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Sexuality and Reproductive Health Following Spinal Cord Injury

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new healthcare technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for healthcare quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.gov.

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Structured Abstract

Context: Spinal cord injury (SCI) is most often the result of a trauma to the spinal cord, but can also be associated with congenital or degenerative disease. In the United States alone, there are currently approximately a quarter million people with SCI. Sexual dysfunction in people with SCI may have both physiological and psychological (e.g., body image, self esteem) elements that can be distressing regardless of the persons' gender, age or culture. Although some men with SCI are unable to have erections, many still maintain the ability to have some erectile function, albeit of insufficient quality and duration for intercourse. Many techniques currently exist to remediate erectile dysfunction in men with SCI. These include devices such as the vacuum erection device as well as the injection of vasoactive drugs into the penis. A recent innovation to improve erectile function in men with SCI has been the approval of the drugs such as sildenafil (Viagra®). Remediation of sexual dysfunction in women with SCI has until recently been largely ignored in the literature.

Objectives: This report focuses on two questions: (1) issues related to fertility, pregnancy rates, and live births in persons with SCI, and (2) issues related to male impotence post-SCI.

Reproductive health: What is the current fertility rate for men and women after SCI?

- Are fertility rates changed by freezing a new patient's sperm?
- Are there better fertility rates using electroejaculation or vibration? Does order of method influence outcome?
- To improve fertility rates, when should invasive techniques such as testicular biopsy or aspiration or ICSI be pursued?
- Are there pregnancy complications and prospective obstetric management issues for SCI females?

Male sexuality: How has the availability of Viagra® and other remediation affected sexual function, frequency of activity, and adjustment after SCI?

- Is Viagra® really more benign than intracavernous injections?
- How does the morbidity of prostaglandin injections compare to the older (less expensive) papaverine?
- What is the morbidity of vacuum tumescence devices?
- What indications, if any, remain for implantable penile prosthetic devices?

Data Sources: The databases searched were Medline (1966–June Week 1 2003), Premedline (June 13 2003) and CINAHL (1975–June Week 1 2003), the Cochrane Central Register of Controlled Trials, (1st Quarter, 2003), SocioFile (1974–June 2003) and PsycInfo (1887–June

Week 1 2003). The annual proceedings (1997–2002, inclusive) of several groups were searched: the American Urological Association, International Society of Sexual and Impotence Research, International Society for the Study of Woman's Sexual Health, American Paraplegia Society, American Association of Spinal Cord Injury Nurses, American Association of Spinal Cord Injury Psychologists and Social Workers, American Association of Sex Educators, Counselors and Therapists, American Spinal Injury Association, American Academy of Physical Medicine and Rehabilitation, and American Congress of Rehabilitation Medicine. Several manufacturers were also approached for potential data including: Eli Lilly Canada Inc., Bayer Group, Unimed Pharmaceuticals Inc., Mentor Corporation, Vivus Inc., Timm Medical Technologies, Schering-Plough Corporation, Pfizer, Sabex 2002 Inc., and Novartis Pharmaceuticals.

Study Selection: All results of searches for evidence were screened against the eligibility criteria. As an extension of the phase I feasibility study, two reviewers were employed at the relevance assessment phase of the evidence review. Two levels of screening for relevance were used, with the first level directed at bibliographic records during phase I, the feasibility study (i.e., title, authors, key words, abstract), and the second level focused on those "full report" articles retrieved based on the results of the first level of screening. Following a calibration exercise, two reviewers independently broad screened the title, abstract, and key words from each bibliographic record for relevance by liberally applying the eligibility criteria. The record was retained if it appeared to contain pertinent study information. If the reviewers did not agree in finding at least one unequivocal reason for excluding a report, it was entered into the next phase of the review. The screening process also identified which of the two questions the record addressed. Excluded studies were noted, as was the reason for their ineligibility.

Data Extraction: Data abstracted included the characteristics of the report (e.g., publication status, language of publication, year of publication), study (e.g., sample size; research design; number of arms), population (e.g., age; percent males; diagnosis description), intervention/exposure (e.g., Viagra® for sexual function; testicular biopsy for fertility rates) and participant dropouts and withdrawals. A qualitative synthesis was completed for all studies included in the evidence report. This was performed on a question-specific basis, with studies grouped according to research design. Each synthesis includes a narrative summary of the key defining features of the study report, if stated, population, intervention/exposure, outcomes, study quality, applicability, and individual study results. Meta-analytical techniques for single proportions were used, when appropriate.

Data Synthesis: A total of 2,420 bibliographic records were retrieved. After duplicate records were removed, 2,082 unique items remained. An additional 46 potentially relevant studies were identified through conference abstracts or were nominated by manufacturers. A total of 2,128 reports were evaluated against the eligibility criteria. In total, 122 reports were included in the systematic review: 66 of the reports examined fertility and 56 reports examined sexual dysfunction in individuals with SCI.

The 122 studies included 6,668 individuals**,** ranging in age from 16 years to 81 years, of which 78% of the studies reported 100% male participation, with 6% reporting all female participation. The complete spectrum of SCI severity was included across the studies. The majority of studies included in this review used a non-comparative study design (61%) to address the question under consideration. The quality of reporting of the 122 studies included was less

than optimal. For example, of the 75 non-comparative studies, none of them reported on all the quality items we used to evaluate their reports.

No studies were found that investigated fertility in females after SCI. For male fertility, ejaculation interventions in the last decade resulted in an overall ejaculation response rate of 95% (random effects pooled estimate: 0.95 [95% C.I. 0.91, 0.99]). Data from 13 studies over the past 10 years documenting pregnancy rates indicate rates of 51% (random effects pooled estimate: 0.51 [95% C.I. 0.42, 0.60]). Data from the 11 studies over the past 10 years documenting live-birth rates indicate live birth rates of 41% (random effects pooled estimate: 0.41 [95% C.I. 0.33, 0.49]).

We found eight reports that examined the phenomena of sexual arousal in response to physical and cognitive stimulation in women. These papers describe the separate roles of physical reflex and cognitive pathways in the sexual response in SCI females, but did not test treatment methods for dysfunction. Several interventions (i.e., behavioral, topical agents, intraurethral Alprosatadil, intracavernous injections, vacuum tumescence devices, penile implants, sacral stimulators, and pharmacological) have been used to evaluate male sexual dysfunction. We identified one study that demonstrated improvement in penile rigidity in 10 SCI males before and after biofeedback, followed by home perineal muscle training exercises. Three non-comparative case-series studies and one controlled trial examined the use of topical vasodilators for erectile dysfunction in 53 SCI males, all demonstrating low efficacy or tolerability. Two case-series studies involving 30 SCI males describe the use of intraurethral Alproatadil for SCI male erectile dysfunction with high tolerability but low efficacy. Eight non-comparative case series involving 263 SCI males using intracavernous penile injections of vasodilating agents described poolable efficacy data along with side-effect profiles. The injection technique was highly efficacious, with a 90% satisfactory erection response rate (random effects pooled estimate: 0.90 [95% C.I. 0.83, 0.97]) and was well tolerated when appropriate precautions were taken. Only two case series involving 50 males examined vacuum tumescence devices. Although well tolerated, only a select group chose to use these devices; those that did choose to use them reported a high level of satisfaction. Nine studies, of which two were RCTs and seven were case-series studies, evaluated Viagra® in 627 SCI males. Although less efficacious than injections, Viagra® resulted in a 79% successful erectile function (random effects pooled estimate: 0.79 [95% C.I. 0.68, 0.90]). In addition, Viagra® was well tolerated and often preferred by SCI males. Finally, five case-series studies examined the efficacy and morbidity of penile implants in 363 male SCI subjects, and demonstrated a high satisfaction rate but also had a much higher complication rate than the other treatment options.

Conclusions: Apart from case reports and opinion pieces, there is a paucity of literature regarding fertility and pregnancy in SCI females. There is a relatively large body of evidence regarding males with SCI. Using vibration and electroejaculation, most SCI males can produce semen for fertility purposes. The level of invasiveness is likely more of a factor than either the choice or the order of these two interventions. Vibration should be tried at least on all upper motor neuron injuries first, with electroejaculation reserved for those individuals in whom vibration failed and those with lower motor neuron injuries. Advanced fertility techniques can increase pregnancy rates for an SCI male to above 50% per couple. Freezing of sperm, unless done in the first one or two weeks after SCI, and even if done earlier, is unlikely to make a significant improvement in SCI fertility rates and therefore is not widely practiced. Penile injection, Viagra®, and vacuum devices can help most erectile function problems in SCI males,

making the need for penile implants less common. These interventions positively affect sexual activity at least in the short-term. Long-term sexual adjustment has not been examined.

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Sexuality and Reproductive Health Following Spinal Cord Injury

Summary

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Introduction

Spinal cord injury (SCI) is most often the result of a trauma to the spinal cord, but can also be associated with congenital or degenerative disease. In the United States alone currently there are approximately a quarter million people with SCI. Every year, approximately 10,000 people in the United States survive an acute traumatic injury to the spinal cord. The majority of these people are male and under the age of 25.[1] In addition to paralysis, persons with SCI will likely experience problems with bladder and bowel control, as well as alterations in sexual functioning.[1,2-4] The impact of a SCI on sexual functioning depends on the degree of the injury and its location on the spinal cord.[5,6] Sexual dysfunction in persons with SCI may have both physiologic and psychological (e.g., body image, self esteem) elements that can be distressing regardless of the person's gender, age, or culture.

Both men and women report a decreased desire for sexual activity following their injury.[7,8] Frequency of sexual activity is also known to decrease after injury in both men and women.[7,8] In men with SCI, factors affecting sexuality typically include erectile and ejaculatory dysfunction.[9-11] Factors affecting women with SCI may include difficulties having comfortable intercourse, and the ability to reach or feel orgasm.[5,12,13]

Although some men with SCI are unable to have erections, many still maintain the ability to have some erectile function, albeit of insufficient quality and duration for intercourse.[14] Possible treatments include devices such as the vacuum erection device as well as the injection of vasoactive drugs into the penis.[15,16] A recent innovation to improve erectile function in men with SCI has been the approval of the drugs such as sildenafil (Viagra®). Infertility is an issue for men with SCI[14,17,18] more than with women. Male infertility results from the combination of ejaculatory dysfunction and abnormal sperm quantity and quality. Techniques to remediate erectile dysfunction and ejaculation have vastly improved the fertility potential of men with SCI.[19-23] Stimulation to obtain ejaculate for insemination of a partner is now routinely performed. Usually, ejaculate is obtained through the use of penile vibratory stimulation or electroejaculation, but other techniques to treat SCI-related male infertility are myriad.

