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A Systematic Review of the Management of Autonomic Dysreflexia Following Spinal Cord Injury

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Abstract

OBJECTIVE—To systematically review the clinical evidence on strategies to prevent and manage autonomic dysreflexia (AD).

DATA SOURCES—A key word search of several databases (Medline, CINAHL, EMBASE and PsycInfo), in addition to manual searches of retrieved articles, was undertaken to identify all English-language literature evaluating the efficacy of interventions for AD.

STUDY SELECTION—Studies selected for review included randomized controlled trials (RCTs), prospective cohort studies, and cross-sectional studies. Treatments reviewed included pharmacological and non-pharmacological interventions for the management of AD in individuals with spinal cord injury. Studies that failed to assess AD outcomes (e.g. blood pressure) or symptoms (e.g., headaches, sweating) were excluded.

DATA EXTRACTION—Studies were critically reviewed and assessed for their methodological quality by two independent reviewers.

DATA SYNTHESIS—Thirty-one studies were assessed, including 6 RCTs. Preventative strategies to reduce the episodes of AD caused by common triggers (e.g. urogenital system, surgery) primarily were supported by Level 4 (pre-post studies) and Level 5 (observational studies) evidence. The initial acute non-pharmacological management of an episode of AD (i.e. positioning the patient upright, loosening tight clothing, and eliminating any precipitating stimulus) is supported by clinical consensus and physiological data (Level 5 evidence). The use of

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antihypertensive drugs in the presence of sustained elevated blood pressure is supported by Level 1 (prazosin) and Level 2 evidence (nifedipine and prostaglandin E2).

CONCLUSIONS—A variety of options are available to prevent AD (e.g., surgical, pharmacological) and manage the acute episode (elimination of triggers, pharmacologic); however, these options are predominantly supported by evidence from non-controlled trials and more rigorous trials are required.

Keywords

autonomic dysreflexia; management; pharmacological; spinal cord injury

INTRODUCTION

Autonomic dysreflexia (AD) is a well-known clinical emergency in individuals who have suffered a spinal cord injury (SCI). It especially occurs in individuals with an injury at level T6 or above.– An episode of AD is characterized by the acute elevation of arterial blood pressure (BP) and bradycardia (slow heart rate), although tachycardia (rapid heart rate) also may occur. Objectively, an increase in systolic BP greater than 20–30 mmHg is considered a dysreflexic episode. However, because the usual resting arterial BP in individuals with cervical and high thoracic SCI is approximately 15 to 20 mmHg lower than in able-bodied individuals,, acute elevation of blood pressure to normal or slightly elevated ranges could indicate AD in this population. AD can present with a variety of symptoms (Table 1) and can vary in intensity from asymptomatic,, to mild discomfort and headache, to a life threatening emergency, such as when systolic blood pressure climbs to 300 mmHg. Untreated episodes of AD may have serious consequences, including intracranial hemorrhage, retinal detachment, seizures and death.–

It has been observed that, the higher the injury level, the greater the degree of clinically-manifest cardiovascular dysfunction.– Another important factor relating to the severity of AD is the completeness of the spinal injury; only 27% of incomplete tetraplegics present with signs of AD, in comparison with 91% of tetraplegics with complete lesions. While AD occurs more often in the chronic stage of SCI at or above the 6th thoracic segment, there also is clinical evidence of episodes of AD in the first days and weeks after injury.,

A variety of non-noxious or noxious stimuli can trigger episodes of AD., However, AD most commonly is triggered by irritation of the urinary bladder or colon. Physiologically, AD is caused by a massive sympathetic discharge triggered by either a noxious or non-noxious stimulus originating below the level of the SCI. Numerous reports of AD have been described in the literature. Symptoms usually are short-lived, either due to treatment or because the episode itself is self-limiting. However, there have been reports of AD, triggered by a specific stimulus, being sustained for periods ranging from days to weeks. Numerous different mechanisms have been proposed as potentially responsible for the development of AD. It is known from animal experiments that autonomic instability following SCI results from changes occurring within the spinal and peripheral autonomic circuits, both in the acute and chronic stages following injury., – Destruction of the descending vasomotor pathways results in the loss of inhibitory and excitatory supraspinal input to the sympathetic

preganglionic neurons, and is currently considered to be the predominant factor underlying the unstable blood pressure that tends to follow SCI. Furthermore, the results of numerous animal and human studies suggest that changes within the spinal cord (specifically spinal sympathetic neurons and primary afferents) underlie the abnormal cardiovascular control and AD following SCI., – Altered sensitivity of peripheral alpha-adrenergic receptors (receptors in the sympathetic nervous system) is one mechanism that may contribute.,

The purpose of this systematic review has been to provide an overview of the clinical evidence supporting the efficacy of the various strategies currently used to prevent and manage AD in the SCI population. These findings were part of the *Spinal Cord Injury Rehabilitation Evidence* project, the details of which are available at www.scireproject.com.

METHODS

A keyword literature search of original articles, previous practice guidelines and review articles was conducted, so as to identify all English-language literature, published from 1950 to 2007, evaluating the efficacy of any intervention related to AD in the SCI population. Population key words - spinal cord injury, paraplegia, tetraplegia, and quadraplegia - were individually paired with autonomic dysreflexia, autonomic, dysreflexia, blood pressure, nifedipine, phenazopyridine, beta blockers, detrusor hyperreflexia and detrusor dyssynergy. Studies which did not have outcomes evaluating AD (e.g. blood pressure) or AD symptoms (e.g., headaches, sweating) were excluded.

The keyword search yielded 2168 articles related to AD following SCI. A total of 2138 articles were removed from the sample, because they did not have outcomes evaluating AD or AD symptoms, leaving 31 articles from which data could be extracted.

The rigor and quality of each study was scored by two independent reviewers. We used the 11-item *Physiotherapy Evidence Database* (PEDro) Scale to score RCTs, and a modified version of the *Downs and Black* (D&B) Tool to score non-RCTs. Maximum scores for the PEDro and D&B instruments are 10 and 28, respectively, with higher scores indicating better methodological quality.

The description by Sackett *et al.* of levels of evidence was used to draw conclusions about the studies based on the study design. We collapsed Sackett's levels of evidence into 5 categories, where *Level 1* evidence was attributed to 'good' to 'excellent' RCTs with a PEDro score ≥6; and *Level 2* evidence corresponded to RCTs with PEDro scores ≤5, non-randomized prospective controlled trials, and cohort studies. Evidence from case control studies was assigned to *Level 3. Level 4* corresponded to evidence from pre-post/post-test or case-series; and evidence was categorized as *Level 5* if it was derived from observational reports, case reports involving a single subject, or clinical consensus. We did not require a minimum sample size per study, due to the relatively limited number of publications in this field. Note that it is possible to have a small RCT (Level 2), but with poor quality (e.g., high drop-out rate, incorrect statistical analyses).

