Spinal Cord (2012) 50, 869–877

www.nature.com/sc

REVIEW

Sexual function and autonomic dysreflexia in men with spinal cord injuries: how should we treat?

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Study design: Systematic review.
Objectives: Review the literature on the acute or prophylactic treatment of autonomic dysreflexia (AD) in the context of sexual activities.
Setting: International
Methods: Medline search using AD and spinal cord injury (SCI). Selected titles for AD treatment included all levels of evidence (randomized placebo control studies, case reports, literature reviews) and all years of publication.
Results: Thirty-seven papers on the specific treatment of AD showed that nifedipine, prazosin, captopril and clonidine are candidates in the context of sexual activities. Prazosin, however, has an initial hypotensive effect requiring to begin treatment 12 h before intercourse, which makes it less ideal for spontaneous sexual activities. Captopril has an initial hypotensive effect and was only studied in acute AD. Its usefulness in prophylaxis remains to be demonstrated. Clonidine has successfully been used clinically for decades, but never studied in randomized control trials. Nifedipine remains the most widely studied and significant treatment of AD whether in acute or prophylactic conditions. Recent concerns suggest increased cardiovascular risks with sublingual nifedipine in non-SCI populations, but negative long-term effects have not been reported in the SCI population.
Conclusion: Sexual function is a priority for men with SCI. As sexual activities, in particular ejaculation, can be a source of AD, adequate treatments and prophylaxis must be considered in the context of sexual activities. Experts must meet and conclude on the thresholds, parameters and treatments that should be considered in the long-term management of AD in the context of sexual function in men with SCI.
Spinal Cord (2012) **50,** 869–877; doi:10.1038/sc.2012.83; published online 7 August 2012

Keywords: spinal cord injury; ejaculation; autonomic dysreflexia; adalat; nifedipine

INTRODUCTION

A spinal cord injury (SCI) disrupts several aspects of life. Among them, sexuality is considered a major concern and described as a priority.[1] Although sexual function is usually lost following natural stimulation,[2] successful treatments are now available, allowing the vast majority of men with SCI to achieve ejaculation.[3–5]

Sexual options for men with SCI

Ejaculation dysfunctions in men with SCI can be treated with a variety of options, starting with commercial vibrators, followed if unsuccessful by the use of the Ferticare device,[6] which has been shown much more effective, followed if still negative by vibrostimulation combined with midodrine.[7] When fertility is aimed for, rectal probe electroejaculation[8,9] and other assisted reproductive technologies can be offered, allowing intravaginal home injection,[10] intrauterine or *in vitro* fertilization.[11]

Sexuality and fertility are therefore definite options for men with SCI, and considering the currently available treatments, more than 90% of men with SCI can achieve ejaculation.[4,5] The resulting response is accompanied with many sexual sensations[12] including orgasm[13,14] despite the spinal cord lesion. Vibrostimulation is a common prescription in this context and a key option, as it can use it at home, with no medical assistance, alone or with a partner. Ejaculation is not only sought for fertility, but also to obtain sexual gratification and relieve spasticity.[15,16]

Despite these beneficial effects, ejaculation may place some individuals with SCI at risk of developing autonomic dysreflexia (AD),[17,18] a condition which raises medical concerns. Although the question is not to deprive men with SCI from experiencing sexual gratification, AD risks warrant further investigation on the prevention strategies that can be proposed for sexual activities.

This paper reviews the literature on the treatment of AD to provide a better information on its prevention and management in the context of sexuality.

MATERIALS AND METHODS

A systematic review of the literature from Pubmed was conducted on studies that provided scientific evidence on the specific treatment of AD following SCI. The search used the keywords autonomic dysreflexia AND spinal cord injury, as well as autonomic hyperreflexia AND spinal cord injury. All years of publication were considered, which ranged from 1956 to 2011. The papers were assessed by two independent reviewers on the basis of their abstract, which had to mention that they specifically investigated a treatment of AD,

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Received 16 January 2012; revised 21 May 2012; accepted 24 May 2012; published online 7 August 2012

that is, with a group comparison or with an indication of a therapeutic effect before and after treatment. The selected papers aimed all levels of evidence, including randomized placebo control, case reports and literature reviews, as long as they pertained to the specific treatment of AD. Because the literature review aimed treatments that can be implemented at home during sexual activities, studies on intravenous treatment were generally rejected, except for one study that used intravenous specifically in the context of ejaculation manoeuver in men with SCI. Also excluded were studies that only mentioned a procedural management of AD in their methods without giving specific results (hence not specifically studying AD treatment). A secondary search using the keywords vibrostimulation AND spinal cord injury, electroejaculation AND spinal cord injury, and ejaculation AND spinal cord injury was performed in this context and ranged from 1948 to 2011. The articles were read to assess whether they mentioned only a procedural management of AD or whether they specifically investigated a treatment of AD.

