclear	Low
Kavia (2009)	Low	Low	Low	Low	Unclear	Unclear	Low
Gajewski, Awad (1985)	Unclear	Unclear	Unclear	Low	Unclear	High	Unclear
Hebjorn (1977)	Unclear	Unclear	Low	Low	Unclear	High	Unclear

Figures

Figure 1: Study Flow Diagram



Figure(s) 2:

Representation of Common Side Effects

Figure 2.1: UTI side effect in relevant studies

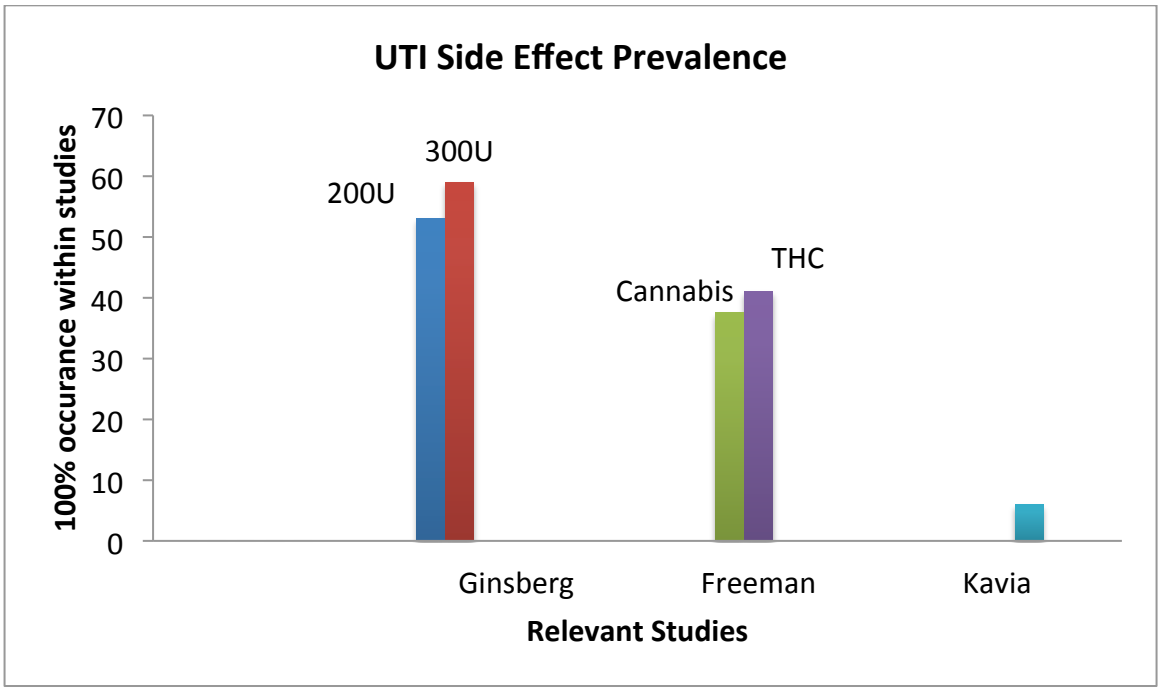


Figure 2.2: Fader Study Oxybutynin vs. Atropine

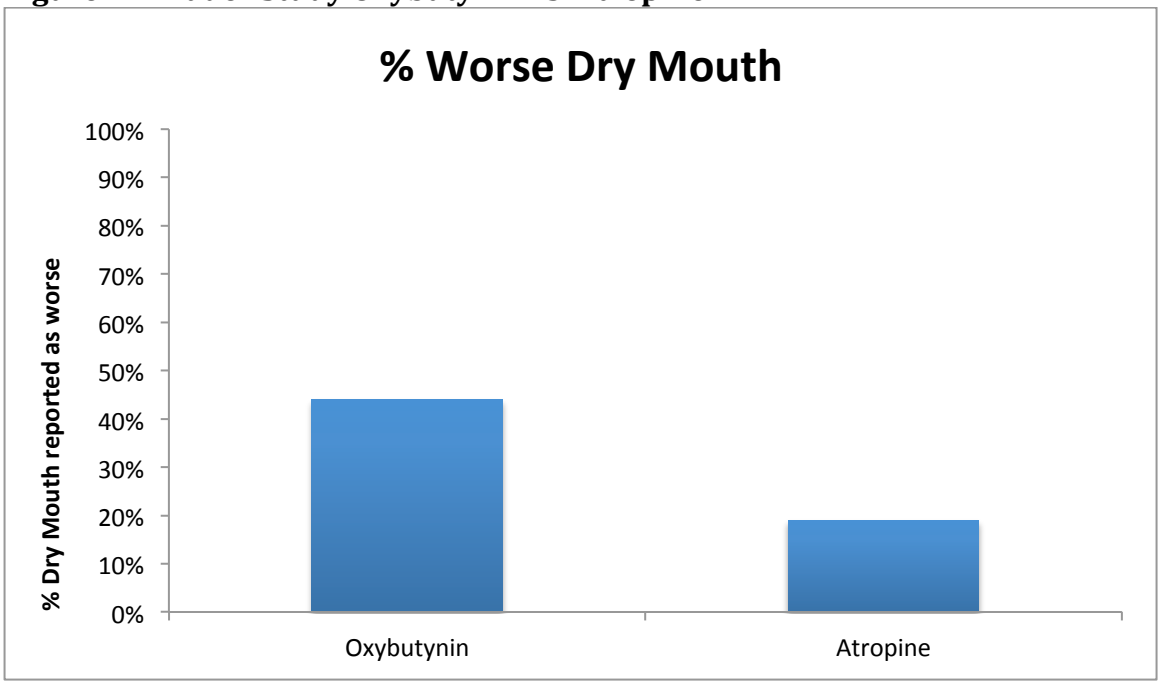


Table 6: Studies not quantifying Side effects

Hebjorn	Nausea, vomiting, headache, vertigo, and depression, fatigue, and dizziness
Gajewski and Awad	Dry mouth, nausea, anorexia, abdominal pain, constipation, dizziness, blurred vision, and headache (68% Oxybutynin), (53% Propatheline)