RESULTS

The 31 selected articles were categorized according to (1) preventative strategies to reduce episodes and symptoms of AD from common triggers (e.g., from the urogenital system, gastrointestinal system, general surgery and exercise);– and (2) therapeutic management strategies, either acute or chronic, for AD., – The management of AD included both non-pharmacological and pharmacological strategies. The pharmacological studies assessed nifedipine (n=5),– captopril (n=1), terazosin (n=3),– prazosin (n=1), phenoxybenzamine (n=2),, prostaglandin E2 (n=1), sildanefil (n=1), and nitrates (n=1). Only 6 of the 31 studies were RCTs., , , , , . The RCTs had PEDro scores ranging from 5 to 10 (good to excellent). The majority of the non-RCT trials had a low Downs and Black score with the majority below 15 out of 28 points.

A. Preventative Strategies

The largest proportion of preventative studies focused on the management of AD triggered by stimuli originating within the urogenital system (n=14). These studies assessed interventions intended to prevent AD during the evaluation of urinary bladder function and during invasive procedures (n=9),– anorectal procedures (n=2),, pregnancy and labour (n=4),– general surgery (n=2),, and functional electrical stimulation (FES) exercise (n=1). The characteristics and outcomes of studies assessing preventative strategies for AD are presented in Table 2.

1. Prevention of AD during bladder procedures—Urinary bladder irritation or distention is the most widely-recognized trigger of AD following SCI., , The first proposed defense against AD triggered by urinary bladder irritation consists of a bladder management program and continuous urological follow-up.– An established bladder management program, with intermittent catheterization or an indwelling Foley catheter, allows individuals with SCI to plan for bladder emptying when convenient or as necessary. However, no studies were identified which specifically assessed the effect of bladder management programs on AD symptoms.

Urological follow-up includes annual urodynamic evaluations and cystoscopy, depending upon the bladder management program. During the last decade, these strategies have decreased the frequency of urinary tract infections and the development of renal failure in individuals with SCI., However, conservative management is not always successful, and alternative strategies (e.g., Botulinum toxin, capsaicin, anticholinergics, sacral denervation and bladder and urethral sphincter surgery) are required to decrease afferent stimulation from the urinary bladder, thereby to prevent the development of AD. In addition, urodynamic and cystoscopy procedures themselves are associated with significant activation of urinary bladder afferents and have the potential to trigger AD;, , , consequently, strategies to reduce afferent stimulation are necessary during these procedures.

1a. Botulinum Toxin for the Prevention of AD Resulting from Detrusor-sphincter Dyssynergia: Two pre-post test studies (n=42), found that the injection of Botulinum toxin into the detrusor muscle or bladder sphincter is an effective method of treating urinary incontinence secondary to neurogenic detrusor over-activity and bladder sphincter

dyssynergia. In these conditions, injections of the Botulinum toxin either allow for increased urinary bladder capacity (i.e., reduced over-activity of the bladder) or facilitate the evacuation of urine (reduced bladder sphincter dyssynergia). The duration of the effect has been reported to be up to 9 months. Both studies assessing the use of Botulinum toxin were Level 4 and demonstrated a positive treatment effect. In fact, following Botulinum toxin treatment for AD associated with bladder emptying, AD appeared to disappear completely in 3 individuals with tetraplegia, with no recurrence even after the toxin presumably had lost all effect.

Conclusion: Based upon the results of 2 pre-post studies,, there is Level 4 evidence that Botulinum toxin injections into the detrusor muscle may be a safe and effective therapeutic option in SCI patients who perform clean intermittent self-catheterization and have incontinence that is resistant to anticholinergic medication.

1b. Intravesical Capsaicin for the Prevention of AD Resulting from Bladder Sphincter Dyssynergia: One RCT (n=23) and one pre-post study (n=7) evaluated the effect of capsaicin, an extract from red peppers. Capsaicin exerts a selective action on certain sensory nerves, most notably those involved in reflex contractions of the bladder after SCI. In their pre-post study, Igawa *et al.* demonstrated that intravesical capsaicin diminishes the number of episodes of AD in patients with SCI during catheterization, suggesting a therapeutic potential of intravesical capsaicin for both AD and detrusor hyperreflexia in SCI patients. Giannantoni *et al.*'s high-quality RCT (PEDro=6) used an analogue of capsaicin (resiniferatoxin RXT) which is more than 1,000 times more potent than capsaicin itself at desensitizing C-fiber bladder afferents, and also identified a reduced number of AD episodes among those receiving active treatment. The investigators also found that the intra-vesical administration of resiniferatoxin was superior to that of intravesical capsaicin, in terms of urodynamic results and clinical benefits in SCI patients within 60 days of treatment, and did not cause the inflammatory side effects associated with capsaicin. However, the long-term effects of capsaicin or resiniferatoxin on AD were not evaluated.

Conclusion: Based upon a single pre-post study, there is Level 4 evidence that intra-vesical capsaicin may be effective at reducing the frequency of AD in SCI. Based on a single RCT, there is Level 1 evidence that intravesical resiniferatoxin is effective at reducing the number of episodes of AD in patients with SCI, and that it is more effective than intravesical capsaicin.

1c. Anticholinergics for the Prevention of AD: Anticholinergics are a class of medication that inhibit the binding of the neurotransmitter acetylcholine to its receptors. Acetylcholine is released by the parasympathetic nerve fibers that innervate the urinary bladder and contribute to detrusor contraction and the activation of bladder afferents. These afferent stimuli are responsible for the activation of spinal sympathetic circuits that triggers AD. Therefore, anticholinergic agents might decrease afferent activation, and consequently AD. However, only one study has examined the use of anticholinergic drugs, and it was a cross-sectional observational study (n=48). Giannantoni and co-investigators found that the use of

anticholinergic drugs was not associated with a reduced incidence of AD, unless it resulted in detrusor areflexia.

Conclusion: Based upon Level 5 evidence from a single cross-sectional correlational study, anticholinergics are not associated with a reduced incidence of AD episodes.

1d. Sacral Denervation: When post-SCI detrusor hyperreflexia does not respond to conservative treatment, and patients are not eligible for ventral sacral root stimulation for electrically-induced micturition, sacral bladder denervation may be considered a stand-alone procedure to treat urinary incontinence and AD. Two Level 4 studies (n=19), on sacral denervation have generated conflicting results. Hohenfellner *et al.* concluded that sacral bladder denervation is a valuable treatment option, based upon their study in which the procedure eliminated detrusor hyperreflexia and AD in all 9 subjects. However, Schurch *et al.* found that complete bladder deafferentation did not abolish AD during bladder urodynamic investigations.

Conclusion: Based upon two Level 4 studies,, it can be said that there is conflicting evidence regarding the effectiveness of sacral deafferentation in the prevention of AD.

1e. Bladder and Urethral Sphincter Surgery: The association between episodes of AD and the presence of detrusor sphincter dyssynergia, and high intravesical and urethral pressure has led to the development of surgical procedures to alleviate voiding dysfunction and, consequently, AD in patients with SCI. Two surgical studies, included indicators of AD (e.g., blood pressure changes). Although the older study, by Barton *et al.*, demonstrated a reduced incidence of AD post external sphincterotomy, such procedures now are rarely performed, because they are associated with significant risks, including hemorrhage and erectile dysfunction, and the need for repeat procedures. Thus, alternatives have been investigated, such as urethral stents and Botulinum toxin (Botox) injections. Augmentation enterocystoplasty has demonstrated long-term success, based upon urodynamic evaluations, and has been found to reduce the symptoms of AD. Enterocystoplasty with a Mitrofanoff Procedure has become a more frequent choice of bladder augmentation in individuals with SCI, due to more favorable long-term outcomes.