RESULTS

The keywords on autonomic dysreflexia AND spinal cord injury gave rise to 558 articles and that on autonomic hyperreflexia AND spinal cord injury to 662 articles. The papers mentioning a specific treatment of AD lead to 50 articles. Considering only those on humans, only written in English or French and eliminating those with intravenous treatments (except for the one specifically dealing with ejaculation manoeuver in men with SCI) left 37 articles pertaining to the specific treatment of AD, although not necessarily restricted to sexual activity. The secondary search relating to sexual activity using the keywords vibrostimulation AND spinal cord injury gave rise to 196 articles, that with electroejaculation AND spinal cord injury 110 articles and that with ejaculation AND spinal cord injury 267 articles. Of these studies 60% mentioned procedural managements of AD but without specific results. Three studies gave some results on a treatment effect on AD and were also found under the keywords on autonomic dysreflexia, therefore, included in the current review.

Autonomic dysreflexia

First described in 1890 by Bolby,[19] AD is now considered a clinical emergency.[20,21] Its primary definition relies on hypertension and is characterized by an increase in systolic blood pressure (SBP) of at least 20 mm Hg.[17,21,22] AD is usually associated with at least one sign of autonomic arousal,[17] but may sometimes occur unperceived.[23] Upon severe conditions, hypertension can reach levels as high as 250 mm Hg[18] SBP, making the individual at risk of organ dysfunction, cardiovascular events or even death if left untreated.

AD is therefore a potentially life-threatening condition. As sexual activities in particular ejaculation can trigger AD,[17] while the individual is at home with no medical assistance, understanding its mechanisms and providing adequate prevention or treatment become a priority in the context of sexuality.

Pathophysiology of AD

The most common sources of AD are summarized in Table 1 and include ejaculation or its treatment. AD generally affects individuals with lesions above T6,[17,20,21] where supraspinal inhibition can no longer act on the sympathetic outflow.

AD is initiated by intense or painful or sustained stimuli,[17] traveling through the somatic and visceral afferents to the thoracic segments of the spinal cord.[24] Postganglionic sympathetic terminals then release norepinephrine (NE)[25,26] that triggers a sudden generalized vasoconstriction, resulting in hypertension and visceral spasms. Visceral spasms further cause vasoconstriction, which further stimulates the sympathetic terminals and self-perpetuates the phenomenon.

Table 1 Common sources of autonomic dysreflexia

Urogenital	*Gastrointestinal*	*Cutaneous*
Bladder and urethral distension	Bowel impaction/ distension	Pressure sore
Urinary infection	Anal stricture	Ingrown toenails
Detrusor-sphincter dyssynergia	Gastro-œsophagal reflux	Burning
Intercourse (ejaculation)	Gastric ulcer	Sun burn
Menses	Cholelithiasis	Insect bites
Kidney stones	Cholecystitis	
Epididymitis/prostatitis		
Testicular torsion		
Triggering procedures	*Limbs*	*Others*
Cystoscopy, cystometry	Changing position	Medication (example: pseudoephedrine)
Electroejaculation	Tight clothing	Exercise
Lithotripsy	Spasticity	Immersion in cold water
Pregnancy, child birth	Fracture, trauma, luxation	Alcohol abuse
Surgery or anesthesia	Deep vein thrombosis	
	Heterotopic ossification	Syringomyelia

Mathias *et al.*[20] demonstrated that NE released from the sympathetic terminals were responsible for AD, as opposed to epinephrine released from the adrenal medulla (that is, greater plasma levels of NE compared with epinephrine). AD is therefore a primary sympathetic phenomenon stimulating predominantly alpha-adrenergic smooth muscles.

Hypertension[25] triggered during AD episodes[17] activates baroreceptors in the carotid sinus and aortic arch, which stimulate two reflexes, one involving the vagal nerve and causing bradycardia, and another involving inhibition of descending sympathetic pathways.[24–27] As this inhibition can no longer reach the spinal segments below the lesion, diverging symptoms are observed above and below the lesion (Table 2).

The hyperactive sympathetic syndrome has been explained by various mechanisms, the first involving the loss of supraspinal inhibition, resulting in the massive reflex discharge described above. Increased liberation of NE in response to normal stimuli and hyper-responsiveness to alpha stimulation[28] have also been suggested, along with a decreased threshold for NE release. Recent evidence[29–31] further suggests that sprouting of visceral or somatosensory afferents occurs following SCI and increases the synaptic potential, thereby lowering the threshold for sympathetic discharge and rendering previously non-painful stimuli sufficient to trigger AD.

