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REVIEW

Treatments for erectile dysfunction in spinal cord patients: alternatives to phosphodiesterase type 5 inhibitors? A review study

This article has been corrected since advance online publication and a corrigendum is also printed in this issue.

G Lombardi[1], S Musco[1], JJ Wyndaele[2] and G Del Popolo[1]

Study design: Review study.
Objectives: Alternative treatments to oral phosphodiesterase type 5 inhibitors (PDE5Is) in individuals with spinal cord lesions (SCLs) and erectile dysfunction (ED).
Setting: Italy.
Methods: Research clinical trials (1999–2014).
Results: Twelve studies were selected. One article documented that 76% of subjects reached satisfactory sexual intercourse (SI) using intracavernosal injection of vasoactive medications (papaverine and prostaglandin E1). One study regarding perineal training showed a significant increase ($P<0.05$) in penile tumescence in 10 individuals with preserved sacral segment. Two studies reported contrasting results on erectile function (EF) using various dosages of oral fampridine (25–40 mg). Furthermore, 95.1% of patients on fampridine 25 mg experienced drawbacks. Disappointing findings were found with intraurethral alprostadil (125–1000 μg) and sublingual apomorphine 3 mg. Two studies concerning penile prosthesis reported valid SI more than 75% of the time with a mean follow-up of 11 years, although around 15% of individuals showed side effects. As for surgical treatments, 88% of males submitted to Brindley sacral anterior root stimulator after sacral dorsal rhizotomy achieved valid erection up to 8 years following the procedure. Three studies documented the impact of definitive sacral neuromodulation implant (Medtronic, Minneapolis, MN, USA) also on EF. After surgery, 20–37.5% of patients with ED recovered normal EF.
Conclusions: Data are scant on the efficacy of ED treatments for SCL subjects who did not respond to PDE5Is. Further research should investigate the effects of any SCL treatments even when they are not strictly used for neurogenic sexual dysfunction.
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INTRODUCTION

Erectile dysfunction (ED) is a common complication in men with spinal cord lesion (SCL).[1] The impact of an SCL on erectile function (EF) depends on the severity and location of the injury.[2–6] Three types of erections after SCL have been described. 'Reflexogenic erection' results from direct stimulation of the genital area, requiring the integrity of the parasympathetic erectile centre (S2-S4). Rigidity of the penis can be obtained when the level of lesion is above T11. This erection is usually sufficient for penetration but often has a short duration.[2–6]

'Psychogenic erection' can be attained through psychic stimulation: visual, auditory and olfactory, as well as from dreams, memories and fantasies.[2,3,6] This erection can be achieved through the integrity of the thoracolumbar sympathetic centre (T11-L2) and with spinal lesions below L2. These erections are usually low quality and of short duration.[2,6] 'Mixed erection' occurs when the SCL is between the two centres, meaning the level of lesion is below L2 and above S2. These erections may differ as to duration and quality.[2,5]

Literature reports that erection is more likely to be reached by subjects with incomplete rather than complete lesion according to the ASIA/AIS Impairment Scale.[2,3,6,7]

Most men with SCL, therefore, require chronic treatment for ED. Maintaining a healthy sex life after SCL is an important priority to many people, considering that the 16–30-year-old age bracket continues to represent the largest group of new traumatic SCL worldwide.[8–9] Managing ED in men with SCL is of paramount importance because it represents a major determinant of their psychological distress.[10] The successful launch of Viagra (sildenafil), in 1998, the first such phosphodiesterase type 5 inhibitors (PDE5Is), revolutionized the treatment of ED in subjects with SCL. Even during initial clinical studies sildenafil proved highly effective in promoting erectile responses in individuals with SCL. Moreover, any adverse effects reported by these patients were mild to moderate and transient.[11–13]

Subsequently, literature reported high percentage efficacy for valid sexual intercourse (SI) and concomitant low percentage of side effects with the other more recent oral PDE5Is: Cialis (tadalafil) and Levitra (vardenafil HCI).[14–16]

Understandably, PDE5Is have become the first-line treatment for ED for neurogenic subjects including those with SCL.[17] However, the three above-mentioned PDE5Is (sildenafil, tadalafil and vardenafil) are not suitable for all SCL patients, particularly those suffering complete