Conclusion: Based upon three pre-post/case series,, there is Level 4 evidence that urinary bladder surgical augmentation may result in a decrease in intravesical and urethral pressure, and may diminish or resolve episodes of AD. Enterocystoplasty may result in better long-term viability, relative to sphincterotomy.

2. Prevention of AD during Anorectal Procedures—Pain or irritation within the colorectal area is the second most common cause of AD. Constipation, hemorrhoids, and anal fissures frequently are observed in patients with SCI and contribute to episodes of AD., , , Furthermore, bowel routines in SCI individuals frequently involve digital stimulation that can trigger AD. Rectosigmoid distension and anal manipulation are common iatrogenic triggers of AD in this population. In two small RCTs (n=70),, topical and local anesthesia of the anorectal area were compared with respect to the prevention of AD during anorectal procedures. Investigators demonstrated that anoscopy, which involves stretching of the anal

sphincters, was a more potent stimulus for AD than flexible sigmoidoscopy, which involves gaseous distention of the rectosigmoid. Anal sphincter stretch and rectosigmoid distention, rather than mucosal stimulation, are likely nociceptive triggers for procedure-associated AD. In one randomized, double-blind, placebo-controlled trial, AD was not abolished during anorectal procedures by applying topical lidocaine in the rectum. However, in a later RCT, the same investigators demonstrated that intersphincteric anal block with lidocaine was effective at limiting anorectal procedure-associated AD. Both anoscopy and flexible sigmoidoscopy cause significant blood pressure elevation.

Conclusion: There is Level 1 evidence (from one RCT) that intersphincteric anal block with lidocaine limits the AD response in susceptible patients undergoing anorectal procedures. There is also Level 1 evidence (from one RCT) that topical lidocaine does not limit or prevent AD in susceptible patients during anorectal procedures.

3. Prevention of AD during Pregnancy and Labour—Based upon North American statistics, women represent a third of the SCI population. In the United states, approximately 3,000 women of childbearing age are affected by SCI each year. The ability of women to have children is not usually affected, once their menstrual cycle resumes. There are increasing numbers of women with SCI who become pregnant and have healthy babies. However, women with SCI are at high risk of developing uncontrolled AD during labor and delivery.,

Recognition and prevention of this life-threatening emergency is critical for the management of labor in women with SCI. In women with SCI, the onset of AD during labour is intermittently timed with uterine contractions. In the majority of women with SCI above T10, the uterine contractions may present only as abdominal discomfort, an increase in spasticity and AD. The results of numerous observational studies and case reports, as well as expert opinions recommend adequate anesthesia in women with SCI during labour and delivery, despite their apparent lack of sensation. However, only four studies (n=54)– with observational evidence have recorded management specific to AD during labour. Epidural anesthesia has been reported to be the best choice for the control of AD. The *American College of Obstetrics and Gynecology* emphasized that it is important that obstetricians caring for these patients are aware of the specific problems related to SCI.

Conclusion: With vaginal delivery or when cesarean delivery or instrumental delivery is indicated, adequate anesthesia (spinal or epidural if possible) is needed. There is Level 4 evidence (from a single case series and 2 observational studies), that epidural anesthesia is preferred and may be effective for most patients with AD during labor and delivery.

4. Prevention of AD during General Surgery—AD may be precipitated by a host of somatic and visceral noxious or non-noxious stimuli below the level of injury. Therefore, a variety of interventions have been used to decrease afferent information to the spinal cord, including peripheral anesthetic blocks, epidural anesthesia, general anesthesia, and even dorsal rhizotomy., , , , Despite the partial or total loss of sensation below the level of injury, it is important to recognize that surgical procedures or manipulations can initiate episodes of AD. Anesthesiologists and surgeons undertaking surgery on SCI patients must be aware of

the interactions of the anesthetic and its effects on AD, and how to prevent or manage AD during these procedures. Two observational studies, have revealed that AD is a common complication during general surgery in individuals with SCI. Up to 90 % of individuals with SCI undergoing surgery with topical anesthesia or no anesthesia develop AD. Moreover, the results of both studies suggest that patients at risk for AD can be protected, either by general or spinal anesthesia.

Conclusion: There is Level 5 evidence (from 2 observational studies), that indicate that patients at risk for AD may be protected against developing intra-operative hypertension by either general or spinal anesthesia. Anesthesiologists and surgeons dealing with SCI patients must know how to recognize AD syndrome, how to prevent its occurrence, and how to manage it once it occurs.

5. Prevention of AD during FES Exercise—FES is a commonly-used modality during the rehabilitation of individuals with SCI., Unfortunately, similar to any non-noxious or noxious stimuli below the level of injury, FES can result in significant afferent stimulation, thereby precipitating the development of AD., One RCT (n=7) evaluated the effect of a topical anaesthetic versus a placebo cream applied to the skin over the quadriceps muscle one hour prior to FES, on two different days. Cardiovascular and AD responses during FES were unaffected by the use of topical anaesthetic cream on the skin at the stimulation site. The authors suggested that mechanisms other than skin nociception contribute to FES-induced AD.

Conclusion: There is Level 1 evidence (from one RCT) that there is no beneficial effect of topical anesthetic in the prevention of AD during FES.

B. Management of Acute AD

Despite appropriate preventative strategies, AD is a common condition among individuals with SCI. As we acknowledged previously, even with a significant increase in arterial blood pressure, episodes of AD may be asymptomatic, especially in individuals with cervical or high thoracic injuries., , As recommended in the *Guidelines of the Consortium for Spinal Cord Medicine* for the management of AD, non-pharmacological measures must be employed initially; if they fail, and systolic blood pressure continues to be at or above 150 mmHg in an adult, 140 mmHg in an adolescent, 130 mmHg in a child 6–12 years old, or 120 mmHg in a child under 5 years old, some type of pharmacological agent should be initiated.

1. Non-pharmacological Management of AD—The initial management of an episode of AD involves placing the patient in an upright position to take advantage of any orthostatic reduction in blood pressure. Having said this, no studies have evaluated the effect of the sitting-up position on blood pressure during episodes of AD. Nonetheless, significant decreases in resting blood pressure have been demonstrated when individuals with SCI are moved from a flat supine position to being tilted or sat up.– It is thought that an upright posture induces pooling of blood in the abdominal and lower extremity vessels, due to the loss of peripheral vasoconstriction that follows SCI, thereby causing a reduction in arterial blood pressure. The next step in managing acute AD must be to loosen any tight clothing

and/or constrictive devices. This procedure allows for further blood pooling in vessels beds below the level of injury, and removes possible triggers for peripheral sensory stimulation. It is critical that blood pressure is checked at least every 5 minutes throughout the episode of AD, until the individual is stable. It then is necessary to search for and eliminate the precipitating stimulus which, in 85% of cases, is related either to bladder distention or bowel impaction., The use of antihypertensive drugs should be considered a last resort, but may be necessary if systolic blood pressure remains 150 mmHg or greater following the steps outlined above. The goals of such an intervention are to alleviate symptoms and to avoid the complications associated with uncontrolled hypertension.–

Conclusion: There is Level 5 evidence based upon physiological studies and clinical consensus for the non-pharmacological management of episodes of AD. Identifying the possible trigger and decreasing afferent stimulation to the spinal cord appear to comprise the most effective non-pharmaceutical therapeutic strategy in clinical practice.