The severity of the AD episodes appears to increase with the levels and extent of injury,[17] higher and complete lesions being more vulnerable.[26] Posttraumatic delays also appear to have a role, as AD usually develops within the first year post injury, although rarely before the first two months post injury.[26]

Clinical management of AD

The Consortium for Spinal Cord Medicine[32] as well as Blackmer[25] and Krassioukov *et al.*'s[33] reviews recommend the use of non-pharmacological manoeuvres as a first treatment of AD. The standard protocol[32] involves uplifting the individual, lowering the lower limbs, removing compressive clothing below the lesion level,

Table 2 Symptoms of autonomic dysreflexia and related mechanisms

Symptoms above the lesion level		*Symptoms below the lesion level*	
Symptom	*Mechanism*	*Symptom*	*Mechanism*
Bradycardia	Parasympathetic response to hypertension mediated by vagus nerve	Hypertension	Sympathetic vasoconstriction of peripheral blood vessels
Pounding headache	Response to sympathetic inhibition above the lesion resulting in vasodilation of intracranial arteries	Profuse perspiration	Sympathetic (cholinergic) stimulation of sweat glands
Flushing of neck and face	Response to sympathetic inhibition above the lesion resulting in vasodilation of cutaneous microcirculation	Pallor and coldness of extremities	Sympathetic vasoconstriction
Increased skin temperature	Response to sympathetic inhibition above the lesion resulting in vasodilation of cutaneous microcirculation	Piloerection (shivering)	Sympathetic sudomotor response of hair follicles
Nasal congestion	Response to sympathetic inhibition above the lesion resulting in vasodilation of nasal mucosa vessels	Contraction of the bladder neck, intestinal and stomach sphincters	Sympathetic (adrenergic) stimulation of the viscera
Blurred vision	Response to sympathetic inhibition above the lesion resulting in vasodilation of ocular vessels	Increased spasticity	Sympathetic (adrenergic) stimulation of smooth and striated muscles

Based on Campagnolo and Merli.[26]

verifying the flow of urinary catheter, voiding the bladder or rectal ampulla, and continuously monitoring blood pressure.

When SBP remains above 150 mm Hg despite these manoeuvres, pharmacological treatment is introduced.[33] Treatments are usually considered when SBP reaches 150 mm Hg based on the criteria for primary hypertension. However, some procedures in rehabilitation, such as cystometry and cystoscopy, trigger rises in SBP, which sometimes exceed this threshold. Although treatment may then be implemented, tolerated thresholds of SBP are seldom described and usually left to clinical experience.

Ejaculation tests in men with SCI similarly involve higher SBP thresholds, which is not necessarily surprising given that non-SCI men show SBP rises from 140 mm Hg to 180 mm Hg at ejaculation.[34] In our clinics, we therefore tend to use a threshold of 180 mm Hg SBP before considering pharmacological intervention[5,7,12] unless the individual reports negative or uncomfortable side effects in which case the test is ceased and treatment implemented if side effects persist and blood pressure fails to diminish. Furthermore, when an individual is at risk of AD, prophylaxis treatment may also be considered.

Pharmacological treatment of AD

Studies specifically investigating the pharmacological treatments of AD include prophylaxis, acute as well as long-term treatments.

Treatment of AD during ejaculation procedures

Few studies have formally investigated the treatment of AD during ejaculation (Table 3), even though hundreds of papers described procedural managements of AD during ejaculation tests.[3,4,8,10,11,15] The outstanding majority of these studies used nifedipine (Adalat)[3,4,8,10,11,15,35,37] treatment. Others however attempted prazosin,[37] sildenafil[38] and prostaglandin E_2,[39] often with inconclusive results.

Nifedipine. Nifedipine is a calcium channel blocker acting on vascular smooth muscles and causing peripheral vasodilatation. Its sublingual absorption is effective within 5–10 min and its oral absorption within 45–60 min.

According to Braddom and Rocco,[24] and Blackmer,[25] nifedipine is the most widely used treatment of acute AD. VerVoort *et al.*[35] ($N=6$) and Steinberger *et al.*[36] ($N=10$) assessed its effectiveness as a preventive treatment of AD during electroejaculation and found that it significantly reduced peak[35,36] and average SBP,[37] as well as AD symptoms[35,36] (such as, headache, sweating, general discomfort).

Sønksen *et al.*[6] provided a comparison between individuals receiving nifedipine before vibrostimulation and those failing to receive such prophylaxis treatment, and showed an absence of AD symptoms in those treated.

Blackmer[25] describes no clinical incident upon nifedipine treatment of AD, but a warning was emitted concerning the risks of cardiac events with sublingual nifedipine in non-SCI[25,40] populations. The warning raised concerns and resulted in the removal of the drug in some hospital settings, thereby motivating the search for alternatives.

Prazosin. Prazosin (Minipress) is a selective antagonist of alpha1-adrenergic receptors, which reduces the overall peripheral resistance associated with sympathetic activity. Its vasodilatation lowers blood pressure without affecting heart rate (HR), except for a slight reflex tachycardia when standing.