[1]Neuro-Urology Department, Careggi University Hospital, Florence, Italy and [2]Department of Urology, Antwerp University Hospital and University of Antwerp, Faculty of Medicine, Antwerp, Belgium
Correspondence: Dr G Lombardi, Neuro-Urology Department, Careggi University Hospital, Largo Palagi 1, Florence 50127, Italy.
E-mail: giuseppelombard63@libero.it
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damage to the sacral segment (S2-S4) and with an absence of reflex erection. As a matter of fact, the percentage of successful SI was statistically significantly lower compared with that of individuals with a preserved sacral segment.[18–19]

The use of oral PDE5Is is contraindicated for men taking nitrates (used on-demand to treat autonomic dysreflexia), and should be used with caution on men with symptomatic hypotension and/or tetraplegia owing to its hypotensive effect.[20]

The aim of this review is to evaluate the role of different ED therapies, excluding PDE5Is, on patients with SCL following the release of the first PDE5Is.

METHODS

Data sources and study selection

This systematic review was conducted according to the *Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement*.[21] A MEDLINE search through PubMed, EMBASE and OVID was carried out using the following terms: 'spinal cord (AND) erectile dysfunction (AND) treatment'. All relevant papers published in English from 1999 to 2014 were retrieved. Search criteria were limited to humans, adults and English full-text clinical trial articles. ED interventions for humans included all possible medications such as oral, creams, intracavernous injection (ICI) of vasoactive agents and intraurethral alprostadil.

The use of devices for ED such as penile rings, vacuum or penile implants were included as well. All identified studies were screened for eligibility, in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*.[22] Two authors (GL, SM) collected data from eligible reports. Disagreements were resolved by consensus and if necessary by third party resolution (GDP).

SEARCH RESULTS

The PRISMA flow chart is shown in Figure 1.

After screening abstracts, 33 eligible reports were identified. Treatment results were not clearly reported in 16 articles. Five studies did not include SCL patients in their cohort of neurological patients. Overall, 12 articles were included in qualitative synthesis. Quantitative synthesis (that is, meta-analysis) was not possible because of the small number of studies and the heterogeneity of treatments.

OUTCOME MEASURES

The majority of the authors used a global efficacy assessment question to measure treatment efficacy.[23–27]

The International Index of Erectile Function questionnaire composed of 15 questions (IIEF-15) was the most common validated questionnaire used to evaluate EF pre- and post treatment.[28–31]

The abridged 5-item version of the International Index of Erectile Function (IIEF-5) was utilized as well.[32–34]

Bodner *et al.*[35] determined the grade of erection reached after various dosages of intraurethral alprostadil (125–1000 μg) by using the Schramek scale (range 1–5). Grades 4 and 5 represented sufficient penile rigidity for SI.

Courtois *et al.*,[36] through a penile strain gauge from the Rigiscan device (TIMM Medical Technologies, Eden Prairie, MN, USA), recorded penile tumescence and rigidity at baseline, at the end of one 15-min session of perineal training, after 4 weeks of home perineal training and following 4 weeks of suspended sexual rehabilitation.

STUDIES AND PATIENT CHARACTERISTICS

None of the authors of any of the studies selected reported the evaluation and degree of patients' residual erection: neither reflex nor psychogenic erection at baseline. Only a few authors included all levels and degrees of lesions according to the ASIA/AIS scale for all SCL patients.[23–25]

To facilitate better understanding, results are reported by dividing the data into two groups: conservative versus surgical treatments.

Conservative treatment studies

Overall six studies were included. Only one study reported the efficacy of behavioural interventions by perineal muscle training exercises.[36]