2. Pharmacological Management of AD—Episodes of AD in individuals with SCI can vary in severity. In some patients and in some instances, they are asymptomatic. In many other instances, they can be managed by the individual, once he or she becomes familiar with his/her own triggers and symptoms. However, in some individuals and instances, it is difficult or seemingly impossible to identify what has triggered the acute elevation in blood pressure, and immediate pharmaceutical medical attention is required. Antihypertensive drugs with a rapid onset and short duration of action should be used in the management of acute episodes The *Consortium for Spinal Cord Medicine* recommends that, if non-pharmacological measures (moving the patient to an upright posture, loosening clothes, reducing irritation to the bladder and bowel, etc.) fail and arterial blood pressure is 150 mmHg or greater, then pharmacological management should be initiated. However, the Consortium does not preferentially identify any particular medication for acute AD management. Numerous pharmacological agents (e.g., nifedipine, nitrates, captopril, terzaosin, prazosin, phenoxybenamine, Prostaglandin E2, and sildanefil) have been proposed for the management of AD episodes., , The majority of the recommendations are based upon experience with and studies on the clinical management of hypertensive crises in able-bodied populations. The characteristics and outcomes of studies assessing pharmacological interventions for the management of AD are presented in Table 3.

2a. Nifedipine (Adalat, Procardia): Nifedipine is a Calcium-channel blocker that selectively inhibits calcium ion influx across the cell membrane of cardiac muscle and vascular smooth muscle, without changing serum calcium concentrations. Nifedipine causes decreased peripheral vascular resistance and a modest fall in systolic and diastolic pressure (5–10 mm Hg systolic), though the drop in blood pressure sometimes can be more dramatic. The drug generally is given for an acute episode of AD using the ‘bite and swallow’ method, in a dose of 10 mg. Five studies (n=59)– have evaluated nifedipine, including two Level 2 controlled, but non-randomized trials, and three Level 4 studies.– Four of these five studies demonstrated a reduction or alleviation of AD with nifedipine., – Nifedipine was successfully tested in one non-RCT involving SCI individuals undergoing electroejaculation. In this study, Steinberger and co-investigators reported that sublingual nifedipine decreased

peak systolic, diastolic and mean blood pressure. Furthermore, Braddom and Rocco surveyed 86 physicians with an average of 16.8 years experience managing SCI patients with AD, and found that the pharmacologic treatment of AD varied greatly from physician to physician; however, antihypertensive medications were the most frequently used medications. Nifedipine was used preferentially by 48% of physicians for minor AD cases, and by 58% of physicians for severe symptomatic AD. Even though nifedipine has been the most commonly-used agent in the management of AD in individuals with SCI,, , , its use has declined recently, Because of concern over the potential for adverse events., There have been no reported serious adverse events from the use of nifedipine in the treatment of AD, albeit, sample size has been small in all the studies. However, a review of nifedipine in the management of hypertensive emergencies not specific to SCI identifies serious adverse effects, like stroke, acute myocardial infarction, numerous instances of severe hypotension, and death. Due to several reports of serious adverse reactions occurring after the administration of immediate-release nifedipine, the *Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure* has discouraged the use of this drug.

Conclusion: There is Level 2 evidence (from 2 prospective, controlled trials), that nifedipine is useful to prevent dangerous blood pressure reactions; e.g. during cystoscopy and other diagnostic or therapeutic procedures in SCI patients with AD. However, there is clinical consensus that the potential exists for serious adverse events with this drug, based upon what has been reported in other, non-SCI populations.

2b. Nitrates (Nitroglycerine, Depo-Nit, Nitrostat, Nitrol, Nitro-Bid): Nitrates have been used for acute episodes of AD because they cause relaxation of vascular smooth muscle, producing vasodilator effects on peripheral arteries and veins. Dilation of post-capillary vessels, including large veins, promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure (preload). Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (after-load). Before nitrates (e.g., nitroglycerin, isosorbide dinitrate, or sodium nitroprusside) are administered, a person with a SCI presenting with acute AD should be questioned regarding their use of sildenafil, however. If this agent has been used within the last 24 hours, it is recommended that an alternative, short-acting, rapid-onset non-nitrate antihypertensive agent be used. Nitrates are the second most commonly used agents after nifedipine in the management of AD in individuals with SCI, Having said this, with the exception of a single case report involving the intravenous administration of nitroprusside, no studies, and only expert opinions support the use of nitrates in patients with SCI.

Conclusion: There is Level 5 evidence (clinical consensus),, but no clinical studies which support the use of nitrates in the acute management of AD post SCI

2c. Captopril: Captopril is a specific competitive inhibitor of angiotensin I-converting enzyme (ACE). During an acute episode of AD, 25 mg captopril often is administered sublingually. In one pre-post study (n=26), captopril was safe and effective for AD management in 4 out of 5 episodes. This prospective, open-labeled study and numerous

expert opinions suggest the use of the captopril as a primary medication in the management of AD, ,

Conclusion: There is Level 4 evidence (from one pre-post study) that captopril may be beneficial in the acute management of AD in SCI patients.

2d. Terazosin: Terazosin is a long-acting, alpha-1 adrenoceptor selective blocking agent. Selective alpha-1 blockade has been suggested as an appropriate pharmacological choice in the management of AD, because of its added effect at the bladder level, which includes inhibition of the urinary sphincter and relaxation of the smooth muscles of blood vessels. Regular doses of Terazosin over weeks or months have been evaluated in three Level 4 studies (n=57),– and appear to be effective in preventing AD without producing erectile dysfunction. In these studies, patients reported moderate to excellent improvement or even complete termination of their dysreflexic symptoms over the 3-month period of Terazosin administration.

Conclusion: There is Level 4 evidence (from 3 pre-post studies)– that the regular use of Terazosin may have positive effects, in terms of alleviating incontinence and preventing episodes of AD.

2e. Prazosin (Minipress): Prazosin is a postsynaptic alpha-1 adrenoceptor blocker, which lowers blood pressure by relaxing blood vessels. It has a minimal effect on cardiac function, due to its alpha-1 receptor selectivity. The recommended starting dose in adults is 0.5 or 1 milligram (mg) 2–3 times daily. In a small (n=15), but high-quality RCT, Prazosin twice daily was well tolerated and did not excessively lower baseline blood pressure; AD episodes also were less severe and shorter in duration over a 2-week period.

Conclusion: There is Level 1 evidence (from one RCT) that Prazosin is superior to placebo in the prophylactic management of AD.