Health care providers have become increasingly aware of the importance of sexuality in the rehabilitation process.[22,23] Current approaches to "best practices" concerning the topic of sexuality and reproductive health in persons with SCI are opinion-based, typically generated by clinical experience with small patient populations in select hospitals and rehabilitation facilities. The Consortium for Spinal Cord Medicine (sponsored by the Paralyzed Veterans of America) has identified the issue of sexuality and reproductive health to be a high priority topic for improving the quality of life for persons with SCI.

Last year, at the request of the Consortium for Spinal Cord Medicine, the Agency for Healthcare Research and Quality (AHRQ) commissioned the University of Ottawa's Evidence-based Practice

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Evidence-Based Practice

Center (UO-EPC) to conduct a feasibility study to determine if there is sufficient credible literature to support a comprehensive systematic review on the topic of "Sexuality and Reproductive Health Following SCI." In this feasibility report a reasonably large body of evidence was identified examining different aspects of sexuality and reproductive health following SCI. In general, these studies are of a lower level of evidence and open to several sources of bias. Therefore, AHRQ requested a comprehensive evidence report that incorporates and builds on findings from the UO-EPC phase I feasibility study.

Key Questions

As a result of findings from the phase I feasibility study, this report focuses on two questions and their sub-questions. Question 1 focuses on issues related to fertility, pregnancy rates, and live births in persons with SCI. Question 2 focuses on issues related to male impotence post SCI.

1. Reproductive health: What is the current fertility rate for men and women after SCI?
   - Are fertility rates changed by freezing a new patient's sperm?
   - Are there better fertility rates using electroejaculation or vibration? Does order of method influence outcome?
   - To improve fertility rates, when should invasive techniques such as testicular biopsy or aspiration or intracytoplasmic sperm injection (ICSI) be pursued?
   - Are there pregnancy complications and prospective obstetric management issues for SCI females?
2. Male sexuality: How has the availability of Viagra® and other remediation affected sexual function, frequency of activity, and adjustment after SCI?
   - Is Viagra® really more benign than intracavernous injections?
   - How does the morbidity of prostaglandin injections compare to the older (less expensive) papaverine?
   - What is the morbidity of vacuum tumescence devices?
   - What indications, if any, remain for implantable penile prosthetic devices?

Methods

A Technical Expert Panel (TEP) consisting of six members was convened to provide advisory support to the project, including refining the questions and highlighting key variables requiring consideration in the evidence synthesis.

Study Identification

Building on a preliminary search strategy conducted by UO-EPC in the feasibility task order, a comprehensive updated search for citations was conducted using six databases (MEDLINE®, PreMEDLINE®, CINAHL®, Cochrane Central Register of Controlled Trials, SocioFile, and PsycINFO). Following the suggestions of the TEP, additional published literature was sought through searches of relevant associations' proceedings for the years 1997-2002. In addition, industry was contacted for ongoing and/or unpublished data. A final set of 2,128 unique references was identified and posted to the UO-EPC's Internet-based software system for review.

Eligibility Criteria

Studies were considered relevant if they described both male and/or female (adult or adolescent) populations with SCI, involved any type of study design; published or unpublished, and reported in English. Studies were also eligible for inclusion if each met predetermined criteria. In reproductive health, design criteria consisted of whether the study discussed a fertility intervention; included a pre and post intervention for fertility rates; contained an original report of a measure of fertility rates in males, females, or both; or whether it reported an original intervention trial after SCI. Eligible interventions included physical, surgical, laboratory techniques, or prescription medications. Eligible fertility outcomes included pregnancies, live birth rates, sperm motility, successful sperm harvesting, ejaculations, sperm count, percent viable sperm, hormonal, ovulation rates, cycle function, other measures of sperm morphology, and volume of ejaculation.

In male sexuality, design criteria consisted of whether the study reported an original intervention trial or series with a pre and post measure for sexual dysfunction after SCI, contained an original report of a measure of sexual dysfunction, or whether the article discussed an intervention for sexual dysfunction. Eligible interventions included cognitive/behavioral, prescription medications, and surgical or hormonal interventions. Eligible outcomes included psychological outcomes (e.g., validated sexual function questionnaire for males and/or females, structured interviews with qualitative analysis, educational component, global efficiency, or patient logs), and/or physiologic outcomes (e.g., penile and/or clitoral engorgement, endocrine, ultrasound testing of testicular size).

As an extension of the phase I feasibility study, two reviewers were employed at the relevance assessment phase of the evidence review. Two levels of screening for relevance were used, with the first level directed at bibliographic records during

phase I, the feasibility study (i.e., title, authors, key words, abstract), and the second level focused on those "full report" articles retrieved based on the results of the first level of screening. Screenings for relevance, assessments of study quality, and data abstraction were completed using the UO-EPC's review management Internet-based software, which resides on a secure Web site.

Calibration exercises preceded each step of the screening process. Excluded studies were noted as to the reason for their ineligibility using a modified QUOROM format.[24] Reports were not masked given the equivocal evidence regarding the benefits of this practice.[25,26] Disagreements were resolved by forced consensus and, if necessary, by a third party.

Data Abstraction

Following a calibration exercise, two reviewers independently abstracted the contents of each included study using an electronic data abstraction form developed especially for this review. Once reviewers completed their work, all work was checked by their counterparts. Data abstracted included the characteristics of the following: report (e.g., publication status, language of publication, year of publication); study (e.g., sample size, research design, number of arms); population (e.g., age, percent males, diagnosis description); intervention/exposure (e.g., Viagra® for sexual function, testicular biopsy for fertility rates); and withdrawals and dropouts.

Study Quality

In this report, study quality was assessed through examination of each individual report rated independently by two assessors. Quality was defined as the confidence that the study's design, conduct, analysis, and presentation has minimized or avoided biases in any comparisons.[27] Several approaches exist to assess quality: components, checklists, and scales. Therefore, a combination of methods was used in an effort to ascertain a measure of reported quality across different study designs.

For RCTs the Jadad scale was used. This is a validated scale consisting of three items that assesses the methods used to generate random assignments, double blinding, and a description of dropouts and withdrawals by intervention group.[28] The scoring ranges from one to five, with higher scoring indicating higher quality. In addition, allocation concealment (i.e., keeping the randomization blind until the point of allocating participants to an intervention group) was assessed as adequate, inadequate, or unclear.[29] An *a priori* threshold scheme was used for sensitivity analysis: a Jadad total score of ≤ 2 indicates low quality with scores > 2 indicating higher quality.

Cohort and case-control study reports were assessed using the Newcastle-Ottawa scale (NOS).[30] The NOS is an ongoing collaboration between the Universities of Newcastle, Australia, and Ottawa, Canada. It was developed to assess the quality of nonrandomized studies with its design, content, and ease-of-use directed to the task of incorporating the quality assessments in the interpretation of meta-analytic results.

Qualitative Data Synthesis

A qualitative synthesis was completed for all studies included in the evidence report. A description is provided of the progress of each citation through the review process, and includes information pertaining to each report, such as their sample size. The qualitative synthesis was performed on a question-specific basis, with studies grouped according to research design (e.g., RCTs, observational studies). Each synthesis includes a narrative summary of the key defining features of the study report, if stated, (e.g., a priori description of inclusion/exclusion criteria), population (e.g., diagnosis-related), intervention/exposure (e.g., use of Viagra®), outcomes, study quality, applicability, and individual study results. A brief study-by-study overview typically precedes a qualitative synthesis.

Quantitative Data Synthesis

For several of the questions investigated in this evidence report, quantitative data synthesis was deemed appropriate. However, most of the studies were non-comparative case series and outcomes were in the form of single proportions (e.g., proportion of couples achieving at least one pregnancy). Current meta-analytic methodology generally focuses on data from studies that include a control group, such as randomized controlled trials. From a meta-analytic perspective, one of the strengths of studies that include control groups is that even if there is some degree of heterogeneity in characteristics such as population or intervention across studies, there may be little statistical heterogeneity in the contrast between outcomes in the treatment and control groups across studies. This protection against heterogeneity is not available in studies without a control group. Judicious selection of comparable studies for inclusion in a meta-analysis of single proportions therefore becomes especially crucial. In the present work, heterogeneity of single proportions was assessed using Pearson's chi-square test. P-values less than 0.10 were taken to indicate statistically significant heterogeneity. Forest plots were constructed using Wilson score confidence intervals around individual study proportions.[31] Pooled estimates and their confidence intervals were obtained using the random effects estimator of Laird and Mosteller.[32]

Results and Discussion

Literature Search

A total of 2,420 bibliographic records were retrieved through database searches. After duplicate records were removed, 2,082 unique items remained. An additional 46 potentially relevant studies were identified through conference abstracts or were nominated by manufacturers. Therefore, a total of 2,128 reports were evaluated against the eligibility criteria and after the initial screening for relevance, 1,627 records were excluded. Although the majority of the initial screening was performed in the phase I feasibility study, the additional studies that were identified when the search was "rerun" at the beginning of this study (n = 98, of which 47 were duplicates) were screened according to phase I criteria. The reasons for exclusion were: not relevant to SCI (n = 530); not relevant to sexuality or reproductive health (n = 410); case report or opinion piece (n = 282); no relevant measure reported (n = 271); not relevant to any of the questions (n = 78); and, report pertaining to adolescent or child only (n = 6). The remaining 501 reports were then retrieved and subjected to a more detailed relevance assessment. Two hundred and forty-five of these reports dealt with issues relating to fertility and 289 of the reports examined sexual dysfunction. After further relevance assessment, 180 of the 246 reports on fertility and 232 of the 289 reports on sexual dysfunction failed to meet the inclusion criteria of phase II. In total, 122 reports were deemed relevant for the systematic review—66 of the reports examined fertility and 56 reports examined sexual dysfunction in individuals with SCI.