Szasz *et al.*[37] attempted prazosin in prophylaxis 6–8 h before vibrostimulation and additionally 2 h before the tests for those with a history of AD. Only a few participants reported mild headache, but no other results are given, in particular, on blood pressure variations.

Braddom and Rocco[24] indicate that prazosin was the third most used medication (36%) in 1991 to treat AD, but mention that the product can cause hypotension or syncope upon the first dose, suggesting to start treatment the evening before.

Sildenafil and prostaglandins. Sildenafil is a type 5 phosphodiesterase inhibitor ($PDEI_5$) delaying the degradation of phosphodiesterase in smooth muscles and resulting in relaxation and vasodilatation. As a vasodilator, it may potentially decrease blood pressure. Sheel *et al.*[38] studied the effectiveness of sildenafil as a prophylaxis treatment of AD

Table 3 Autonomic dysreflexia associated with vibrostimulation or electroejaculation

Author reference	*Methodology*	*End point*
VerVoort *et al*.[35]	Population: $N=6$: C4–C7 SCI Intervention: Electroejaculation with or without nifedipine (10 mg sublingual 10–15 min before stimulation)	Maximum SBP on average decreased from 205 mm Hg to 182 mm Hg Relieved or significantly reduced of AD symptoms No adverse effect (for example, hypotension or tachycardia) Increased sperm retrieved (86.4% vs 33%)
Steinberger *et al*.[36]	Population: $N=10$: >T5 SCI Intervention: Electroejaculation with or without nifedipine (20 mg sublingual 15 min before stimulation)	Mean SBP decreased from 163 mm Hg to 143 mm Hg BP were lower in 8/10 patients with less AD symptoms One patient had side effect (hypotension)
Sønksen *et al*.[6]	Population: $N=66$: C2–T9 (55), T10–L1 (11) SCI Intervention: Nifedipine (10 mg) sublingual 10 min before PVS if history of AD and lesion $\geqslant$T6	No patient experienced AD symptoms with nifedipine compared with five patients without preventive nifedipine
Szasz *et al*.[37]	Population: $N=35$: C5–T4 (18), T5–T10 (10), T11–L1 (7) SCI Intervention: Prazosin PO (1 mg) 6–8 h before PVS. Additional 0.5 mg PO 2 h pre-PVS if history of AD	Participant experienced no other AD symptoms than mild headaches
Sheel *et al*.[38]	Population: $N=13$: C2–T5 SCI Intervention: PVS with or without sildenafil citrate (25–100 mg PO>10 min. before stimulation)	No effect on cardiovascular responses (BP and HR)
Frankel *et al*.[39]	Population: $N=3$: C5–T4 SCI Intervention: Electroejaculation with or without intravenous prostaglandin E_2	BP decreased during stimulation BP was lower at rest

Abbreviations: AD, autonomic dysreflexia; BP, blood pressure; HR, heart rate; PO, per os; PVS, penile vibrator stimulation; SBP, systolic blood pressure; SCI, spinal cord injury.

during vibrostimulation in men with lesions located above T6, but found no significant results. Severe hypotension in contrast was observed on some tetraplegic individuals.

Frankel *et al*.[39] found that intravenously prostaglandin E2, another vasodilator, reduced blood pressure during electroejaculation, but the report only concerned three cases.

Treatment of AD during other AD triggering procedures

Other procedures, in particular, in urology are known to trigger AD and require preventive or acute treatments (Table 4).

Cystometry, cystoscopy. Dykstra *et al*.[41] studied the effect of sublingual nifedipine during cystoscopy and found that it significantly decreased mean SBP and diastolic blood pressure (DBP). Lindan *et al*.[42] similarly found that it decreased blood pressure within 30–40 min. Thyberg *et al*.[43] showed that prophylactic nifedipine significantly reduced maximum SBP and DBP, and blood pressure during cystometry.

Extracorporeal shock wave lithotripsy. Kabalin *et al*.[44] reported successful control of blood pressure with sublingual nifedipine during AD triggered by extracorporeal lithotripsy. Burstein *et al*.[45] similarly showed a decrease in blood pressure from 240/123 mm Hg to 120/70 mm Hg in an individual experiencing AD during extracorporeal lithotripsy.

Nifedipine therefore shows significant effect not only as an acute treatment, but also as a prophylactic treatment of AD. However, as nifedipine can decrease resting blood pressure,[42] individuals who are vulnerable to hypotension (in tetraplegia) must be monitored before considering its prophylactic use.

Treatment of AD in other conditions

When individuals with SCI show a resting hypertension above 150 mm Hg SBP, with no identified cause, pharmacological treatment is implemented. Most reports again mention not only nifedipine, but also prazosin, captopril, clonidine and alpha1-adrenergic antagonists (Table 5).