2f. Phenoxybenzamine hydrochloride (Dibenzyline): Phenoxybenzamine (trade name = Dibenzyline) is a long-acting, adrenergic, alpha-receptor blocking agent that can increase blood flow to skin, mucosa, and abdominal viscera, and can lower both supine and erect blood pressures. The initial dose is 10 mg of phenoxybenzamine hydrochloride bid, with incremental increases daily, usually up to 20–40 mg 2–3 times per day.

Conclusion: Study results are conflicting with respect to using phenoxybenzamine for AD in SCI patients, with no effect on AD occurrence or severity in one study and a positive treatment effect in the other.

2g. Prostaglandin E2: Prostaglandins comprise a group of hormone-like substances that participate in a wide range of bodily functions, such as the contraction and relaxation of smooth muscle, the dilation and constriction of blood vessels, and control of blood pressure. Frankel and Mathias studied five SCI subjects, among whom, 3 underwent electrical ejaculation both with and without Prostaglandin E2, and found that the level of BP recorded during electrical ejaculation decreased with the drug.

Conclusion: There is Level 2 evidence from a very small prospective controlled study that the level of BP recorded during electrical ejaculation is substantially reduced with Prostaglandin E2.

2h. Sildanefil (Viagra): Sildanefil is an inhibitor of phosphodiesterase type 5 (PDE5). It causes increased levels of cGMP in the corpus cavernosum, as well as smooth muscle relaxation and increased inflow of blood to the corpus cavernosum. At recommended doses, Sildenafil does not have these effects in the absence of sexual stimulation. The recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity; but may be taken anywhere from 4 hours to 0.5 hour before-hand. The drug is known to potentiate the hypotensive effects of nitrates and, therefore, nitrates in any form are contraindicated with sildanefil use, and vice versa. The effect of sildenafil on AD has been recorded in one RCT (n=13). Although sildenafil decreased resting BP, there was no effect on the magnitude of AD resulting from vibrostimulation in men with SCI.

Conclusion: Based on a single RCT, there is Level 2 evidence that sildaenafil citrate has no effect on changes in BP during episodes of AD initiated by vibrostimulation in men with SCI.

2i. Other Pharmacological Agents Tested for the Management of AD: The use of other pharmacological agents for the management of AD in individuals with SCI has been reported in the literature (e.g., expert opinion, case reports), but the evidence is insufficient to warrant their recommendation. These drugs include phenazopyridine for AD associated with cystitis; magnesium sulfate for AD associated with labour or life-threatening AD in intensive care; and diazoxide (Hyperstat) for acute AD episodes. In addition, there have been reports on the use of beta blockers, mecamylamine (Inversine) and hydralzine (Apresoline) for the general management of AD symptoms in individuals with SCI.

DISCUSSION

The objective of this review was to evaluate the latest evidence from clinical literature on present strategies in the management and prevention of AD, as well as present latest basic science and clinical data on mechanisms and pathophysiology of this condition. The very small number of RCTs (n=6), , , , , demonstrates the difficulty of applying this type of review to assessing AD. In many instances (e.g., acute life-threatening episodes of AD), it would be unethical to have a ‘no treatment’ control group, when a well-established protocol for the management of AD has been proposed by the *Consortium for Spinal Cord Medicine*, based upon physiological evidence and clinical consensus. Education on the causes of AD, appropriate bladder and bowel routines, and pressure sore prevention, appear to be the most effective measures for prevention of AD in individuals with SCI. However, for each individual, the identification and elimination of specific triggers for AD also should be employed to manage and prevent this condition., , Based upon the physiological mechanisms of AD, it is assumed that a multi-modal protocol to reduce triggers of AD would be most effective and there is a need to formally evaluate a combined approach. The most effective approach to AD seems to be preventing it. This includes careful evaluation of individuals with SCI and early recognition of possible triggers that could result in AD. Improved

clinician awareness of AD and greater attention to eliminating noxious stimuli in individuals with SCI is a priority. Clinicians, family members, and caregivers should be aware that increased afferent stimulation (e.g., via surgery, invasive investigational procedures, and labour) in persons with SCI will increase their risk for AD; and that a variety of procedures can be used to prevent AD episodes.

When conservative management of AD with an established bladder program is not sufficient, detrusor hyperreflexia can be treated pharmacologically and in more difficult cases, with surgery. However, note that all the pharmacological interventions (except for intra-vesical resiniferatoxin) and surgical interventions were lacking in controlled trials. The lack of controlled trials (even those involving other deemed therapeutic interventions) seriously undermines the strength of this evidence. On the positive side, several of these studies have established effects over long periods (e.g., the positive effect of botulinum toxin on detrusor hyperreflexia over nine months, and the positive effect of augmentation enterocystoplasy on detrusor hyperreflexia over one year).

We emphazis that AD is often not recognized outside of specialized SCI rehabilitation facilities. Despite appropriate medical care and advances in our understanding of the possible pathophysiology of AD, the majority of individuals susceptible to AD (those with cervical and high thoracic SCI) experience numerous episodes of AD during their acute and sub-acute rehabilitation period., Unfortunately, the level of awareness of AD among family physicians, and medical personal in ER or ambulance services appears to be low, especially as it pertains to SCI patients (unpublished observations). This reinforces the need to educate and empower individuals with SCI and their families, so that they can direct their own treatment. This reinforces the need to educate and empower individuals with SCI and their families, so that they can direct their own treatment. Furthermore, all individuals with SCI should carry a Medical Emergency Card for Autonomic Dysreflexia. This card provides a short description of AD as a medical emergency, and gives brief details on its causes, presentation and management. The ultimate goal in the management of AD in individuals with SCI is protecting them from its development and ensuring appropriate and timely intervention. However when non-pharmacological measures fail and systolic blood pressure remains elevated, pharmacological agents should be initiated. Nifedipine, nitrates, and captopril are the most commonly used and recommended agents for the management of acute AD episodes,, , and are supported by Level 2, 5 and 4 evidence, respectively. To date, no RCTs have been conducted to determine which of these agents is best, however.

In some instances, individuals with SCI should be supplied with short-acting antihypertensive agents, like nifedipine or nitrates, which they can take themselves, prior to seeking medical attention. However, if their symptoms continue and/or their blood pressure does not stabilize, they must proceed or be brought to the nearest emergency department for further management.

CONCLUSION

There was a severe lack of controlled trials in the management and prevention of AD. A variety of options are available to prevent AD (e.g., surgical, pharmacological), but only

intersphincteric anal block with lidocaine when undergoing anorectal procedures had evidence using a control group (Level 1). The identification and elimination of specific triggers for AD (e.g., distended bladder) are considered the first line of treatment based on physiological rationale and expert consensus, but there are virtually no controlled trials which evaluate these effects. When non-pharmacological actions fail in an acute episode, pharmacological agents are required and nifedipine, nitrates, and captopril are the most commonly used and recommended agents. However, only nifedipine is supported by controlled trials (Level 2). RCTs to determine which of these agents or combinations of therapies are effective are severely needed.