Study Results

The 122 studies included 6,668 individuals, ranging in age from 16 years to 81 years, of which 78 percent of the studies enrolled only men, with 6 percent reporting all female participation.* As might be expected, the complete spectrum of SCI severity was included across the studies. Eighty-seven studies (71 percent) reported on the level of lesion, however, only 18 (15 percent) reported on American Spinal Injury Association level. However, final classifications of data on severity of SCI injuries are complicated in this review due to inconsistencies in the reporting of severity of injury. The majority of studies included in this review used a non-comparative study design (61 percent) to address the question under consideration. For example, a group of males might be given a specific intervention to improve ejaculation rates. Typically, the authors did not select a comparator group and only reported specific outcomes on this group. Few RCTs exist to evaluate the efficacy of male sexual dysfunction and the majority of those are duplicate publications, perhaps giving the impression of being more broadly evaluated than one might think on first impressions. The quality of reporting of the 122 studies included here is less than optimal. For example, of the 75 non-comparative studies, none of them reported on all the quality items we used to evaluate their reports. The highest number of quality criteria met was 16/19 items, and this was achieved by only one (1 percent) of the 75 studies.[33]

Question 1. What is the current fertility rate for men and women after SCI?

Fertility in females after SCI

There were no studies found that investigated this question.

Fertility in males after SCI

Ejaculation rates. Different aspects of male infertility have been studied. Reports in the literature on this topic can be grouped, and some information pooled. Much of the earlier work in this area centers on interventions to aid males with SCI to ejaculate, either during sexual activities with their partners or in a clinic situation to harvest semen for implantation. Different authors and clinics have chosen different methodologies to aid ejaculation in males with SCI. They include intrathecal or subcutaneous physostigmine with masturbation, penile vibration techniques with or without pharmacologic enhancement, or electroejaculation.

Ejaculation rates results from 22 studies that used vibration and/or electrode stimulation in males with SCI. Overall, these interventions resulted in an overall ejaculation response rate of 86 percent (random effects pooled estimate: 0.86, 95% C.I. 0.80, 0.93). When data from studies examining vibration and/or electrode stimulation to provoke ejaculation are pooled, a large degree of heterogeneity is observed. This observation reflects the inclusion of early studies that were aimed at establishing optimal parameters for the technique (e.g., vibration amplitude, electricity parameters), as well as the inclusion of more recent studies which implemented the now common practice of first starting with vibration and later including electroejaculation to increase success rates.

Pregnancies and live births. Not all authors chose to present both pregnancy and live birth data. However, there is no suggestion in the literature that the spontaneous abortion rate of a pregnancy conceived from an SCI male exceeds that of the general population; therefore, we chose to combine both sets of data. These results represent the number of couples who have achieved at least one pregnancy or live birth over the number of couples who tried to conceive. It is very important to note that some authors reported their fertility rates after very simple

* "Couples" were counted as a single case pertaining to number of participants enrolled. Fourteen percent of the included studies reported on the enrollment of couples only or couples together with single-case male participants

procedures such as vibration or electrode ejaculation, whereas some studies were performed in clinics that greatly increased the odds of achieving pregnancy by adding a variety of advanced fertility techniques. Data from the 17 studies documenting pregnancy rates were pooled and indicate pregnancy rates of 51 percent (random effects pooled estimate: 0.51, 95% C.I. 0.42, 0.60). Data from the 13 studies documenting live-birth rates were pooled and indicate live birth rates of 40 percent (random effects pooled estimate: 0.40, 95% C.I. 0.33, 0.48). The heterogeneity of these pooled results is explained by the addition of advanced fertility techniques that increase the success rates for these endeavors by up to four times, compared with insemination alone.

Are fertility rates changed after freezing a new patient's sperm?

There is little data to support the practice of freezing the sperm of SCI males after 16 days post-injury, and that even the advantages of early freezing (within the first 2 weeks) is outweighed by the loss of sperm motility during the procedure, since with modern techniques one is virtually certain of obtaining fresh sperm from the SCI male when he is ready to conceive a child in later years.

Are there better fertility rates using electroejaculation or vibration? Does order of method influence outcome?

We were unable to locate any documents demonstrating a superior fertility outcome between vibration and electroejaculation. Therefore, we compared the side-effect profile of the two procedures to determine risk-benefit. Of the 21 studies identified that reported ejaculation rates with technique, 10 reported adverse events.[34-43] Often, authors combined procedures, although they did not always separate the side effects by procedure. However, papers that combined the procedures demonstrated that the vibration technique is less likely to be successful for lower motor neuron (areflexic) injuries than with spastic injuries, and electroejaculation is more likely than vibration to cause autonomic dysreflexia in patients with spastic injuries.[35,37] Electroejaculation also has the added side effects of inflammation to the rectal mucosa[39] and stimulation pain[34,38,39,44] in incompletely injured patients. Therefore, most clinics that combine these techniques usually try vibration first followed by electroejaculation in the areflexic subjects that tend to not respond to vibration alone.

To improve fertility rates, when should invasive techniques such as testicular biopsy or intracytoplasmic sperm injection be used?

Invasive techniques to enhance fertility (advanced fertility [AF] techniques) such as in vitro fertilization and ICSI have been used more in recent studies. By grouping the 18 studies above that reported either pregnancies or live births according to whether they used or did not use AF techniques, one can assess how using AF techniques impacts fertility rates. In doing so, one easily observes that to achieve pregnancy and birth rates approaching 50 percent or greater SCI couples need to use an AF technique. Testicular biopsy or vas aspirations should be reserved for those patients who cannot achieve sperm harvesting or whose harvested sperm by the above techniques is of very low quality. ICSI can greatly enhance success in those individuals whose sperm quality is insufficient for intrauterine insemination.

Are there pregnancy complications and prospective obstetric management issues for SCI females?

We did not find any reports that provided the necessary data for us to project the number and frequency of complications and other obstetric issues in females with SCI. There are numerous case reports, however, without the larger sample size obtained with a case-series study, it is difficult to conduct further research or inform practice or policy regarding this important health issue.

Question 2. How has the availability of Viagra® and other remediation affected sexual dysfunction and adjustment after SCI?

Interventions for female sexual dysfunction

We found six articles that used a case-control design[5,45-49] and one article that used a RCT design[50] to examine the phenomena of sexual arousal in response to physical and cognitive stimulation in women with SCI.

Male sexual dysfunction

Most of the literature discusses male erectile dysfunction after SCI. Aside from a number of RCTs evaluating Viagra®, all of the studies that we identified which addressed this topic were case-series studies. The most common problems faced when trying to analyze this literature is that many authors chose different outcome measures. For example, some authors use a validated erectile grading system such as Schramek's, whereas others used their own grading system; some authors used all or parts of the International Index of Erectile Function (IIEF) sexual satisfaction rating scale, whereas others designed their own scales. When authors use either an on/off grading system or a common question on the IIEF, we have pooled the data when appropriate. Interventions discussed in this review include: behavioral interventions, topical medications, intraurethral alprostadil, intracavernous injections, vacuum tumescence devices, penile implants, sacral stimulators, and Viagra® (sildafenil).

Is Viagra® really more benign than intracavernous injections?

Intracavernous injections have a significantly higher efficacy than Viagra® (90 percent versus 79 percent). To compare the side-effect profile of intracavernous injections with that of Viagra®, we extracted data from the studies described above that reported side effects. It can be noted that careful dosage adjustment is necessary with the papaverine or papaverine/phentolamine combinations. When used alone, prostaglandin E1 has few side effects outside of its cost. If subjects are reliable and if they have little sensation there seems to be few advantages of Viagra® over intracavernous injections aside from subject and partner preference. Although other phosphodiesterase inhibitors have come to market since sildanefil, no SCI treatment data for these drugs were available at the time of this review.

How does the morbidity of prostaglandin injections compare with the older, less expensive papaverine or phentolamine?

Although similar in efficacy, prostaglandin E1 is less stable at room temperature and much more expensive than papaverine or phentolamine. Proponents cite a shorter half-life (less chance of priapism) and less injection-site pain and scarring as reasons to use this substance despite its expense. We identified six noncomparative case-series studies[51-56] and one RCT[57] that reported the numbers of side effects. Although the efficacy of these two treatments is similar, priapism and discomfort are reported more frequently with papaverine.

What is the morbidity of vacuum tumescence devices?

When used with proper clinic instruction and according to the specifications of the manufacturers, these devices have a very low morbidity rate with no irreversible morbidities noted. Although there are case reports of penile ischemia in the literature, these case reports serve only as a warning not to leave the device on too long and cannot help us with ascertaining a complication rate.

What indications, if any, remain for implantable penile prosthetic devices?

It is notable that although penile implants result in a high level of satisfaction for those clients who do not have complications, the serious complication rate is as high as 10 percent. Furthermore, patients who have an implant removed are no longer candidates for other treatment options as they are likely to have damage to the penile tissues that would make them nonresponsive to intracavernous injections or vacuum devices. Very few patients will not respond to any of the more benign techniques.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the University of Ottawa Evidence-based Practice Center, Ottawa, Canada under Contract No. 290-02-0021. It is expected to be available in December 2004. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 109, *Sexuality and Reproductive Health Following Spinal Cord Injury*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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Evidence Report

Chapter 1. Introduction

Overview

Spinal cord injury (SCI) is most often the result of a trauma to the spinal cord, but can also be associated with congenital or degenerative disease. In the United States alone, there are currently approximately a quarter million people with SCI.[1] Every year, there are approximately 10,000 people in the U.S. who survive an acute traumatic injury to the spinal cord, the majority of whom are male and under the age of 25.[2] Persons with SCI experience a myriad of acute and long-term physical and psychosocial consequences that impact on their quality of life. In addition to paralysis, persons with SCI will likely experience problems with bladder and bowel control, as well as alterations in sexual functioning.[1,3-5]

The impact of a SCI on sexual functioning depends on the degree of the injury and its location on the spinal cord.[6,7] Sexual dysfunction in persons with SCI may have both physiological and psychological (e.g., body image, self esteem) elements that can be distressing regardless of the persons' gender, age or culture. The balance between physiologic and psychosocial elements coupled with factors such as gender, age and culture will all influence how a person with SCI adjusts to their new sexual identity.