Nifedipine. Rooney *et al*.[46] reported successful treatment of an early case of AD (<72 h) with sublingual nifedipine in a tetraplegic man suffering from ileus. Chaves *et al*.[47] reported successful treatment of AD with sublingual nifedipine in a tetraplegic woman submitted to a cough manoeuvre. Vaidyanathan *et al*.[48] successfully treated recurrent AD with sublingual nifedipine in a tetraplegic man with chronic aortic dissection. Skowronski *et al*.[49] reported beneficial effect sublingual nifedipine in a tetraplegic parturient.

Prazosin. Krum *et al*.[22] found that prazosin, as an alpha1-adrenergic antagonist, was superior to placebo as a continuous treatment of AD in individuals experiencing AD for a week.

Captopril. Following the warning concerning the increased risks of cardiac conditions with sublingual nifedipine, Esmail *et al*.[50] assessed the effectiveness of captopril sublingual. Captopril is an angiotensin-

Table 4 Autonomic Dysreflexia related to urologic procedures

Author reference	*Methodology*	*End point*
Nifedipine (adalat/procardia)		
Lindan *et al.*[42]	Population: $N=12$: C4–C6 SCI Intervention: (1) Nifedipine (20 mg) PO twice a day x$\geqslant$24 h versus Phenoxybenzamine (10 mg) PO twice a day x$\geqslant$4 h before cystometry (2) Nifedipine (10 mg) PO if AD attacks triggered by cystometry (3) Nifedipine (10 mg) PO 30 min before urologic manipulations	Neither drugs prevented AD during bladder distension, neither drugs prevented AD during other noxious stimuli, four patients with phenoxybenzamine and three with nifedipine developed severe hypotension Effective management of all cases of acute AD with nifedipine ($N=7$) None of the patients developed AD ($N=4$) with preventive nifedipine
Dykstra *et al.*[41]	Population: $N=7$: C3–C6 SCI Intervention: (1) Nifedipine (10 mg) sublingual if AD symptoms or >180/110 mm Hg triggered by cystoscopy (2) Nifedipine (10 mg) PO 30 min before cystoscopy if AD in previous cystoscopy	Mean SBP and AD symptoms significantly decreased for all patients ($N=7$) Effective prevention of AD for all patient when given orally 30 min before cystoscopy ($N=3$) No adverse effect of drug observed in both acute management and prophylaxis
Thyberg *et al.*[43]	Population: $N=10$: >T5 SCI Intervention: Nifedipine (10 mg) sublingual 10 min before cystometry	Mean and maximum SBP/DBP with nifedipine (118/83 mm Hg) significantly decreased compared with cystometry without nifedipine (147/110 mm Hg) Maximum SBP and DBP decreased for all patients
Kabalin *et al.*[44]	Population: $N=20$: C3–C6 (10), T1–T6 (7), T9–T12(3) SCI Intervention: Nifedipine (10–30 mg) sublingual if AD triggered by ESWL	Effective control of BP elevation in all acute AD ($N=19$) 6 out of 19 patients received intravenous atropine due to severe reflex bradycardia caused by AD
Burnstein *et al.*[45]	Population: $N=1$: C5–C6 SCI Intervention: Nifedipine (10 mg) sublingual during ESWL	Important decreased in SBP after 30 min (from 150 mm Hg to 80 mm Hg) requiring ephedrine and atropine to compensate for low BP and bradycardia

Abbreviations: AD, autonomic dysreflexia; BP, blood pressure; DBP, diastolic blood pressure; ESWL, extracorporeal shock wave lithotripsy; PO, per os; SBP, systolic blood pressure; SCI, spinal cord injury.

converting enzyme inhibitor, which blocks the renin–angiotensin–aldosterone system and causes a reduction in peripheral arterial resistance, without changing cardiac output. Esmail *et al.*[50] found that the drug significantly reduced SBP during AD in four out of five participants, one requiring rescue therapy with nifedipine.

Clonidine. Clonidine (Catapres) is an alpha2-adrenergic agonist that causes inhibition of the sympathetic outflow and decreases vascular resistance. According to Blackmer,[25] clonidine is a common treatment of AD, and according to Braddom and Rocco[24] 8% of experts use clonidine as an acute treatment of AD. No systematic studies, however, can be found on the product, although four case reports show clinical improvements.

Wright *et al.*[51] successfully treated a paraplegic man suffering from a neuroblastoma and experiencing AD upon bowel distension with clonidine. Hall *et al.*[52] showed that clonidine lowered peaks of pressure during dressing changes in a tetraplegic man suffering from buttock ulcer. Roche *et al.*[53] described five cases of hypertension secondary to idiopathic high levels of catecholamines in paraplegic individuals, where four out of five responded positively to clonidine suppression. Skowronski *et al.*[49] successfully treated AD with intramuscular clonidine (in addition to sublingual nifedipine) to reduce pressure spikes in tetraplegic parturients.