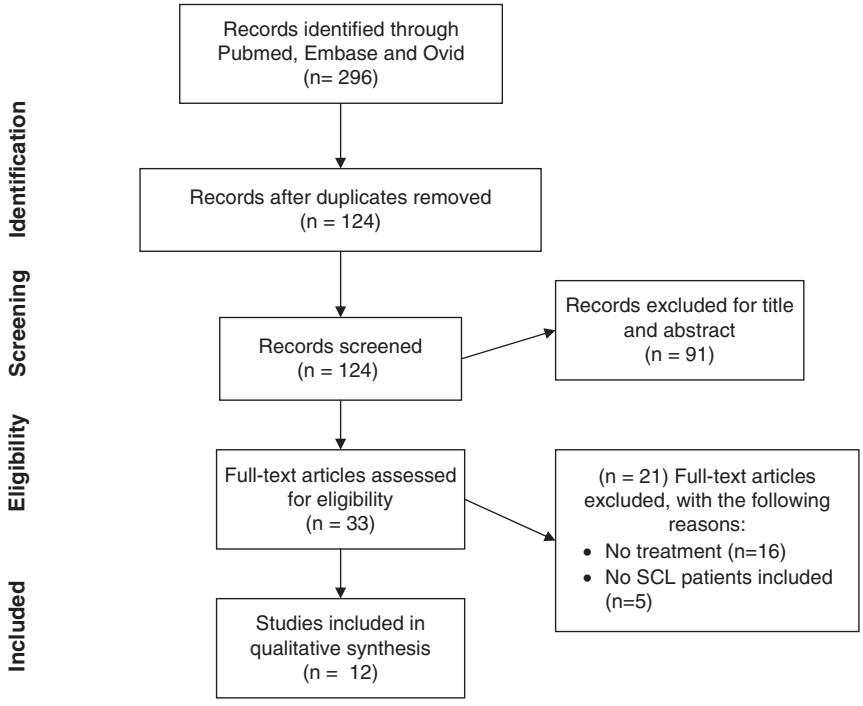

Figure 1 PRISMA flow chart.

Table 1 Study types and results of conservative treatments for ED alternatively to phosphodiesterase type 5 inhibitors

	Treatments (dosage)	*Study design*	*Outcome measures*	*No. of Pts included*	*Efficacy on ED*	*Side effects*
Zaslau *et al.*[23]	ICI combination of papaverine and prostaglandin E1 (mean dosage 0.29 cc)	Ambulatory visits followed by 3 months home therapy only in responders	SQ[a]	37	Ambulatory sessions: 28/37 (76%). At the end of 3-month therapy: 21/28 patients (75%)	Home therapy: 2/28 (8.3%) dropped out owing to pain
Strebel *et al.*[31]	Apomorphine (3 mg SL)	Fixed dosage of Apomorphine 3 mg SL for 8 weeks	IIEF-15[b]	22	2/22 (9%) achieved valid sexual intercourse with the treatment. IIEF-15[b] scores are NA	2/22 patients (9.1%) dropped out: 1: palpitations and unspecified blood pressure problems 1: Severe nausea and headache
Cardenas *et al.*[29]	Fampridine (25 mg or 40 mg) vs placebo	*Three randomized groups:* Fampridine SR 25 mg bid (22 pts), Fampridine SR 40 mg bid (26 pts) and Placebo (24 pts)	IIEF-15[b]	91 (72 males and 15 females)	Improvement of erection frequency in patients on fampridine ($P = 0.02$)	16/91 discontinued the treatments for AEs.The most frequent side effect associated with discontinuation was dizziness: 7 patients (8%).
Bodner *et al.*[35]	Alprostadil (125–1000 μg)	Medicated transurethral system was used to deliver alprostadil (MUSE)	Schramek grading scale	15	3/15 (20%) achieved a valid erection (score 4) for sexual intercourse with 1000 μg	3/15 (20%) showed transient hypotension because penile ring was not used
Cardenas *et al.*[30]	Fampridine 25 mg vs placebo	Study SCI-F301[c] *Two randomized groups*: fampridine 25 mg b.i.d or placebo for 12 weeks	IIEF-15[b]	212 (185 males and 27 women)	Improvement of EF ($P=0.016$) and OF ($P=0.032$) on IIEF-15[b] in the group of fampridine in only one study (SCI-F301[c])	22/212 (10.4%) left the study owing to side effects. The most frequent was dizziness in 7/114 patients (6.1%) using fampridine
Courtois *et al.*[36]	Perineal training	One-day ambulatory session of PT combined with biofeedback and subsequently 4 weeks of PT home program	Rigiscan	10	Significant increase in penile circumference (average of 3.22 cm) and maximal tumescence (average of 3.90 cm) after 4 weeks home PT	Not reported

Abbreviations: AE, adverse event; ED, erectile dysfunction; EF, erectile function; ICI, intracavernous injection; IIEF-5, 5-item version of the International Index of Erectile Function; NA, not available; OF, orgasm function; PT, perineal training; Pts, patients. *The number and percentage of this AE were not reported.
[a]Self-questionnaire.
[b]International index of erectile function composed of 15 items.
[c]Double-blind, placebo-controlled trial conducted at 45 centres in the United States from July 2002 to February 2004.