Both men and women report a decreased desire for sexual activity following their injury.[8,9] Frequency of sexual activity is also known to decrease after injury in both men and women.[8,9] In men with SCI, factors affecting sexuality typically include erectile and ejaculatory dysfunction.[10-12] Factors affecting women with SCI may include difficulties having comfortable intercourse, and the ability to reach or feel orgasm.[6,13,14] Many authors and clinicians include issues of infertility, pregnancy and delivery when speaking of broader issues of sexuality and disability.

Although some men with SCI are unable to have erections, many still maintain the ability to have some erectile function, albeit of insufficient quality and duration for intercourse.[15] Many techniques currently exist to remediate erectile dysfunction in men with SCI. These include devices such as the vacuum erection device as well as the injection of vasoactive drugs into the penis.[16,17] A recent innovation to improve erectile function in men with SCI has been the approval of the drugs such as sildenafil (Viagra®).

Remediation of sexual dysfunction in women with SCI has until recently been largely unreported. However, it has been suggested that treatment of sexual dysfunction in women should focus on improving the ability of women with SCI to become aroused and to achieve orgasm.[3]

The ability to become a parent is an important issue for younger people with SCI. For women with SCI, their hormonal status generally remains unchanged, except for a temporary period of amenorrhea following their injury.[18,19] They can usually carry a child safely to term and may be able to deliver a child naturally depending on the medical status and physical

Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.goc/clinic/epcindex.htm

limitations to do with the abdomen, spine or pelvis.[19] However, infertility is an issue for men with SCI.[15,20,21] Infertility results from the combination of ejaculatory dysfunction and abnormal sperm quantity and quality. Techniques to remediate erectile dysfunction and ejaculation have vastly improved the fertility potential of men with SCI.[22-26] Stimulation to obtain ejaculate for insemination of a partner is now routinely performed. Usually, ejaculate is obtained through the use of penile vibratory stimulation or electroejaculation, but other techniques to treat SCI-related male infertility are myriad.

Health care providers have become increasingly aware of the importance of sexuality in the rehabilitation process.[25,26] Current approaches to "best practices" concerning the topic of sexuality and reproductive health in persons with SCI are opinion-based, typically generated by clinical experience with small patient populations in select hospitals and rehabilitation facilities. The Consortium for Spinal Cord Medicine (sponsored by the Paralyzed Veterans of America) has identified the issue of sexuality and reproductive health to be a high priority topic for improving the quality of life for persons with SCI.

Phase 1 Feasibility Study

Last year, at the request of the Consortium for Spinal Cord Medicine, the Agency for Healthcare Research and Quality (AHRQ) commissioned the University of Ottawa's evidence-based practice center to conduct a feasibility study to determine if there is sufficient credible literature to support a comprehensive systematic review on the topic of "Sexuality and Reproductive Health Following SCI."

The Consortium for Spinal Cord Medicine drafted eight specific questions that address the key issues on the topic of sexuality and reproductive health in persons with SCI (Table 1). We developed a search strategy based on these questions to examine the existing evidence base regarding the topic of "Sexuality and Reproductive Health Following SCI." We anticipated that there may be specific gaps in the literature, with data absent or scant for some of the questions.

Table 1. Key issues on the topic of sexuality and reproductive health in persons with SCI as identified by the Consortium for Spinal Cord Medicine

1.	When do people become sexually active after SCI?
2.	What is the frequency of sexual activity in the years post injury?
3.	What is the current fertility rate for men and women after SCI?
4.	How has the availability of Viagra® and/or other remediation affected sexual function, frequency of activity, and adjustment after SCI?
5.	What are the unique issues of sexuality for women after SCI?
6.	Are there interventions shown to improve sexual responsiveness in women with SCI?
7.	What is the optimal sequencing of effective procedures when pursuing fertility in the SCI male?
8.	When is the most effective time to present information on sexuality after SCI?

In addressing the original question regarding the feasibility of a comprehensive systematic review of sexuality and fertility in SCI, we conclude that such a review is feasible on the whole, but only useful in the specific. That is, some of the questions have enough evidence from which a review could generate useful recommendations, however, other topics would not be answerable given the current state of the literature.

Summary of Findings—Existing Evidence Base

What is the current fertility rate for men and women after SCI? We concluded that there is a sufficient body of literature to complete a comprehensive systematic review and meta-analysis on issues relating to fertility/pregnancy rates/live births in persons with SCI. Although most of these studies only report frequency data and/or percentage of "success," they report sufficient data to provide meaningful information. Along this suggestion we believe there is sufficient usable data to permit a systematic review and possibly a meta-analysis for other topics such as pregnancy complications and prospective obstetric management.

How has the availability of Viagra® and/or other remediation affected sexual function, frequency of activity, and adjustment after SCI? We concluded that a systematic review and meta-analysis could be carried out specifically addressing treatments available for treating impotence in males with SCI. The permits of such an undertaking would need to be considered in light of the possible duplication of reports we identified. As such, and if not corrected, the estimates from such a meta-analysis could lead to biased estimates of the intervention's effectiveness.

What are the unique issues of sexuality for women after SCI? There is a new and growing body of literature addressing sexual issues in females with SCI. Many of these studies are relatively well designed qualitative interviews and surveys, often involving significant numbers of patients. The literature does address the unique issues of sexuality in women. *We did not believe that a systematic review addressing this question would provide additional insights to clinicians and others.*

Are there interventions shown to improve sexual responsiveness in women with SCI? There are as of yet few published trials of interventions to improve sexual responsiveness in women after SCI**.** *We did not believe that a systematic review on this topic would provide meaningful information.*

What is the optimal sequencing of effective procedures when pursuing fertility in the SCI male? This question is not well addressed in the current literature, except to say that with increasing options available the situation is improving. The literature widely accepts that fertility is not substantially altered in women after SCI. Furthermore, in males, fertility rates can only be deduced in those who choose to be fertile, and will vary according to the degree of pursuit of invasive procedures. However, there is a reasonable body of studies regarding the success rates of individual techniques and a systematic review would help guide clinicians in choosing the order of techniques to apply based on cost, success and potential side effects.

When do people become sexually active after SCI?, What is the frequency of sexual activity in the years post injury?, and When is the most effective time to present information on sexuality after SCI? We found almost no useful literature addressing these questions, although well structured interviews with rigorous attention to qualitative design could answer all three of these questions, i.e., when do patients become active, how active do they become, and when do they want information. Unfortunately, the literature regarding these questions is largely based on

the expression of the clinician, rather than the opinion of the patient. *Therefore, we concluded that a systematic review would not be useful.*

Conclusions

In summary, we identified a reasonably large body of evidence examining different aspects of sexuality and reproductive health following SCI. In general, these studies are of a lower level of evidence and open to several sources of bias. On the basis of this report, AHRQ requested a comprehensive evidence report that incorporates and builds on findings from the Ottawa EPC Phase I Feasibility Study.

Obviously, not all sexual health questions could be addressed in a systematic review of the literature. There are many other noteworthy questions, including questions on impact of quality of life on sexual health, the differences in practice from specialized to general centers, and many questions regarding quality of life and women's sexual health. These questions are not addressed in sufficient thoroughness in the literature to warrant a systematic review. Also, systematic reviews of qualitative literature likely would not add any new insights to this field of practice. This was discussed somewhat in the feasibility study mentioned earlier. The Consortium of Spinal Cord Medicine helped focus this review by posing a series of questions for a systematic review, based on their clinical experience and on the results of the Phase 1 Feasibility Study.

Chapter 2. Methods

Overview

The UO-EPC's evidence report on sexuality and reproductive health following SCI is based on a systematic review to identify, and synthesize the results from studies addressing two key questions put forth by the Consortium for Spinal Cord Medicine. Together with content experts, UO-EPC staff identified specific issues integral to the review. A Technical Expert Panel (TEP) provided expert guidance as to the conduct of the systematic review. Synthesis tables (i.e., evidence tables) presenting the key study characteristics and results from each included study were developed. Summary tables were derived from the synthesis tables. The methodological quality of the included studies was appraised, and individual study results were summarized.

Key Questions Addressed in This Report

As a result of findings from the phase I feasibility study, the comprehensive report will focus on two questions and their sub-questions. Question 1 focuses on issues related to fertility, pregnancy rates, and live births in persons with SCI. Question 2 focuses on issues related to male impotence post SCI.

1. Reproductive health: What is the current fertility rate for men and women after SCI?

    - Are fertility rates changed by freezing a new patient's sperm?

    - Are there better fertility rates using electroejaculation or vibration? Does order of method influence outcome?

    - To improve fertility rates, when should invasive techniques such as testicular biopsy or aspiration or ICSI be pursued?

    - Are there pregnancy complications and prospective obstetric management issues for SCI females?

2. Male sexuality: How has the availability of Viagra® and other remediation affected sexual function, frequency of activity, and adjustment after SCI?

    - Is Viagra® really more benign than intracavernous injections?

Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.goc/clinic/epcindex.htm

- How does the morbidity of prostaglandin injections compare to the older (less expensive) papaverine?

- What is the morbidity of vacuum tumescence devices?

- What indications, if any, remain for implantable penile prosthetic devices?

Study Identification

Search Strategy

A search strategy was developed and tested in Medline (Search Strategy 1, Appendix A), and modified as necessary for other databases (Search Strategy 2, Appendix A). The strategy was based on a preliminary strategy proposed by UO-EPC in a feasibility task order, and was modified in consultation with three members of the review team (DD, JB and VC). The strategy was designed to be highly sensitive and was not restricted by study design, language of publication or publication status. Some of the databases searched were nominated by AHRQ in the work assignment, other databases were selected to provide more complete coverage of key journals nominated by the reviewers; for instance, both SocioFile and PsycInfo provide much more complete indexing coverage of the key journal Sexuality and Disability then does Medline, and so these databases were included.