Terazosin. Terazosin (Hytrin) is an alpha1-adrenergic antagonist similar to prazosin but with a longer duration of action (24 h as opposed to 6–12 h). Similar to prazosin, it can cause orthostatic hypotension upon the first dose and it is recommended to start treatment the night before. According to Blackmer,[25] terazosin is among the most widely used treatment for recurrent AD.

Vaidyanathan *et al.*[54] showed that terazosin relieved the symptoms of recurrent AD in spinally injured individuals. Chancellor *et al.*[55] showed that it significantly improved the severity and frequency of AD episodes long term, but did not change the intensity of headaches. Swierzewski *et al.*[56] showed that daily terazosin during a month abolished or reduced AD episodes in four individuals with SCI.

Doxazosin. Doxazosin (Cardura) is another alpha1-adrenergic receptors antagonist successfully used[44] to treat a tetraplegic man undergoing chronic aortic dissection. Despite this study, actually combining doxazosin with long-acting nifedipine,[52] Krassioukov *et al.*,[33] Blackmer,[25] Braddom and Rocco[24] all fail to include dozazosin as a recognized treatment of AD.

Phenoxybenzamine. Phenoxybenzamine is a long-acting non-selective antagonist of alpha-adrenergic receptors which, according to Braddom and Rocco[24] in 1991, was the second most used drug for the treatment of minor AD. Krassioukov *et al.*,[33] however, mention that there is conflicting evidence on its effectiveness. Lindan *et al.*[42] compared it with nifedipine in prophylaxis during cystometry and found that both drugs reduced resting blood pressure, but failed to prevent AD during bladder distension. Both medications caused hypotension at rest, requiring discontinuation of treatment or reduction of dose in some participants. McGuire *et al.*[57] reported

Table 5 Autonomic Dysreflexia related to other stimuli

Captopril (capoten)		
Esmail *et al.*[50]	Population: $N=5$: >T6 SCI Intervention: Captopril (25 mg) sublingual if SBP $\geqslant$150 mm Hg	SBP reduction in 4/5 patients during AD SBP reduction in all patients during AD when nifedipine (10 mg) sublingual is added as a rescue therapy Mean SBP reduction after 30 min compared to baseline (178 mm Hg vs 110 mm Hg)
Antagonist of alpha1-adrenergic receptors		
Krum *et al.*[22]	Population: $N=15$: $\geqslant$T6 SCI Intervention: Randomized controlled trial: prazosin (3 mg) PO twice a day ($N=8$), placebo ($N=7$) for 2 weeks	Prazosin group had shorter and less AD symptoms, reduced maximum SBP and less antihypertensive medication use
Chancellor *et al.*[55]	Population: $N=21$: C3–T5 SCI Intervention: terazosin (5 mg) PO once a day for 3 months	Decrease in score severity (symptoms) and in frequency of AD episodes at 1 and 3 months At 3 months, no significant effect on SBP
Swierzewski *et al.*[56]	Population: $N=12$: C4–C8 (6), T7–L1 (6) SCI Intervention: terazosin (5 mg) PO at night for 4 weeks	AD was modified in four patients: abolished ($N=3$), decrease severity/episode ($N=1$) Positive change in detrusor compliance and bladder pressure
Vaidyanathan *et al.*[54]	Population: $N=24$: $\geqslant$T4 SCI Intervention: terazosin (0.5–10 mg) PO once a day according to age with increasing dose	Resolution of AD symptoms Mild and transient side effects (e.g., hypotension) Medication interrupted in one case (important dizziness)
Vaidyanathan *et al.*[48]	Population: $N=1$: 61 year-old man, C5 SCI Chronic aortic dissection Intervention: Doxazosin (8 mg) PO twice a day and nifedipine SR (10 mg) PO twice a day	Effective treatment for recurrent episodes of AD
Clonidine (catapress)		
Wright *et al.*[51]	Population: $N=1$: 22 year-old man, T4 SCI Neuroblastoma Intervention: Clonidine (0.2 mg) PO twice a day	Fewer episodes of hypertension and BP reduction at rest
Hall *et al.*[52]	Population: $N=1$: 32 year-old man, C5–C7 SCI AD during dressing changes for a pressure ulcer Intervention: Clonidine (0.2 mg) PO twice a day	Effective control of BP during dressing changes
Roche *et al.*[53]	Population: $N=5$: paraplegia<T8 SCI Idiopathic catecholamine increase Intervention: Clonidine suppression test	Effective suppression test in four out five patients Two patients required long-term medications to control BP
Skowronski *et al.*[49]	Population $N=$unknown(<5), tetraplegic pregnant women In labor Intervention: Nifedipine sublingual or clonidine intramuscular (dose unknown) if acute AD	Effective management of acute AD No adverse effect with clonidine
Adalat (nifedipine)		
Rooney *et al.*[46]	Population: $N=1$: 19 year-old man, C5 SCI Spinal artery thrombosis Intervention: Nifedipine (10 mg) sublingual during acute AD due to ileus	Effective treatment of acute AD when combined with bowel decompression
Chaves *et al.*[47]	Population: $N=1$: 55 year-old woman, C5–C6 SCI Leukoencephalopathy Intervention: Nifedipine (dose unknown) sublingual during acute AD due to assisted cough maneuver	Elevation of bed head during cough maneuver associated with occasional use of sublingual nifedipine prevented further episodes of AD