Appendix 1: Search Strategy

#1(multiple sclerosis) or (demyelinating diseases) or (transverse myelitis) or (neuromyelitis optica) or (optic neuritis)
#2(encephalomyelitis acute disseminated) or (devic)
#3MeSH descriptor Multiple Sclerosis explode all trees
#4MeSH descriptor Demyelinating Diseases, this term only
#5MeSH descriptor Optic Neuritis explode all trees
#6MeSH descriptor Encephalomyelitis, Acute Disseminated, this term only
#7MeSH descriptor Myelitis, Transverse, this term only
#8incontinence
#9urinary frequency
#10urinary retention
#11urinar*
#12MeSH descriptor Urinary Incontinence explode all trees
#13MeSH descriptor Urinary Retention explode all trees
#14anticholinergic*
#15tolterodine
#16propiverine
#17oxybutynin
#18trospium
#19propantheline
#20flavoxate
#21methantheline OR solifenacin OR darifenacin
#22meladrazine
#23terodiline
#24resiniferatoxin
#25MeSH descriptor Flavoxate explode all trees
#26MeSH descriptor Flavones explode all trees
#27MeSH descriptor Muscarinic Antagonists explode all trees
#28(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#29(#8 OR #9 OR #10 OR #11 OR #12 OR #13)
#30(#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27)
#31(#28 AND #29 AND #30)

((("Urinary Incontinence"[Mesh]) OR ("Urinary Retention"[Mesh:noexp]) OR ("urinary symptom*") OR (incontinence) OR ("urinary frequency") OR ("urinary retention") OR ("urinar*")) AND (("Flavoxate"[Mesh:noexp]) OR ("Flavones"[Mesh]) OR ("Muscarinic Antagonists"[Mesh:noexp]) OR ("Propantheline"[Mesh]) OR ("Imipramine"[Mesh:noexp]) OR (anticholinergic*) OR (tolterodine) OR (propiverine) OR (oxybutynin) OR (trospium) OR (propanthelline) OR (propantheline) OR (flavoxate) OR (solifenacin) OR (methanteline) OR (darifenacin) OR (imipramine) OR (amitryptiline))) AND ((((("Multiple Sclerosis"[mh]) OR ("Myelitis, Transverse"[mh:noexp]) OR ("Demyelinating Diseases"[mh:noexp]) OR ("Encephalomyelitis, Acute Disseminated"[mh:noexp]) OR ("Optic Neuritis"[mh])) OR ((("multiple sclerosis") OR ("neuromyelitis optica") OR ("transverse myelitis") OR

(encephalomyelitis) OR (devic) OR ("optic neuritis")) OR ("demyelinating disease*") OR ("acute disseminated encephalomyelitis"))) AND (((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT ((animals[mh]) NOT ((animals[mh]) AND (human[mh])))))

(('urine incontinence'/exp) OR ('urine retention'/exp) OR ('urinary symptom':ab,ti OR incontinence:ab,ti) OR (urinar*:ab,ti) OR ('urinary frequency':ab,ti) OR ('urinary retention':ab,ti)) AND (('flavoxate'/exp) OR ('flavone derivative'/exp) OR ('muscarinic receptor blocking agent'/exp) OR ('propantheline bromide'/exp) OR ('imipramine'/exp) OR (anticholinergic*:ab,ti OR tolterodine:ab,ti OR propiverine:ab,ti) OR (oxybutynin:ab,ti OR trospium:ab,ti OR propanthelline:ab,ti OR solifenacin OR methanteline OR darifenacin OR propantheline:ab,ti) OR (flavoxate:ab,ti OR imipramine:ab,ti OR amitryptiline:ab,ti))) AND ((('encephalomyelitis'/exp) OR ('demyelinating disease'/exp) OR ('multiple sclerosis'/exp) OR ('myelooptic neuropathy'/exp) OR ('multiple sclerosis':ti,ab) OR ('neuromyelitis optica':ab,ti) OR (encephalomyelitis:ab,ti) OR (devic:ti,ab)) AND (('crossover procedure'/exp) OR ('double blind procedure'/exp) OR ('single blind procedure'/exp) OR ('randomized controlled trial'/exp) OR (random*:ab,ti) OR (factorial*:ab,ti) OR (crossover:ab,ti) OR (cross:ab,ti AND over:ab,ti) OR (placebo:ab,ti) OR ('double blind':ab,ti) OR ('single blind':ab,ti) OR (assign*:ab,ti) OR (allocat*:ab,ti) OR (volunteer*:ab,ti))) AND [humans]/lim AND [embase]/lim