The databases searched were Medline (1966- June Week 1 2003), Premedline (June 13 2003) and CINAHL (1975 to June Week 1 2003) using Search Strategy 1, and Cochrane Central Register of Controlled Trials, (1st Quarter, 2003), SocioFile (1974 to June 2003) and PsycInfo (1887 to June Week 1 2003) using Search Strategy 2.

Following the suggestions of the technical expert panel the proceedings of the following associations were searched for the years 1997 and 2002 (inclusive): American Urological Association, International Society of Sexual and Impotence Research, International Society for the Study of Woman's Sexual Health American Paraplegia Association, American Association of Spinal Cord Injury Nurses, American Association of Spinal Cord Injury Psychologists and Social Workers, American Association of Sex Educators, Counselors and Therapists, American Spinal Injury Association, American Academy of Physical Medicine and Rehabilitation, and American Congress of Rehabilitation Medicine.

At the suggestions of the technical expert panel and in addition to Eli Lilly Canada Inc. (producer of Cialis) and Bayer Group (producer of Levitra), the following manufacturers were also contacted: Unimed Pharmaceuticals Inc., Mentor Corporation, Vivus Inc., Timm Medical Technologies, Schering-Plough Corporation, Pfizer, Sabex 2002 Inc., and Novartis Pharmaceuticals.

The search strategy was identical to that used in the UO-EPC phase 1 feasibility study.

Eligibility Criteria

Published and unpublished studies, reported in English, involving any research design (e.g., randomized controlled trials [RCTs]), language of publication, and enrolling both male and female, adult and adolescent populations with SCI, were eligible for inclusion if each also met the criteria outlined in Table 2.

Table 2: Inclusion criteria

Parameter	Reproductive health	Male sexuality
Design	Does the article discuss a fertility intervention; does the article include pre and post intervention fertility rates; does the article contain an original report of a measure of fertility rates in males, females or both; and does the article report an original intervention trial after spinal cord injury?	Does the article report an original intervention trial or series with a pre and post measure for sexual dysfunction after spinal cord injury?; does the article contain an original report of a measure of sexual dysfunction?; and does the article discuss an intervention for sexual dysfunction?
Intervention	*Physical:* masturbation, intercourse; *Device:* vibration, electrode ejaculation, home insemination; *Prescription medications:* sympathetic agonists, physostigmine, etc.; *Surgical intervention;* vas aspiration, testicular biopsy, ICSI, artificial insemination, spinal cord stimulators; or *Laboratory techniques.*	*Cognitive/behavioral:* Masturbation, intercourse; *Device:* penile rings, vibrators, vacuum devices; *Prescription medications:* Intracavernous injections, oral, subcutaneous injections, intrameatal MUSE, creams; *surgical intervention;* penile implants, spinal cord stimulators or h*ormonal interventions.*
Outcome	Pregnancies, live birth rates, sperm motility, successful sperm harvesting, ejaculations, sperm count, % viable sperm, hormonal, ovulation rates, cycle function, other measures of sperm morphology, volume of ejaculation.	*Psychological:* Validated sexual function questionnaire for males and/or females, structured interviews with qualitative analysis, educational component, global efficiency, or patient logs; or *Physiologic:* Penile and/or clitoral engorgement, endocrine, ultrasound testing of testicular size.

Study Selection Process

All results of searches for evidence were provided to reviewers for screening against eligibility (inclusion/exclusion) criteria. As an extension of the phase I feasibility study, two reviewers were employed at the relevance assessment phase of the evidence review. Two levels of screening for relevance were used, with the first level directed at bibliographic records during phase I, the feasibility study (i.e., title, authors, key words, abstract), and the second level focused on those "full report" articles retrieved based on the results of the first level of screening.

Screenings for relevance, assessments of study quality, and data abstraction were completed using the UO-EPC's review management Internet-based software which resides on a secure website. In the case of relevance assessment, the software simultaneously presents the bibliographic record to be screened and the eligibility questions with which to do so.

Following a calibration exercise which involved screening ten sample records using an electronic form developed and tested especially for this review (Appendix B), two reviewers independently broad screened the title, abstract, and key words from each bibliographic record for relevance by liberally applying the eligibility criteria. The record was retained if it appeared to contain pertinent study information. If the reviewers did not agree in finding at least one unequivocal reason for excluding it, it was entered into the next phase of the review. The reasons for exclusion were noted using a modified QUOROM format (Appendix C).[28] The screening process also identified which of the two questions the record addressed.

Reports were not masked given the equivocal evidence regarding the benefits of this practice.[29,30] To be considered relevant at this second level of screening, all eligibility criteria had to be met. Disagreements were resolved by forced consensus and, if necessary, third party intervention. Excluded studies were noted as to the reason for their ineligibility (see List of Excluded Studies at the end of the report).

Data Abstraction

Following a calibration exercise involving two studies, two reviewers independently abstracted the contents of each included study using an electronic Data Abstraction form developed especially for this review (Appendix D). Once a reviewer completed their work, they then checked all of the data abstracted by their counterpart. Data abstracted included the characteristics of the:

- report (e.g., publication status, language of publication, year of publication);
- study (e.g., sample size; research design; number of arms);
- population (e.g., age; percent males; diagnosis description);
- intervention/exposure (e.g., Viagra® for sexual function; testicular biopsy for fertility rates);
- withdrawals and dropouts.

Summarizing the Evidence

Overview

The evidence is presented three ways. Evidence tables in the appendices offer a detailed description of the included studies (e.g., study design, population characteristics, intervention/exposure characteristics), with a study represented only once. The tables are

organized by research question and design (e.g., RCTs with male sexuality interventions; observational studies examining male sexuality interventions; observational studies examining fertility rates; etc.).

Question-specific summary tables embedded in the text report each study in abbreviated fashion, highlighting some key characteristics, such as comparators and sample size. This allows readers to compare all studies addressing a given question. A study can appear in more than one summary table given that it can address more than one research question.

Study Quality

Evidence reports include studies of variable methodological quality. Differences in quality across and within study designs may indicate that the results of some studies are more biased (i.e., systematic error) then others. Systematic reviewers need to take this information into consideration to reduce or avoid bias whenever possible. There is considerable evidence that low-quality reports, compared with higher quality ones, can introduce bias into the estimates of an intervention's effectiveness.[31] In this report, study quality was assessed through examination of each individual report. No attempt was made to contact the authors of any report. Quality was defined as the confidence that the study's design, conduct, analysis, and presentation has minimized or avoided biases in any comparisons.[32] Several approaches exist to assess quality: components, checklists and scales. For this report, we have elected to use a combination of methods in an effort to ascertain a measure of reported quality across different study designs.

For RCTs the Jadad scale was used (Appendix D). This validated scale includes three items that assess the methods used to generate random assignments, double blinding, and a description of dropouts and withdrawals by intervention group.[33] The scoring ranges from one to five, with higher scoring indicating higher quality. In addition, allocation concealment [i.e., keeping the randomization blind until the point of allocating participants to an intervention group] was assessed as adequate, inadequate or unclear (Appendix D).[34] An *a priori* threshold scheme was used for sensitivity analysis: a Jadad total score of ≤ 2 indicates low quality with scores > 2 indicating higher quality; for allocation concealment, adequate = 1, inadequate = 2 and unclear = 3.

Cohort and case-control study reports were assessed using the Newcastle-Ottawa scale (NOS). The NOS is an ongoing collaboration between the Universities of Newcastle, Australia and Ottawa, Canada. It was developed to assess the quality of nonrandomised studies with its design, content and ease-of-use directed to the task of incorporating the quality assessments in the interpretation of meta-analytic results. A "star system" has been developed in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure for case-control studies, or the outcome of interest for cohort studies. The goal of this project is to develop an instrument providing an easy and convenient tool for quality assessment of nonrandomised studies to be used in a systematic review.

The inter- and intra-rater reliability of the NOS have been established. The face content validity (i.e., the extent to which the instrument appears reasonable on superficial inspection) of the NOS has been reviewed based on a critical review of the items by several experts in the field who evaluated its clarity and completeness for the specific task of assessing the quality of studies to be used in a meta-analysis. Further, its criterion validity has been established with comparisons to more comprehensive but cumbersome scales. The NOS developers continue to

develop appropriate measurement properties for the instruments' development.[27] Quality assessments of non-comparative case series reports were assessed using a 19-item instrument adapted from Opthalmology (Appendix D).[2] We did not conduct any sensitivity analysis of quality assessments on the observational studies, as there is little by way of guidance to suggest what a poor quality study's score would be based on for these assessment instruments.

Qualitative Data Synthesis

A qualitative synthesis was completed for all studies included in the evidence report. A description is provided of the progress of each citation through the review process, and includes information pertaining to each report, such as their sample size. The qualitative synthesis was performed on a question-specific basis, with studies grouped according to research design (e.g., RCTs, observational studies). Each synthesis includes a narrative summary of the key defining features of the study report, if stated, (e.g., *a priori* description of inclusion/exclusion criteria), population (e.g., diagnosis-related), intervention/exposure (e.g., use of Viagra®), outcomes, study quality, applicability, and individual study results. A brief study-by-study overview typically precedes a qualitative synthesis.

Quantitative Data Synthesis

For several of the questions investigated in this evidence report, quantitative data synthesis was deemed appropriate. However, most of the studies were non-comparative case series and outcomes were in the form of single proportions (e.g. proportion of couples achieving at least one pregnancy). Current meta-analytic methodology generally focuses on data from studies that include a control group, such as randomized controlled trials. From a meta-analytic perspective, one of the strengths of studies that include control groups is that even if there is some degree of heterogeneity in characteristics such as population or intervention across studies, there may be little statistical heterogeneity in the contrast between outcomes in the treatment and control groups across studies. This protection against heterogeneity is not available in studies without a control group. Judicious selection of comparable studies for inclusion in a meta-analysis of single proportions therefore becomes especially crucial. Random effects techniques for pooling results attempt to adjust for the presence of statistical heterogeneity, but necessarily provide weaker inferences, and do not obviate the need for careful investigation of sources of statistical heterogeneity.