Abbreviations: AD, autonomic dysreflexia; BP, blood pressure; PO, per os; SBP, systolic blood pressure; SCI, spinal cord injury; SR, slow release.

positive effects of phenoxybenzamine, but animals studies showed tumor growths, suggesting a potential carcinogenic effect.[24,42] Phenoxybenzamine has therefore been eliminated as a treatment of AD.

DISCUSSION

All in all, studies on the acute and prophylactic treatment of AD in individuals with SCI emphasize the effectiveness of nifedipine. Despite these results, the use of nifedipine has been questioned in a meta-analysis, yet performed on another population than SCI, but indicating that its sublingual use may increase the risk of myocardial infarction, stroke and severe hypotension.[40] These warnings have motivated the search for alternatives. Yet, no adverse effects have been reported in the SCI population.[32]

Among alternatives, prazosin, clonidine and captopril have been found potential candidates. Prazosin,[37] however, has a long delay of action (6–8 h), which requires a preliminary dose 12 h before its use (to counteract initial hypotension). This makes it less ideal for spontaneous sexual activities, especially as individuals with SCI complain that treatments for sexual dysfunctions often jeopardize the spontaneity of sexual acts. Prazosin, in this context, may be better suited for planned fertility tests rather than spontaneous sexuality. Prazosin also acts on smooth muscles and may increase the risk of retrograde ejaculation,[37] again placing the drug as a less ideal candidate for sexual function.

Captopril is another product recommended as an alternative to nifedipine. Although successful for the treatment of acute AD,[33,50] its ability to prevent AD in prophylaxis during sexual activities remains unknown. Knowing that it has an initial hypotensive effect, its prophylactic use must be commended with care on tetraplegic individuals showing resting hypotension.

Clonidine has not been formally studied in randomized trials, but has been used in clinical practice for decades to prevent AD. Published case reports support its effectiveness for the acute and chronic treatment of AD in individuals with SCI.[24,25,50,52,53] It may be a good candidate as a prophylactic treatment of AD in the context of sexual activities.

Sildenafil[38] and prostaglandins,[40] which can be used by men with SCI to control unstable or dysfunctional erections, have given inconclusive results. Although sildenafil failed to prevent AD,[38] it was associated with severe hypotension (75 mm Hg) at baseline in a small number of tetraplegic men ($N = 8$) but with significant results. Such findings reinforce the need and interest of clinical trials on the use of sildenafil at home for tetraplegic individuals.

Products such as terazosin, doxazosin and phenoxybenzamine have been ruled out as prophylactic treatments in the context of sexual activities based on their long delay of action, poor or lack of effect and hypotensive or carcinogenic potential. New treatments in contrast have not yet been tested empirically for the acute or preventive treatment of AD. Nitrol paste rapidly controls hypertension[58] but its use may not be ideal with sexual activities where PDE5 inhibitors are also considered (risks of syncope).

Studies describing procedural management of AD mentioned nitroglycerine,[57–61] a compound which we exclude because of the risks of severe hypotension when combined with PDE5 inhibitors. Others mention nicardipine,[62] another calcium channel blocker but not available in North America. Earlier studies also mentioned phentolonium,[63] dihydralazine,[64] and general anaesthesia[3,15,65–68] during electroejaculation procedures,[60,61] but are not conceivable at home.

All in all, the current review emphasizes the effectiveness of nifedipine and leaves relatively few options for the treatment of AD in the context of sexual activities. With the currently provided approaches to anejaculation in men with SCI, in particular vibrostimulation and midodrine easily used at home, the question of AD risks and management become essential. Both vibrostimulation and midodrine maximize ejaculation, but both carry the risk of AD. Studies on midodrine,[7] however, do not show higher increases in SBP at ejaculation compared with vibrostimulation alone, but increases in baseline SBP (that lowers the threshold for ejaculation).[7] AD risk with midodrine is therefore similar to that with vibrostimulation and seems related to the occurrence of ejaculation itself. Upon AD risks, the Consortium for Spinal Cord Medicine[32] suggests that the ideal drug should have a rapid onset, short duration of action, few side effects, and be safely used at home. In this context, nifedipine remains an ideal candidate. Given the recent concerns on cardiovascular events, perhaps oral nifedipine would be preferred over sublingual to reduce its rapid and steep action precipitating cardiovascular risks.