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Table 1

Signs and Symptoms of Autonomic Dysreflexia in Patients with Spinal Cord Injuries

- severe headache
- feeling of anxiety
- profuse sweating above the level of injury
- flushing and piloerection (body hair ‘stands on end’) above the injury
- dry and pale skin due to vasoconstriction below the level of injury
- blurred vision
- nasal congestion
- bradycardia, cardiac arrhythmias, atrial fibrillation

Table 2

Prevention of AD

Author, Year; Country Methodological Score Research Design Total Sample Size	Methods	Outcome	
Botlium toxin			
Dykstra et al. 1988; USA Downs & Black score=12 Pre-post Level 4 N=11 (with AD=7)	**Population:** Detrusor-sphincter dyssynergia. **Treatment:** Low dose botulinum-A toxin at the neuromuscular junction. **Outcome Measures:** Urethral pressure, AD symptoms.	**1** **2** **3**	Urethral pressure profile decreased 27 cm H_20 (n=7). Self assessed improvement in AD symptoms in 5 of 7 AD patients. Toxin effects lasted an average of 50 days.
Schurch et al. 2000; Switzerland Downs & Black score=11 Pre-post Level 4 N=21	**Population:** Traumatic SCI: 18 paraplegics, 3 tetraplegics; mean 60.2 months post-injury, incontinence resistant to anticholinergic medication **Treatment:** Botulinum-A toxin injection (200–300 units) into detrusor muscle. **Outcome Measures:** Voiding and detrusor pressure, diary of incontinence, AD symptoms at 6, 16, and 36-wks.	**1** **2**	At 6-wk follow-up, 17 out of 19 patients were completely continent. 3 tetraplegic patients with severe AD upon bladder emptying experienced total, permanent resolution of symptoms post-treatment.
Capsaicin			
Giannantoni et al. 2002; Italy PEDro=6 RCT Level 1 N=23	**Population:** Refractory detrusor hyperreflexia. **Treatment:** a) single dose of 2 mM. capsaicin in 30 ml ethanol plus 70 ml 0.9% NaCl or; b) 100 mM. resiniferatoxin in 100 ml 0.9% NaCl **Outcome Measures:** Urodynamics; frequency of daily catheterizations, incontinent episodes and side effects.	**1** **2** **3**	Capsaicin group showed no significant urodynamic or clinical improvement at 30 and 60 days. Resiniferatoxin group demonstrated significant urodynamic improvement at 30 ($p<.05$) and 60 days ($p <0.001$). Most patients receiving capsaicin, but none receiving resiniferatoxin, developed AD, limb spasms, suprapubic discomfort and hematuria.
Igawa et al. 2003; Japan Downs & Black score=13 Pre-post Level 4 N=7	**Population:** 5 cervical and 2 thoracic spine injury patients. **Treatment:** bladder instillation with capsaicin solution under general anesthesia. **Outcome Measures:** BP, HR, serum catecholamines, blood ethanol concentration.	**1** **2**	Capsaicin attenuated elevated BP secondary to bladder distension (empty or full) ($p<.01$) post-treatment. In all individuals, episodes of AD became negligible and well-tolerated for >3 months.
Anticholinergics			
Giannantoni et al. 1998; Italy Downs & Black score=13 Observational Level 5 N=48	**Population:** SCI patients. **Treatment:** Anticholinergic drugs **Outcome Measures:** Neurological, urological and urodynamic evaluation; BP, HR, AD symptoms.	**1** **2**	Presence of uninhibited detrusor muscle contractions and bladder distension both contributed to AD crisis. Treatment with an anticholinergic drug was not sufficient to prevent AD starting from the bladder, unless it induced detrusor areflexia.
Sacral Denervation			
Schurch et al. 1998; Switzerland Downs & Black score=15 Case Series Level 4 N=10	**Population:** SCI patients with AD. **Treatment:** Sacral deafferentation. **Outcome measures:** Continuous non-invasive recordings of BP and HR during urodynamic recordings, pre- and post-operative data.	**1** **2**	Marked elevation in SBP and DBP during the urodynamic examination in 8 patients, despite complete intra- operative de-afferentation of the bladder in 5 patients. AD persisted in pts with SCI even post complete sacral de-afferentation, consistently occurring during the stimulation-induced voiding phase.

Author, Year; Country **Methodological Score** **Research Design** **Total Sample Size**	**Methods**	**Outcome**
Hohenfellner et al. 2001; Germany Downs & Black score=11 Pre-post Level 4 N=9	**Population:** Detrusor hyperreflexia. **Treatment:** Sacral bladder denervation. **Outcome Measures:** Bladder capacity, BP, symptomatic AD.	**1** Episodes of detrusor hyperreflexia and AD were eliminated in all cases. **2** In the 5 patients with AD, both SBP and DBP were reduced (196±16.9 to 124±9.3 mmHg; and 114±5.1 to 76±5.1 mmHg, respectively).
Bladder and Urethral Sphincter Surgery		
Barton et al. 1986; USA Downs & Black score=12 Case Series Level 4 N=16	**Population:** 5 thoracic and 8 cervical SCI, 47–285 months post- injury. **Treatment:** Modified transurethral external sphincterotomy with follow up to 26 wks. **Outcome Measures:** Bladder and urethral pressures and volumes, BP.	**1** Decreased intravesical and urethral pressures versus before sphincterotomy ($p<.001$). **2** Decreased BP responses during urodynamic stimulation ($p<.01$). **3** Other cardiovascular responses related to AD during bladder filling were markedly attenuated.
Sidi et al. 1990; USA Downs & Black score=11 Pre-post Level 4 N=12	**Population:** C5-T11 SCI; 9 complete, 3 incomplete, 2–27 yrs post-injury. **Treatment:** Augmentation enterocystoplasty Indications for treatment: incontinence in 10 patients; upper urinary tract deterioration in 5 and persistent AD in 3 patients. **Outcome Measures:** Functional bladder capacity, levels of blood urea nitrogen, creatinine, electrolytes.	**1** 11 out of 12 patients were continent on clean intermittent self-catheterization every 4–6 hours at 4 months post-op. **2** Of the 3 patients who received an artificial urinary sphincter, 2 became continent after sphincter activation and 1 achieved continence without sphincter activation. No patients experienced symptoms of AD during intermittent catheterization postoperatively.
Anorectal Procedures		
Cosman & Vu 2005; USA PEDro=9 RCT Level 1 N=25	**Population:** Complete SCI, mean 15–25 yrs post-injury, C7±3 level of injury. **Treatment:** Inter-sphincteric anal block with either: a) 300 mg 1% lidocaine or; b) normal saline (placebo) before sigmoidoscopy or anoscopic hemorrhoid ligation procedure. **Outcome Measures:** BP.	**1** Patients receiving lidocaine had reduced increases in SBP (22±14 mmHg) relative to patients assigned placebo (47±31 mmHg) ($p=0.01$), suggesting reduced AD risk.
Cosman et al. 2002; USA PEDro=8 RCT Level 1 N=45	**Population:** Chronic, complete SCI, injury level of T6 or above, undergoing anoscopy and/or flexible sigmoidoscopies. **Treatment:** a) 2% topical lidocaine jelly (n=18) or; b) non- medicated lubricant (n=32) prior to procedure. **Outcome Measures:** BP.	**2** Topical lidocaine had no significant effect on mean maximal SBP (increased 35±25 mmHg vs. 45±30 mmHg in lidocaine and control groups, respectively). **3** Greater SBP increase with anoscopic procedure compared to sigmoidoscopic procedures (49±29 vs. 25±20 mmHg, respectively).
Pregnancy and Labour		
Cross et al. 1992; USA Downs & Black score=4 Case Series Level 4 N=22	**Population:** 11 cervical, 11 thoracic SCI. **Treatment:** Epidural anesthesia **Outcome Measures:** Presence of autonomic hyperreflexia, type of anesthesia, type of delivery, complications.	**1** AD was experienced in 9/16 patients >T6. **2** 1 patient had two grand mal seizures during labour, possibly triggered by severe AD and the subsequent intravenous administration of diazepam. **3** Epidural anesthesia appeared effective for the control of AD in the 6 patients to whom it was administered.
Hughes et al. 1991; UK Downs & Black score=4 Observational Level 5 N=15	**Population:** 17 pregnancies in 15 women with SCI, level of injury: T4-L3. **Treatment:** management and outcome of pregnancies in women with SCI.	**1** Labour tended to be diagnosed by dysreflexic symptoms or membrane rupture with confirmation by palpation of contractions and vaginal examination.