In the present work, heterogeneity of single proportions was assessed using Pearson's chi-square test. P-values less than 0.10 were taken to indicate statistically significant heterogeneity. Forest plots were constructed using Wilson score confidence intervals around individual study proportions.[35] Pooled estimates and their confidence intervals were obtained using the random effects estimator of Laird & Mosteller.[36]

Chapter 3. Results

Results of Literature Search

A total of 2,420 bibliographic records were retrieved through database searches (QUOROM flow chart, Appendix C). After duplicate records were removed, 2,082 unique items remained. An additional 46 potentially relevant studies were identified through conference abstracts or were nominated by manufacturers. A total of 2,128 reports were evaluated against the eligibility criteria and after the initial screening for relevance, 1,627 records were excluded. Although the majority of the initial screening was performed in the phase I feasibility study,[37] the additional studies that were identified when the search was "rerun" at the beginning of this study (n = 98, of which 47 were duplicates) were screened according to phase I criteria. The reasons for exclusion were: not relevant to SCI (n = 530); not relevant to sexuality or reproductive health (n = 410); case report or opinion piece (n = 282); no relevant measure reported (n = 271); not relevant to any of the questions (n = 78); and, report pertaining to adolescent or child only (n = 6). The remaining 501 reports were then retrieved and subjected to a more detailed relevance assessment. Two hundred and forty-five of these reports dealt with issues relating to fertility and 289 of the reports examined sexual dysfunction. After further relevance assessment, 180 of the 246 reports on fertility and 232 of the 289 reports on sexual dysfunction failed to meet the inclusion criteria. The reasons for exclusion are listed in the QUORUM flow chart (Appendix C). In total, 122 reports were deemed relevant for the systematic review—66 of the reports examined fertility and 56 reports examined sexual dysfunction in individuals with SCI. The Evidence Tables are presented in Appendix E. Evidence Tables1 to 3 present the fertility rate evidence from non-comparative case-series studies (Evidence Table 1), case-control studies (Evidence Table 2) and conference proceedings (Evidence Table 3). Evidence Tables 4 to 6 outline the evidence from RCTs (Evidence Table 4), other study designs (Evidence Table 5) and conference proceedings (Evidence Table 6), regarding the use of sildenafil (Viagra®).

Report and Study Design Characteristics of Included Studies

The 122 studies included 6,668 individuals[1], ranging in age from 16 years to 81 years, of which 78% of the studies enrolled only men and 6% of studies reporting all female participation.[2]

As might be expected, the complete spectrum of SCI severity was represented in the included studies. Eighty-seven studies (71%) reported on the level of lesion; 18 (15%) reported on the American Spinal Injury Association level of injury. With regards to the reporting of severity of

[1] "Couples" were counted as a single case when pertaining to number of participants enrolled.
[2] 14% of the included studies reported on the enrollment of couples only or together with single-case male participants.

Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.goc/clinic/epcindex.htm

injury, inconsistencies were observed between studies. The majority of studies used a non-comparative study design (61%) to address the question under consideration; for example, studies examining ejaculation rates in men with SCI typically did not include a comparator group but reported only on specific outcomes of a particular intervention to improve ejaculation rates. Few RCTs were identified that evaluated the efficacy of male sexual dysfunction, and the majority of these were duplicate publications. The quality of reporting of the 122 included studies was less than optimal. For example, of the 75 non-comparative studies, none reported on all of the quality items that were used to evaluate the reports. The highest number of quality criteria met was 16/19 items, and this was achieved by only one (1%) of the 75 studies.

Fertility in Females After SCI

There were no studies found that investigated this question.

Fertility in Males After SCI

We identified 22 non-comparative case series, including 806 men, which addressed ejaculation rates in men with SCI using vibration or electroejaculation.[38-59] Three other case-series studies directly examined differences between the two techniques.[60-62] We identified two articles that described the details of electroejaculation techniques and precautions in SCI males; however, these studies did not specifically address any of the questions posed by the consortium.[63,64]

Several authors reported results of electroejaculation and/or vibration studies using numerical breakdowns that could not be pooled.[24,65,66] Koletis et al. described his clinical results with electroejaculation in some detail, but did not define the ejaculatory outcomes well, or report the incidence of side effects.[24] Likewise, several abstracts either did not describe results in sufficient detail to abstract the data,[65,66] or more complete description of the data was found in other publications.[67]

The use of physostigmine injection for ejaculation is described in two articles involving 57 SCI males.[68,69]

We identified 18 non-comparative case series, including 398 couples, reporting on pregnancies and/or live births.[41,44,48,50-55,57-59,69-74] One additional case series describing IVF after electroejaculation included SCI patients but did not adequately breakdown the success rates by diagnosis.[75]

Nine studies involving 294 SCI males were designed to look at specific effects of medical and physical factors on SCI male fertility;[56,76-83] however, these studies did not specifically address any of the questions posed by the consortium.

Five studies reporting on 69 SCI males described other more invasive techniques used to harvest semen.[84-88]

Finally, a further 12 articles reported on semen examination techniques or on various semen characteristics in SCI males, often to further delineate reasons for infertility and discuss possible treatments.[83,89-99] However, these studies did not address specifically any of the questions posed by the consortium. These articles are referred to again in the discussion as they highlight treatment implication.

Interventions for Female Sexual Dysfunction

We identified seven studies—six case-control studies[6,100-104] and one RCT[105]—including 132 females with SCI, that addressed interventions for female sexual dysfunction.

Male Sexual Dysfunction

We identified four studies, of which three were non-comparative case-series studies[106-108] and one was a placebo-controlled clinical trial,[109] that evaluated the use of topical agents (n = 53 patients) for sexual dysfunction in men with SCI. Eight studies, all of which were non-comparative case-series studies, examined intracavernous injections (n = 273).[110-117] Five case-series studies evaluated penile implants (n = 363).[118-122] Nine studies, of which two were RCTs[123,124] and seven were case-series studies,[125-131] evaluated Viagra® (n = 627). The remaining studies examined the use of other interventions for male sexual dysfunction including: behavioural methods (one case series[132]; n = 10); intraurethral Alprosatadil (two non-comparative case series;[133,134] n = 30); vacuum devices (two case series;[135,136] n = 50); sacral stimulators (one case series;[137] n = 33); side effects associated with Viagra® (10 studies—five RCTs[123,138-141] and five case-series studies[126-128,130,131]) and, side effects associated with intracavernous injections of prostaglandin and/or papaverine (seven studies—six non-comparative case-series[112,113,115-117,142] and one RCT;[143] n = 287). In one methodological article, rectal probe electrical stimulation is described as a treatment for erection.[64] In 1998, Potter[144] describes a non-statistical trend to improvement in sexual function with fampiridine SR (4-aminopyradine) in a small group of 29 patients .

We identified two studies that described the psychosocial benefits of treating impotence in SCI males;[145,146] however, these studies did not specifically address any of the questions posed by the consortium. In 1992, Jaworski and colleagues used a case-control study design to describe a positive impact on marital relationships in 30 couples post-penile implant or intracavernous injection, and in 1993, Richards et al. used a noncomparative case-series design to describe similar results in 17 couples.[145,146] Both emphasized the need for a wider approach to treating relationship issues after SCI, rather than emphasizing erectile function alone.

General Results

Although a large body of literature exists regarding sexuality and SCI, some general observations should be made. First, the literature includes many reports of nonoriginal data or summaries of previously published work. Multiple review articles exist and sometimes new case-series data is added to previous work within a review article. Although we highlight such articles, we were unable to use this data in either our summary or pooled analysis since we could not determine the quality of the articles without complete information on the source of the data.

Second, most comparable data for treatment intervention is presented in case-series format. It is of course impossible to conduct RCTs for fertility interventions as clients are unlikely to subject themselves to invasive interventions in self-paying clinics on a random basis. It is also difficult to conduct RCTs for many of the previously invasive sexual dysfunction treatments such as injections and implants, since subjects are unlikely to inject unknown substances into

their penises or undergo disfiguring surgery in a trial. Nevertheless, the quality of reporting of many of these case-series studies could have been improved with simple reporting of complete methodology, including how missing data is dealt with, reports on dropouts, follow-up efforts and consistent reporting on side effects.

Finally, the RCTs included in this report suffer due to inconsistent and often incomparable outcome measures preventing pooling of the relevant data. In addition, there is an unfortunate tendency for duplicate publication, whereby data from the same group of patients, but on different aspects of the same trial, is published multiple times in different journals, with the author list rearranged. This results in the false impression that more studies exist with an overall larger group of patients.

We will discuss the results relating to each of the questions posed by the consortium.

Question 1. What is the Current Fertility Rate for Men and Women After SCI?

Fertility in Females After SCI.

There were no studies found that investigated this question.

Fertility in Males After SCI

Ejaculation rates. Different aspects of male infertility have been studied. Reports in the literature on this topic can be grouped, and some information pooled. Much of the earlier work in this area centers around interventions to aid males with SCI to ejaculate, either during sexual activities with their partners or in a clinic situation to harvest semen for implantation. Different authors and clinics have chosen different methodologies to aid ejaculation in males with SCI. They include intrathecal or subcutaneous physostigmine with masturbation, penile vibration techniques with or without pharmacologic enhancement, or electroejaculation.

In 1992, Leduc et al.[69] published the largest study to date of physostigmine in 37 patients with SCI. Side effects included ten episodes of autonomic dysreflexia, five episodes of nausea and vomiting, one episode of hallucination and one episode of dizziness. Patients required multiple medications to inhibit the side effects of physostigmine. Only antegrade ejaculation was counted and the success rate was 54%. The success rate of physostigmine was lower then that obtained with the other techniques described below, and physostigmine also demonstrated a significantly higher side-effect profile. This drug is now very difficult to obtain and this procedure should be considered for historical reference only.

The most common techniques used for semen harvesting include vibration or electrode ejaculation techniques. Many clinics do both procedures, starting with vibration and then going to electrode ejaculation if vibration is unsuccessful. We identified 22 case-series studies that used these techniques. These studies originated in the US, UK and Australia, encompassed a total of 806 patients, and spanned the time period from 1981 to 2002.[38-59] These case-series studies ranged in quality from 2/19 to 12/19 (Summary Table 1). Fourteen percent of the above studies met 11 of 19 (58%) quality criteria.