The other studies showed the effectiveness and safety of pharmacological treatments.[23,29–31–35] See Table 1.

Mean time since SCL occurred varied from 6 months to 7.1 years.[23,36]

The mean age was around 39 years (range 34.7–43.7).[23,36]

Three authors included only incomplete lesions (B, C, D) according to the ASIA Impairment Scale grade (AIS).[29,30,36] Of those, two included patients with lesion between C4- and T10.[29,30] Only one author included 10 patients who had been treated previously and satisfied with sildenafil.[31]

Surgical treatment studies

Overall six studies were included (see Table 2).

The mean time since SCL varied from 2 months to 11.2 years post lesion.[24,27] The mean age was around 43 years (range 31–48).[24,27] Only two out of six studies included subjects with incomplete lesions according to the ASIA Impairment Scale grade (AIS).[7,33,34]

Three papers on the use of a permanent sacral neuromodulation (SNM) implant (InterStim system, Medtronic, Minneapolis, MN, USA) to treat neurogenic lower urinary tract symptoms investigated its effect on EF as well. The authors did not clearly mention the parameter settings used in three SNM studies.[27,33,34]

Lombardi *et al.*[33, 34] performed monolateral SNM on S3 foramina only on patients with incomplete SCL. It is worth noting that 20 out of 22 patients were using PDE5I drugs to achieve valid erection for SI before SNM surgery. On the contrary, Sievert *et al.*[27] bilaterally implanted the S3 roots of 10 patients with complete SCL according to the ASIA/AIS Impairment Scale during their shock phase.[7]

In another study, all subjects with complete SCL underwent implantation of a Brindley sacral anterior root stimulator after rhizotomy of posterior sacral roots.[26]

Two studies reported on various types of penile prosthesis. Specifically, Zermann *et al.*[24] used the semirigid Jonas, self-contained inflatable AMS hydroflex and AMS dynaflex, whereas Kim *et al.*[25] implanted only a malleable penile prosthesis (AMS 600). In one study, all patients had undergone implantation from 1980 to 1996.[24] In the other study, only 9 out of 48 patients (18.7%) had previously attempted sildenafil therapy before the penile implant.[25]

EFFICACY AND SAFETY

Conservative treatments

Satisfactory results were documented in a study exclusively using ICI of PGE1 and papaverine. During ambulatory visits, 28 subjects (76%) responded to injection. Patients who did not respond to injections of 1.0 cc were considered treatment failures.[23]

The home perineal muscle training showed a statistically significant but a temporary increase in penile tumescence circumference. In no patient was valid penile rigidity found.[36]

The more recent article reporting two identical double-blind placebo-controlled studies with Fampridine (Phase III) showed that two IIEF-15 domains (erectile and orgasmic function) were significantly improved at the end of the 12-week treatment compared with

Table 2 Study types and results of surgical treatments for ED

	Treatments	*Outcome measures*	*No. of Pts included*	*Mean follow-up*	*Efficacy*	*Side effects*
van der Aa *et al.*[26]	SDR+ SARS	Subjective assessment questionnaire	33	~ 8 years	29 patients (87.8%) maintained a valid erection for sexual intercourse	3/33 cerebral-spinal fluid collection 3/33 receiver failure with the need of a new implant.
Lombardi *et al.*[33]	Monolateral (S_3) permanent SNM implant	IIEF-5[a]	9	~ 5 years	3 patients (33.3%) with ED at baseline showed normal scores	2/3 underwent a controlateral SNM implant during follow-up for recovering clinical efficacy on N-LUTS and EF.
Lombardi *et al.*[34]	Monolateral (S_3) permanent SNM implant	IIEF-5	16	~ 5 years	6(37.5%) were 'responders' and maintained normal scores	2/3 underwent a controlateral SNM implant during follow-up for recovering clinical efficacy on N-LUTS and EF
Sievert *et al.*[27]	Bilateral (S_3) SNM implant	Global assessment question	10	~ 2 years	2 (20%) subjectively improved	6/10 underwent a new implant for onset NDO
Ziemann *et al.*[24]	Different types of penile prosthesis	Global assessment question	92	~ 7 years	77(83.7%) achieved sexual intercourse	12/92 patients did not use the prosthesis because erection instability and concordphenomenon
Kim *et al.*[25]	Malleable penile prosthesis (AMS 600)	Global assessment question	48	~ 12 years	44 (91.7%) achieved sexual intercourse	8/48 subjects: 4 had infections, 2 erosions, 1 pain, 1 dissatisfaction (small size of penile prosthesis)