When to use acute pharmacological or prophylaxis treatment for AD

Aside from these concerns on the ideal medication for AD in individuals with SCI, questions have been raised during this review on the threshold and parameters that should be considered for AD management. The Consortium for Spinal Cord Medicine suggests that a threshold of 150 mm Hg SBP be considered to implement pharmacological treatment, based on the treatment of primary hypertension in non-SCI populations.[32] However, rehabilitation practice, particularly urology, often exceeds this threshold to complete cystometric or cystoscopic procedures. Although clinical judgement then decides on when and whether to treat AD, no published data appears to be available on the range and parameters that are considered in such cases.

Ejaculation tests performed on men with SCI can also exceed the threshold of 150 mm Hg SBP, in particular because normal ejaculation in able-bodied men already involves 140 to 180 mm Hg peaks.[33] Although severe hypertension in men with SCI has exceeded these values,[18] the maximum threshold that should be allowed during ejaculation tests is not discussed. The Paraplegic Veterans of America guidelines mention a threshold of 150 mm Hg SBP to implement treatment. This threshold suggests that many, if not most ejaculation tests with tetraplegic men, should provide AD treatment. This further raises the question of home use of vibrostimulation and the concerns associated with nifedipine risks. A discussion among professionals should probably be encouraged for a consensus to be reached on these thresholds and issues, especially upon home ejaculation.

Aside from these SBP values, DBP and HR are seldom mentioned as parameters of AD or as a sign of successful treatment. The primary definition of AD relies on hypertension, but specific criteria are seldom given for DBP (>90 mm Hg)[17] and none for HR, even though both are considered in the diagnosis of both primary hypertension (SBP consistently >140 mm Hg, DBP consistently >90 mm Hg).[69] In our practice, DBP can rise beyond 100 mm Hg at ejaculation, which raises the question of silent hypertension. The importance of HR can similarly be raised. As bradycardia often occurs during AD, values below 40 beats per min are considered critical by our teams, but fortunately have never been observed during our ejaculation tests.

While attempting prophylactic treatment of AD based on (any of) the above criteria, a new problem is raised when the individual's resting blood pressure is particularly low, for example, in tetraplegic

men. Men with such lesions often exhibit initial SBP within 80–90 mm Hg, which questions the minimal threshold that can be accepted before a prophylaxis treatment can be planned. The literature is silent on this issue. The same applies for the other cardiovascular parameters, DBP or HR. Knowing that men with SCI experience sexual activities at home, and knowing that options such as vibrostimulation and oral midodrine are available to help them achieving ejaculation,[3–7] these issues become essential in the management of sexual function in individuals with SCI.

While debating on the thresholds and parameters to be considered, individuals with SCI may be systematically encouraged to purchase a sphygmomanometer, especially those with higher lesions (>T6) and vulnerable to AD. McBride *et al.*[70] showed that SBP could triple at ejaculation in tetraplegic individuals and while these cases are isolated in the literature and in our clinical experience, SBP rises between 200 and 230 mm Hg are encountered. Silent AD can further be observed at these values, making the warning more critical for individuals at risk. Although seldom discussed during intercourse—perhaps because natural ejaculation is rarely observed in men with SCI—information on AD should be provided to every individual at risk. Perhaps an assessment of ejaculation should be systematically offered before leaving rehabilitation to avoid undue risk at home. Educating the individuals about the various signs of hyper or hypotension, other than readings from the sphygmomanometer may also be considered (especially if they fail to use it during spontaneous sexual activities). In this context, we developed a questionnaire[13] to help men with SCI recognizing the signs of autonomic responses during ejaculation. It could be useful to identify signs of AD, particularly in the context of silent or asymptomatic AD.[23]

CONCLUSION

Concerns about AD during sexual activity and about the long-term management of sexual function in individuals with SCI raise several issues: (1) determining the SBP threshold at which pharmacological treatment of AD should be implemented or systematic prophylaxis considered (especially at home), (2) exploring whether DBP and/or HR parameters should also be considered in the decision, (3) which DBP/HR thresholds should then be considered before implementing treatment, (4) whether patients should be systematically assessed for ejaculation before leaving rehabilitation, (5) whether they should be encouraged to purchase a sphygmomanometer, (6) what signs if any should be emphasized to draw the patients' attention on hyper or hypotension and (7) how to educate patients on silent AD.

When treatment is implemented, nifedipine appears to be the best candidate despite recent concerns about its long-term cardiovascular risks in non-SCI populations. The Consortium for Spinal Cord Medicine,[32] however, reveals no negative side effects on patients with SCI. Perhaps oral rather than sublingual nifedipine would be more secure.

Experts should meet and conclude on the thresholds and parameters to be considered in AD to provide a safe prevention during sexual activities, especially knowing that sexuality is a priority for individuals with SCI.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank Dr Nancy Michelle Robitaille for her comments on the Ethics proposal from this paper.

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