We were able to pool ejaculation results from 22 of these case-series studies that used vibration and/or electrode stimulation in males with SCI (Figure 1). Overall, these interventions resulted in an overall ejaculation response rate of 86% (random effects pooled estimate: 0.86 95% C.I. 0.80, 0.93). It is worth noting that with the exception of the study by Chung et al.,[54]studies published from 1997 onwards report response rates of 100%. When data from studies examining vibration and/or electrode stimulation to provoke ejaculation are pooled, a large degree of heterogeneity is observed. This observation reflects the inclusion of early studies that were aimed at establishing optimal parameters for the technique (e.g., vibration amplitude, electricity parameters), as well as the inclusion of more recent studies which implemented the now common practice of first starting with vibration and later including electroejaculation to increase success rates.

Figure 1: Meta-Analysis—Ejaculation

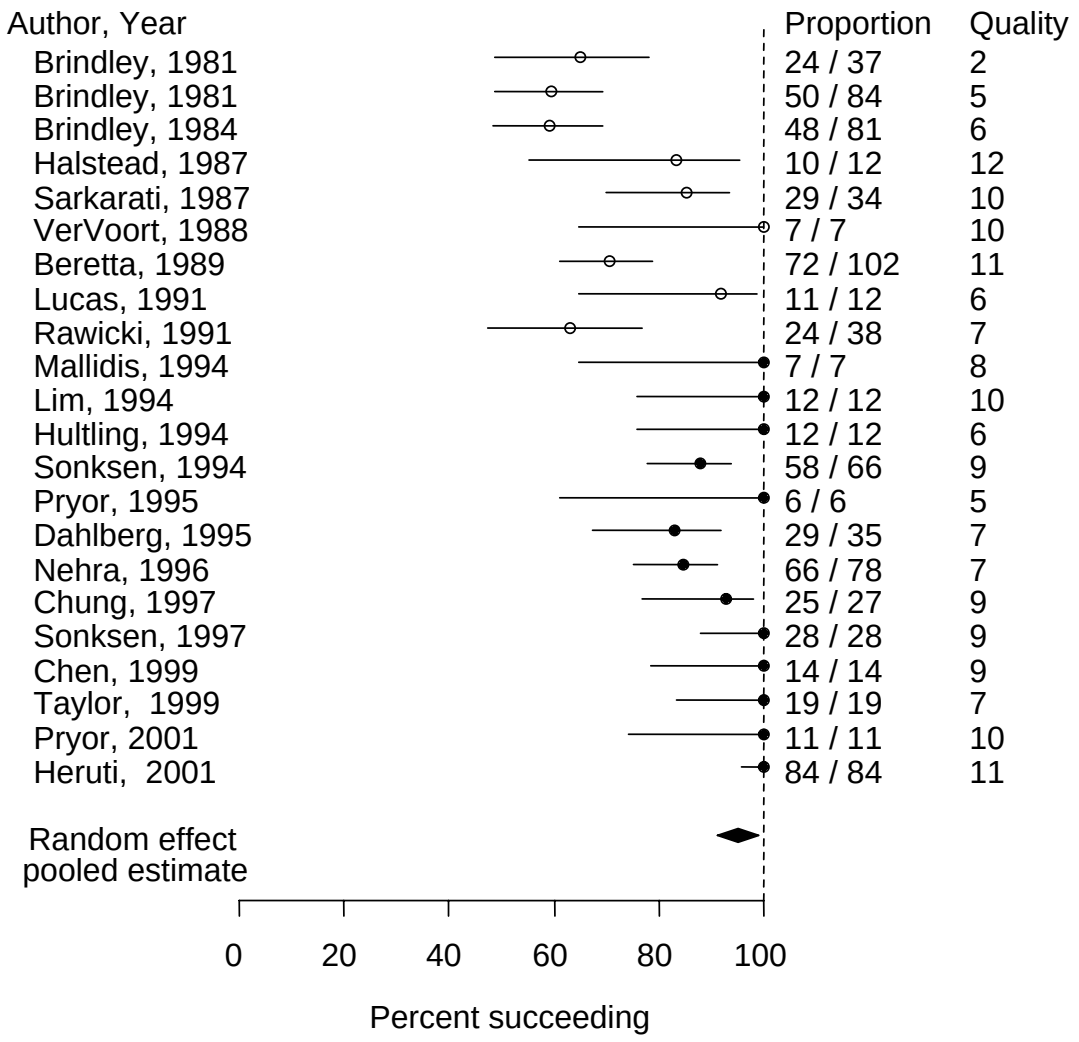

Figure 1: Forest plot of the success rate of vibration and/or electrode stimulation in noncomparative case-series studies that reported ejaculation as an outcome. The data was pooled and the overall estimate and its confidence interval was calculated using the random effects estimator of Laird & Mosteller.[36] Quality scores are out of a possible 19. Estimates from studies prior to 1993 are denoted by open circles. Only results from the past 10 years (1993-2003) were pooled to account for changes in techniques and technology.

Reports of other techniques used to harvest semen from males with SCI were identified (Summary Table 1) and include: electrical stimulation of the seminal vesicles and vas deferens;[84] vas cannulation with implanted sperm reservoirs;[85] testicular biopsy;[86,87] and microsurgical aspiration of the vas deferens.[88]

Summary Table 1: Success rates of various techniques used to obtain semen in men with SCI

Author, Year	Study Design	Number of patients	Technique	Success rates	Quality
Bensman & Kottke, 1966	Noncomparative case series	5	Electrostimulator	Sperm obtained in 3/5 from retrograde ejaculate; no motile sperm in 2/5; in 1/3 with 410K sperm/cm4, 20-30% of the sperm had abnormal forms	4/19
Brackett et al., 2000	Case-control	12	Vas aspirated to ejaculated sperm	Vas aspirated sperm motility and viability plus or minus standard error of mean were significantly higher than mean ejaculated sperm motility and viability (54.4% +/- 5.0% and 74.1% +/- 5.3% versus 14.1% +/- 2.6% and 26.1% +/- 4.9%, respectively)	7* (NOS)
Brindley et al., 1986	Noncomparative case series	12	Implanted sperm reservoir	8 pts (67%) motile spermatozoa were recovered 2 pregnancies (17%) achieved with subsequent live births (by AIH).	6/19
Hirsch et al., 1994	Case-control	10	Testicular biopsy	Spermatogenesis similar between SCI men and controls	4* (NOS)
Perkash et al., 1985	Noncomparative case series	30	Electrical stimulator	Sperm count in n=18 men >40 million Total sperm count in 22 pts >20 million Normal Sperm morphology: mean 55%, range 40-75% Sperm progressive motility <20% in 27 of 35 specimens No motile in 10 specimens & less than 10% motile in 13; 10%-20% motile in 4 pts; >30% motile in 5 pts	7/19
NOS = Newcastle Ottawa Scale					

Pregnancies and live births. Not all authors chose to present both pregnancy and live birth data. However, there is no suggestion in the literature that the spontaneous abortion rate of a pregnancy conceived from an SCI male exceeds that of the general population; therefore, we chose to combine both sets of data. These results represent the number of couples who have achieved at least one pregnancy or live birth over the number of couples who tried to conceive. It is very important to note that some authors reported their fertility rates after very simple procedures such as vibration or electrode ejaculation, whereas some studies were performed in clinics that greatly increased the odds of achieving pregnancy by adding a variety of advanced fertility techniques.

Seventeen studies published between 1987 to 2001, involving a total of 400 patients from the US, UK and Australia, have documented pregnancy rates.[41,44,44,48,48,50,51,51,52,52-54,54,55,55,57-59,59,69,69-71,71,72,72-74,147] Thirteen studies published between 1991 to 2001, involving a total of 341 patients from Canada, US, UK and Australia, have documented live-birth rates.[70] Eleven of these studies overlap and report both pregnancy and live-birth rates.[44,48,51,52,54,55,59,69-72]

Data from the 17 studies documenting pregnancy rates were pooled and indicate pregnancy rates of 51% (random effects pooled estimate: 0.51 95% C.I. 0.42, 0.60) (Figure 2). The data suggest considerable improvement in pregnancy rates, from the dismal 0% reported by Halstead in 1987[41] to the more recently reported rates of 74%[57] and 73%.[58] The quality of these studies ranges from 5/19 to 12/19 (Summary Table 3). Twenty percent of the pregnancy studies met 11 of 19 (58%) quality criteria. Data from the 13 studies documenting live-birth rates were pooled and indicate live birth rates of 40% (random effects pooled estimate: 0.40 [95% C.I. 0.33, 0.48]) (Figure 3). The heterogeneity of these pooled results is explained by the addition of advanced fertility techniques that increase the success rates for these endeavors by up to four times, compared with insemination alone. Once again, an improvement in live birth rates over time has occurred with Lucas reporting a success rate of fourteen percent in 1991 and Elliot of sixty-two percent five years later. The quality of these studies ranges from 5/19 to 12/19 (Summary Table 4). Eight percent of the live birth studies met 11 of 19 (58%) quality criteria.