Abbreviations: ED, erectile dysfunction; EF, erectile function; IIEF-5, 5-item version of the International Index of Erectile Function; NDO, neurogenic detrusor overactivity; N-LUTS, neurogenic lower urinary tract symptoms; SARS, sacral anterior root stimulator; SDR, sacral dorsal rhizotomy; SNM, sacral neuromodulation.
[a]International index of erectile function composed of 15 items.

placebo only in one study (SCI-F301). The other study (SCI-F 302) comprising 203 subjects overall reported that 95.1% of them expressed drawbacks.[30]

Bodner *et al.*[35] administered various dosages of alprostadil (125–100 μg) by medicated transurethral system (MUSE). Only three subjects (20%) achieved an erection suitable for SI, although these patients were dissatisfied with the quality of their erection and chose to discontinue treatment. Moreover, all 15 patients had to use a penile ring to prevent hypotension to the medication. All 15 returned to ICI therapy.

Strebel *et al.*[31] showed that only two patients (9.1%) were able to have a valid erection by using apomorphine 3 mg SL. These two patients were more satisfied in terms of erection and modality of assumption than they were with sildenafil. Nine patients (41%) mentioned side effects, and two more patients discontinued treatment after the first dosage because of intolerance.[31] (see Table 1).

Surgical treatments

Lombardi *et al.*[33,34] found in two studies that overall nine patients with SCL obtained normal EF (IIEF-5 score $\geqslant 22$) at 3 months post permanent SNM and during final follow-ups.

At baseline, all the individuals who reached a normal IIEF-5 score post SNM suffered from neurogenic non-obstructive urinary retention.

However, four out of nine patients (44.4%) lost their clinical voiding and EF benefits during follow-up, although no possible reasons were identified, such as modification of their neurological status. All four subjects recovered the same remarkable clinical improvement in both functions with a new implant in the opposite sacral S3 root.

In these two studies, 11 patients did not have satisfactory SI with SNM at the first follow-up and hence resumed their previous PDE5Is therapy.

Sievert *et al.*[27] mentioned that two patients showed an improvement in EF only after stimulation programming was varied from that used for bladder dysfunction.

Concerning penile prosthesis, Zermann *et al.*[24] found that SI was possible for more than 80% of subjects in medium and long-term follow-ups for those patients exclusively submitted to penile prosthesis for ED. Kim *et al.*[25] stated that the penile prosthesis was removed and never replaced during the follow-ups for 4 of the 48 patients (8.3%): 2 because of prosthesis infection, 1 because penile flair and erosion appeared at the glans penis and 1 owing to urethral erosion.

In one study, 29 out of 33 males (87.8%) were implanted with a Brindley sacral anterior root stimulator after rhizotomy of posterior sacral roots for severe neurogenic detrusor overactivity and were able to have coitus in the medium and long-term follow-up. No one reported side effects such as bladder or bowel incontinence during sexual activity.[26]

DISCUSSION

Literature reported few studies on alternative treatments available to treat ED in subjects with SCL other than oral PDE5Is. In none of the selected studies did any author report the residual erection of these patients at baseline nor assess statistically whether the type and degree of their residual erection were possible predictable factors for a treatment's success.[23–25]

There are several possible reasons for the scarcity of data on ED therapies other than oral PDE5Is.

First, the efficacy of PDE5Is is evident also in the medium and long term.[37,38] On the other hand, other conservative treatments such as apomorphine SL (a dopamine-receptor agonist, mainly used in Parkinson disease) or intraurethral alprostadil showed unsatisfactory preliminary results both in terms of efficacy and safety.[31,35] Such disappointing findings discouraged further clinical investigations on these drugs.