Author, Year; Country Methodological Score Research Design Total Sample Size	Methods	Outcome
	Outcome Measures: antenatal care and problems, labour diagnosis and outcome.	**2** Initial management of AD included elevation of the head of the bed, nifedipine and nitrates. **3** AD most effectively controlled by identifying and interrupting the triggering afferent input.
Cross et al. 1991; USA Downs & Black score=4 Observational Level 5 N=16	**Population:** 7 cervical, 9 thoracic SCI. **Treatment:** Questionnaire and hospital records review. **Outcome Measures:** Outcomes of pregnancies.	**1** Among the 16 women, 25 pregnancies occurred, resulting in 22 babies & 3 spontaneous abortions. **2** 2/15 vaginal deliveries and 5/7 caesarian sections had AD during delivery, with 4 of these receiving epidural anesthesia for control of AD. **3** 1 patient required epidural catheter 5 days postpartum to control AD.
Ravindran et al. 1981; USA Downs and Black score=6 Case report Level 5 N=1	**Population:** 19 yr-old, female with C5 complete tetraplegia admitted to the obstetrical intensive care unit for intra-amniotic prostaglandin F2-alpha injection for uterine evacuation of a dead fetus of 20 wks gestation **Treatment:** Sodium nitroprusside (100 mg/min to 700 mg/min). **Outcome Measures:** BP, and AD symptoms.	**1** 100 mg/min of sodium nitroprusside decreased SBP from 170 mmHg to 120 mmHg caused by vaginal speculum introduction. **2** Prostaglandin induced uterine contraction further elevated BP to 200/70 mmHg; headache and sweating. **3** Administration of 700 mg/min of sodium nitroprusside decreased SBP and alleviated AD. **4** Following cessation of uterine contraction, pt developed hypotension (70/30 mmHg) requiring vasopressor therapy. **5** Sodium nitropruside was stopped and epidural analgesia initiated for further management of AD.
Surgery		
Lambert et al. 1982; USA Downs & Black score=14 Observational Level 5 N=50	**Population:** Injury level T6 and above, complete SCI, mean 6.5 yrs post-injury. **Treatment:** Retrospective review of 78 procedures. Three groups: **1** topical anesthesia, sedation or no anesthesia (n=19); **2** general anesthesia (n=13) and; **3** spinal anesthesia (n=46). **Outcome Measures:** BP.	**1** Intra-operative hypertension occurred more prominently with topical or no anesthesia (15/19) compared to general anesthesia (3/13) or spinal anesthesia (3/46). **2** Intra-operatively, systolic BP increased significantly by 37 mmHg in patients receiving topical or no anesthesia. No significant difference in BP change between the general and spinal anesthesia groups (p=. 11).
Eltorai et al. 1997; USA Downs & Black score=4 Observational Level 5 N=591	**Population:** Injury level C1-T10, mean of 22.3 yrs post-injury. **Treatment:** Retrospective review of anesthetic methods during surgery. **Outcome Measures:** BP.	**1** AD occurred most commonly during the start of anesthesia (induction), the greatest frequency being when no anesthesia was provided. **2** During induction, SBP increased in 69%, 65% 62%, 52%, 52%, and 89% of cases during the usage of combined anesthetics (local anesthesia and intravenous sedation), intravenous sedation, local anesthesia, spinal or epidural anesthesia, and general anesthesia, respectively.

Author, Year; Country **Methodological Score** **Research Design** **Total Sample Size**	**Methods**	**Outcome**
FES Exercise		
Matthews et al. 1997; Canada PEDro=7 RCT Level 4 N=7	**Population:** Injury level C4-C7, complete SCI, 3–21 yrs post-injury. **Treatment:** Randomized to: **a.** topical anesthetic; or **b.** placebo creams applied to quadriceps during graded FES exercise. **Outcome Measures:** HR, BP, serum catecholamines.	**1** No differences in HR, BP or catecholamine responses or FES force were seen between intervention and comparison groups.

HR: heart rate; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure

Table 3

Pharmacological management of AD

Author, Yr; Country Methodological Score Research Design Total Sample Size	Methods	Outcome	
Nifedipine (Adalat, Procardia)			
Thyberg et al. 1994; Sweden Downs & Black score=11 Pre-post Level 4 N=10	**Population:** Cervical or high thoracic SCI. **Treatment:** 10 mg nifedipine sublingually during cystometry. **Outcome Measures:** BP and HR.	**1** **2** **3**	Patients demonstrated decreased maximum SBP and DBP after the administration of nifedipine. Maximum SBP decreased from 147 mmHg to 118 mmHg. The decrease in BP was due to a decrease in baseline pressure and BP response during cystometry.
Kabalin et al. 1993; USA Downs & Black score=10 Case Series Level 4 N=20	**Population:** 10 tetraplegics, 10 paraplegics. **Treatment:** 10–30 mg nifedipine sublingually during Estracorporal Shock Wave Lithotripsy (ESWL) for kidney stone treatment. **Outcome Measures:** ECG, BP, pulse rate, peripheral oxygen saturation.	**1** **2** **3**	All but one SCI patient demonstrated AD during ESWL with maximal increase in SBP of 74 mmHg. Nifedipine was administered sublingually and controlled BP elevation. For severe, acute increases in BP, ESWL stimulation was momentarily discontinued until pharmacological control of the BP was achieved, after which treatment was continued.
Dykstra et al. 1987; USA Downs & Black score=10 Pre-post Level 4 N=7	**Population:** Complete, cervical injuries. **Treatment:** 10 mg nifedipine during cystosopy procedure. **Outcome measures:** BP, AD symptoms.	**1** **2**	Nifedipine alleviated AD when given sublingually during cystoscopy, and prevented AD when given orally 30 min before cystoscopy. No adverse drug effects were observed.
Steinberger et al. 1990; USA Downs & Black score=9 Prospective Controlled Trial Level 2 N=10	**Population:** Injury levels T5 and above, mean 9 yrs post-injury. **Treatment:** 10–30 mg nifedipine sublingually 15 min prior to electroejaculation, versus no nifedipine. **Outcome Measures:** BP, voltage and current delivered during electroejaculation.	**1** **2** **3**	In 9/10 patients, BPs were markedly lower after nifedipine pretreatment. Compared with no treatment, SBP during electroejaculation was lower with nifedipine pretreatment (168 mmHg vs. 196 mmHg). In 9/10 patients, tolerance to electrical stimulation was greater post nifedipine pretreatment.
Lindan 1985; USA Downs & Black score=8 Prospective Controlled Trial Level 2 N=12	**Population:** Tetraplegic individuals. **Treatment:** 12 patients received phenoxybenzamine (10 mg bid) vs. nifedipine (20 mg bid) at least 4 days prior cystometry. 11 patients also were tested for the efficacy of 10 mg nifedipine (sublingually or by mouth) for controlling AD symptoms. **Outcome Measures:** BP.	**1** **2**	Neither drug prevented AD secondary to bladder filling, and a significant number of patients developed hypotension. Sublingual nifedipine (10 mg) was effective at managing acute attacks of AD.
Nitrates			
Ravindran et al. 1981; USA Downs and Black score=6 Case report Level 5 N=1	See the Pregnancy and Labour section in Table 2.		
Captopril			

Author, Yr; Country **Methodological Score** **Research Design** **Total Sample Size**	**Methods**	**Outcome**	
Esmail et al. 2002; Canada Downs & Black score=9 Pre-post Level 4 N=7	**Population:** 26 consecutive patients with SCI above T6. **Treatment:** Administration of a) captopril 25 mg sublingually if SBP was at or above 150 mmHg, b) 5 mg of immediate-release nifedipine if SBP remained elevated 30 minutes after captopril administration. **Outcome Measures:** SBP	**1** **2** **3**	33 AD episodes documented, among which 18 episodes in 5 patients were treated with drug therapy. Captopril alone was effective in 4/5 initial episodes. Mean SBPs at baseline and 30 min after captopril were 178 ± 18 mmHg and 133 ± 28 mmHg, respectively. The addition of nifedipine successfully reduced SBP in the remaining patients.
Terazosin			
Swierzewski et al. 1994; USA Downs & Black score=11 Pre-post Level 4 N=12	**Population:** 6 paraplegic, 6 quadriplegic. **Treatment:** nightly Terazosin administration for 4 wks (5 mg starting dose). **Outcome Measures:** Physical examination, cystoscopy, AD symptoms.	**1** **2**	Detrusor compliance improved in all patients during the treatment phase. Change in bladder pressure and the safe bladder volume were statistically and clinically significant.
Vaidyanathan et al. 1998; UK Downs & Black score=10 Pre-post Level 4 N=24	**Population:** 18 adults with tetraplegia, 3 children with ventilator-dependent tetraplegia, and 3 adults with paraplegia. All had AD in the absence of an acute precipitant. **Treatment:** Administration of Terazosin with starting dose of 1 mg (adults) or 0.5 mg (children). Step-wise incremental dose increases were given at 3–4 day intervals. **Outcome Measures:** Drug- induced hypotension, adverse effects, AD symptoms	**1** **2** **3** **4**	Terazosine abolished AD in 3 patients and decreased the incidence and severity of symptoms in 1 patient. AD symptoms subsided completely with Terazosin therapy in all the patients. Adult patients required a dose between 1 to 10 mg and children required between 1 to 2 mg. Side effects of postural hypotension and drowsiness were transient and mild. One tetraplegic patient developed persistent dizziness and therapy was discontinued.
Chancellor et al. 1994; USA Downs & Black score=10 Pre-post Level 4 N=21	**Population:** Complete SCI; injury level C3-T5 **Treatment:** Terazosin administration. **Outcome Measures:** BP and AD frequency and severity scores.	**1** **2** **3** **4**	Decrease in the AD severity score versus baseline at one week, 1 month and 3 months. Degree of muscle spasm and degree of headache did not improve. Decrease in the frequency of AD at 1-week follow-up, and was maintained at 1 and 3 months. SBP not statistically changed versus baseline after 3 months of Terazosin (p=.26).
Prazosin (Minipress)			
Krum et al. 1992; Australia PEDro=6 RCT Level 1 N=15	**Population:** Injury level T6 or above, at least 2 episodes of AD in the last 7 days. **Treatment:** Double-blind, randomized to prazosin 3 mg bid. (n=8) or placebo (n=7) for 2 weeks. **Outcome Measures:** Severity of AD, BP.	**1** **2**	Prazosin was well tolerated and did not significantly lower resting BP. Compared to baseline, the prazosin group had fewer severe episodes of AD (reduced rise in BP, shorter symptom duration, and less need for acute antihypertensive medication). The severity of headache during individual AD episodes also was diminished with prazosin therapy.
Phenoxybenzamine (Dibenzyline)			
Lindan 1985; USA Downs & Black score=8 Pre-post Level 4 N=12	**Population:** Tetraplegic individuals. **Treatment:** Phenoxybenzamine (10 mg bid) versus nifedipine (20 mg bid) for 4 days prior cystometry.	**1**	Neither drug effectively prevented AD secondary to bladder filling, and a significant

Author, Yr; Country **Methodological Score** **Research Design** **Total Sample Size**	**Methods**	**Outcome**	
	Outcome Measures: BP during cystometry.		number of patients developed troublesome hypotension.
McGuire et al. 1976; USA Downs & Black score=6 Case Series Level 4 N=9	**Population:** SCI individuals with severe AD **Treatment:** Phenoxybenzamine (alpha-sympatholytic agent) **Outcome Measures:** BP, bladder and urethral pressures.	**1** **2**	Sublingual dose of nifedipine (10 mg) was effective at managing acute attacks of AD. Subjects experienced a dramatic relief in AD symptoms.
Prostaglandin E2			
Frankel & Mathias 1980; UK Downs & Black score=8 Prospective Controlled Trial Level 2 N=3	**Population:** Complete SCI, C5-T4, 5–108 months post-injury. **Treatment:** Trans-rectal electrical ejaculation with and without intravenous administration of Prostaglandin E2. **Outcome Measures:** HR, BP, ECG.	**1** **2**	Resting BP decreased and resting HR increased with Prostaglandin E2. BP decreased during electrical stimulation, which enabled tolerance of more intense stimulation and successful ejaculation in 2 patients.
Sildanefil (Viagra)			
Sheel et al. 2005; Canada PEDro=5 Level 2 N=13	**Population:** Males with cervical (n = 8) or thoracic (n = 5) SCI. **Treatment:** Oral dose of sildenafil citrate (25–100 mg) versus no medication during penile vibratory stimulation. **Outcomes Measures:** ECG, BP.	**1** **2**	Sildenafil decreased baseline BP in cervical SCI. Administration of sildenafil had no effect on HR or BP during AD triggered by penile vibratory stimulation in men with SCI.

HR: heart rate; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; ECG: electrocardiogram