In addition, controversial results in terms of effectiveness on EF were noted using various dosages of Fampridine (also known by its chemical name of 4-aminopyridine or 4-AP), a specific drug used for neurological spasticity, on patients with incomplete SCL. Furthermore, a high percentage of side effects was recorded in the two selected studies.[29,30]

Again, taking into account other conservative treatments, the early perineal training was exclusively offered to patients with incomplete SCL, but no valid penile rigidity was found. Further studies are needed to assess a possible additional clinical effectiveness whether administered in combination with pharmacological therapy or not.[36]

Surgical implantations of the Brindley system or permanent SNM are options for treating neurogenic bladder dysfunction refractory to conservative approaches.[26,27,33,34] It is worth saying that, in the last two decades, sacral rhizotomy followed by the implant of the Brindley system, which has been recommended only for patients with complete SCL, is performed less and less mainly because of the introduction and efficacy of intradetrusor botulinum toxin A.[39,40]

However, overall, about 30–35% of men with SCL and ED do not respond to PDE5Is therapy. In particular, the highest rate of failure is documented in SCL with complete damage of the sacral segment (S2-S4).[41,42]

Although ICI vasoactive drugs or vacuum devices are recommended as possible second-line treatment according to international guidelines, nowadays, insufficient findings have been collected on SCL patients refractory to PDE5Is.[17]

In the study using ICI vasoactive medications, although the author did not assess baseline residual erection, individuals with all types and degrees of SCL reached a high percentage of satisfactory SI. However, none of the individuals included had been previously treated with PDE5Is for their ED.[23]

The two studies of penile prosthesis showed satisfactory results on ED.[24,25] In fact, more than 80% of individuals were able to have successful intercourse in the medium and long term. However, most of their population was included from the pre-PDE5Is era. It is important to underline that these two studies included the largest cohort of patients with several levels and degrees of lesions. However, the individuals included were not previously treated with PDE5Is; hence, the number of patients who would not have needed to undergo a penile implant because of good PDE5Is response is unknown.

SNM seems to have positive results in more than one pelvic dysfunction, including ED. It is well known that neurological patients suffer from concomitant pelvic dysfunctions.[43]

The notable clinical improvement in EF post SNM could be partially explained as a secondary effect on the amelioration of neurogenic lower urinary tract symptoms. A direct action of SNM on EF is also feasible, in that the lead of the sacral neuromodulator is generally implanted at the sacral S3 foramen, thus stimulating the pelvic and pudendal nerves.[33,34] This direct effect supports the positive clinical findings on female sexuality, also in neurological women.[44,45] Actual data regarding SNM on EF are still insufficient, although subjects with SCL suffering from non-obstructive urinary retention seem to be the best candidates for achieving valid erection.[33,34]

Lombardi *et al.*[33,34] hypothesized that SNM could act on ED by activating the parasympathetic nervous system that influences both detrusor contraction and EF, in that both reflex erection and micturition are dependent on an intact sacral conus and its reflex loops. This thesis was supported by the fact that overall the four patients who simultaneously lost their clinical improvements in both functions subsequently recovered both after the contro-lateral sacral S3 root was newly implanted.

To better understand the mechanism of action of SNM, it is mandatory that validated questionnaires for pelvic dysfunctions, including EF (that is, IIEF-15), should always be used prior to SNM and at follow-ups. This methodology could help define and clarify common criteria for stratifying patient response on EF (that is, 'responders', 'non-responders' or 'worsened'). Thus, the correlation between clinical response and stimulus parameters such as the amplitude in volts, pulse width (μs) rate, mode (cycling versus continuous stimulation) could be useful to determine the appropriate settings for EF.

According to positive preliminary findings of neuromodulation on sexuality, possible future investigations on neurological patients should evaluate the impact on sexual function of neuromodulation techniques, which are currently used for other pelvic dysfunctions.[46,47]

Furthermore, the use of testosterone alone or in combination with PDE5Is on subjects with SCL and hypogonadism may likely represent a therapeutic option, taking into account that some studies detected around 40% of SCL men with low serum testosterone levels.[48,49]

In conclusion, sexual dysfunction in SCL patients, including ED, is a complex multi-factorial task. Impairment of sexual function is influenced not only by the neurological lesion (primary effect) but also is often amplified by secondary disorders such as bladder and bowel dysfunctions, spasticity, fatigue, pain and impaired motility.[50] Therefore, any ED treatment for neurological patients should follow up consistently and be adjusted throughout their lifetime.

CONFLICT OF INTEREST

Dr Giulio Del Popolo is a consultant at Hollister, Ipsen, Allergan, Wellspect and Apogepha; speaker at Astellas, Allergan and Sigma Tau; and involved in trial participation at Pfizer, Allergan, Ipsen, Recordati and Astellas. The remaining authors declare no conflict of interest.

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