Figure 2: Meta-Analysis—Pregnancy

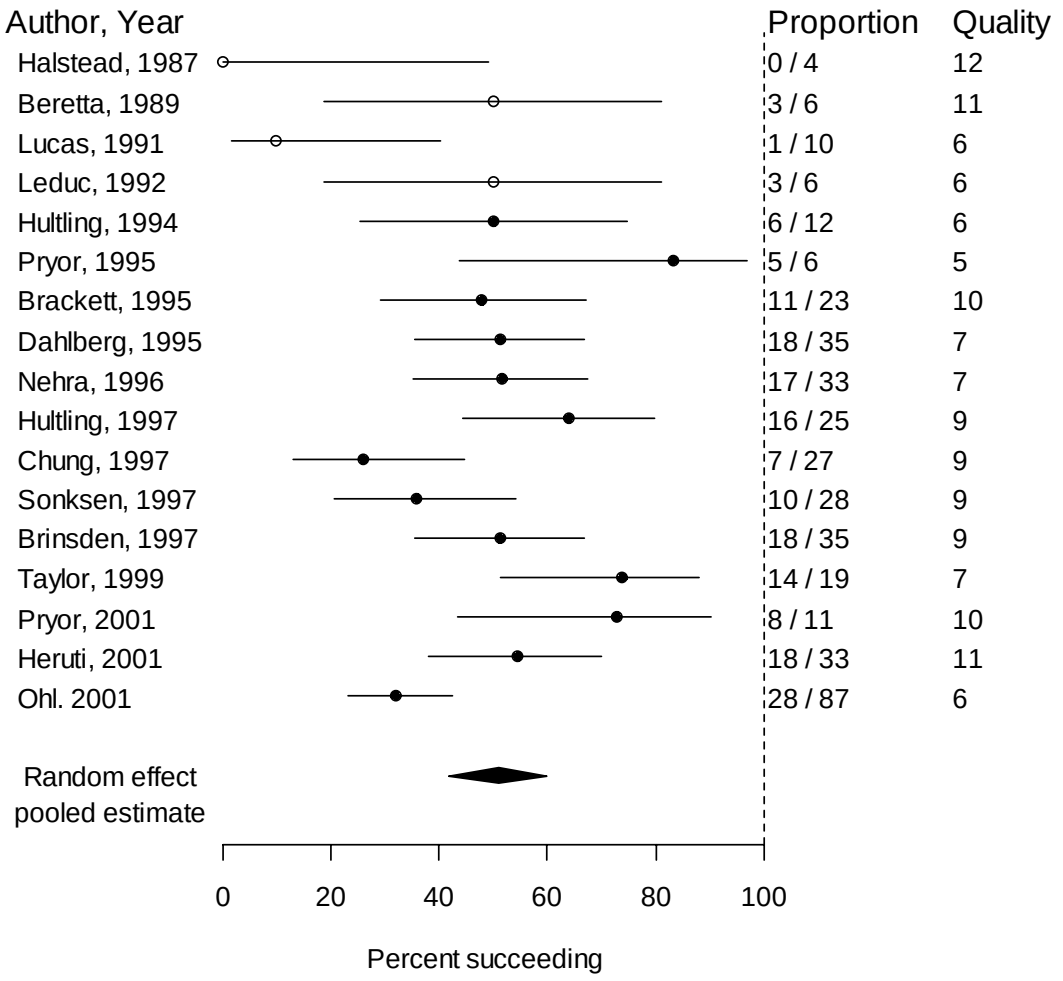

Figure 2: Forest plot of the success rate for pregnancy in the noncomparative case-series studies that reported pregnancy as an outcome. The data was pooled and the overall estimate and its confidence interval was calculated using the random effects estimator of Laird & Mosteller.[36] Quality scores are out of a possible 19. Estimates from studies prior to 1993 are denoted by open circles. Only results from the past 10 years (1993-2003) were pooled to account for changes in techniques and technology.

Figure 3: Meta-Analysis—Live Birth

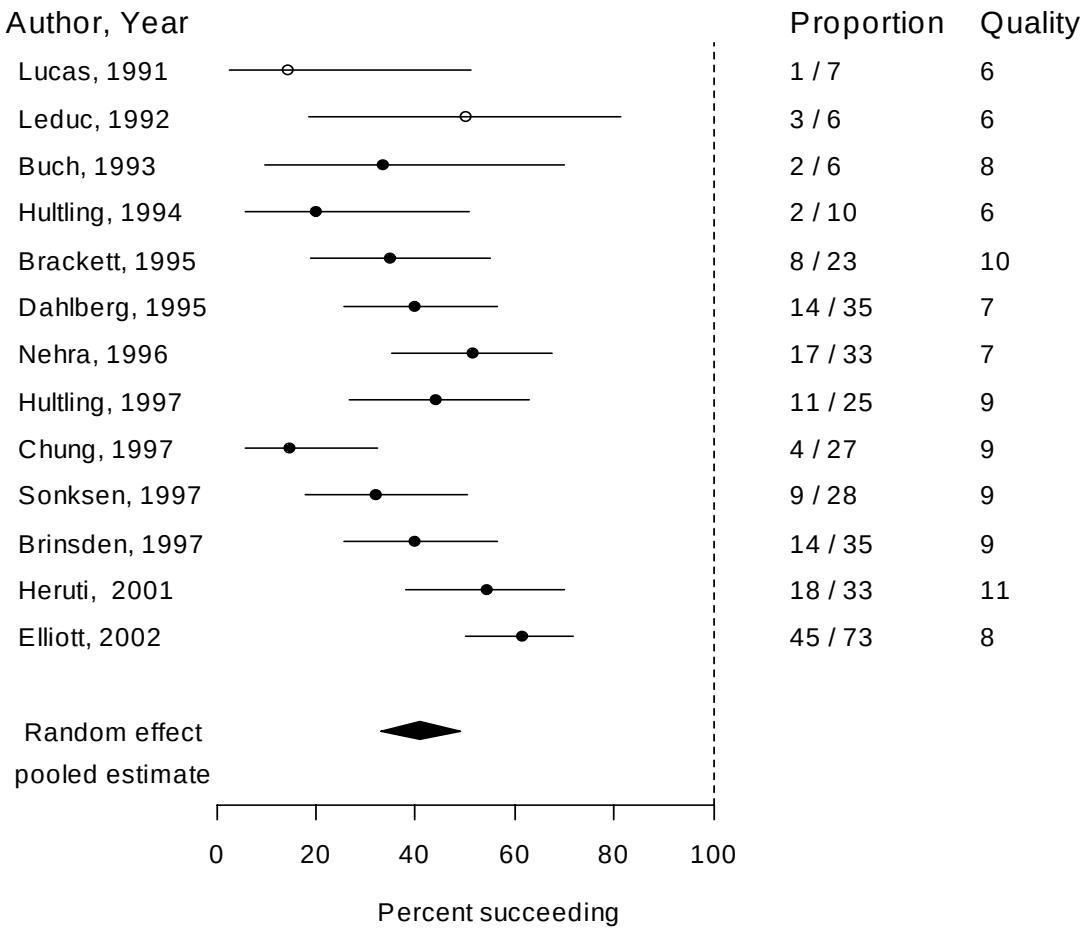

Figure 3: Forest plot of the success rate of live birth in noncomparative case-series studies that reported live birth as an outcome. The data was pooled and the overall estimate and its confidence interval was calculated using the random effects estimator of Laird & Mosteller.[36] Quality scores are out of a possible 19. Estimates from studies prior to 1993 are denoted by open circles. Only results from the past 10 years (1993-2003) were pooled to account for changes in techniques and technology.

Are Fertility Rates Changed After Freezing a New Patient's Sperm?

Only one study indirectly addressed this question (Summary Table 2). In 1994, Padron et al.[148] evaluated the effect of cryopreservation on the quality of sperm in SCI males, and determined that semen obtained from SCI males freezes as reliably as semen obtained from "controls." However, for both groups, when the optimal method of vapor freezing was used there was still a reduction in sperm motility of approximately 65%. This reduction in motility would obviously be more significant for the SCI group, a group that already has reduced sperm motility as a characteristic of its semen quality.

Summary Table 2: Study examining the impact of freezing sperm

Author, Year	Study Design	Number of patients	Fertility Rate	Quality
Padron et al., 1994	Controlled clinical trial	9	Frozen sperm from SCI men retain motility similar to that of normal men	Not applicable (non-RCT)

Are There Better Fertility Rates Using Electroejaculation or Vibration? Does Order of Method Influence Outcome?

We identified four trials that directly compared vibration and electroejaculation for inducing ejaculation in SCI males.[60-62,149] In a controlled clinical trial published in 1997, Brackett et al.[61] collected semen using vibration and/or electroejaculation from 77 males with SCI. Although total semen volume and sperm counts were similar, the percent motile sperm and percent sperm with rapid linear motion were significantly higher in the vibration-induced samples. This was observed for the vibration compared to electroejaculation groups, as well as within the ten patients who had both procedures performed. This study was a non-RCT and therefore could not be quality assessed using the Jadad scale.

In the same year, Ohl et al.[60] published results from an RCT that used both vibration and electroejaculation in a random fashion to obtain ejaculate from 11 males with SCI. They found that the antegrade specimen of the vibration-induced ejaculate had a higher quality (i.e., more motility) than the electroejaculate-induced antegrade specimens, however, the electroejaculated group had a higher retrograde volume, evening out the total motile sperm count (greater total volume in electroejaculated samples, better quality in vibration induced samples). The authors reported that the electroejaculate group experienced more pain, and all patients preferred the vibration procedure. This study received a quality score of 2/5 on the Jadad scale.

In 1998, Le Chapelain[150] analysed semen samples from 39 male SCI subjects and described improved semen quality with vibration-induced ejaculation compared with either electroejaculation or physostigmine.

Finally, Park et al.[62] reported an abstract in 1999 that used a case-control design to examine both electroejaculation and vibration in 17 males with SCI. Although sperm quality was superior using vibration, this technique was unsuccessfull for those with lesions at and below T10, requiring electroejaculation to be used with the lower lesions.

We were unable to locate any documents demonstrating a superior fertility outcome between vibration and electroejaculation. Therefore, we compared the side-effect profile of the two procedures to determine risk-benefit (Summary Table 3). Of the 21 studies identified that

reported ejaculation rates with either technique (Figure 1), ten reported adverse events.[40-43,45,47,49,50,53,59] Often, authors combined procedures, although they did not always separate the side effects by procedure. However, papers that combined the procedures demonstrated that the vibration technique is less likely to be successful for lower motor neuron (areflexic) injuries than with spastic injuries, and electroejaculation is more likely than vibration to cause autonomic dysreflexia in patients with spastic injuries.[41,43] Electroejaculation also has the added side effects of inflammation to the rectal mucosa[47] and stimulation pain[40,45,47,60] in incompletely injured patients. Therefore, most clinics that combine these techniques usually try vibration first followed by electoejaculation in the areflexic subjects that tend to not respond to vibration alone. It is recognized that techniques of vibration and electroejaculation, as well as techniques for blocking episodes of autonomic dysreflexia have changed over time and therefore the relative risks of the two techniques may not be comparable as described in the papers examined.

Summary Table 3: Success rates and complications observed with electroejaculation and/or vibration

Author/Year	Procedure	Success Ratio*	Complications
Sarkarati et al. (1987)	Vibration Electroejaculation	29/34	Pain in 4/34 pts.(electroejaculation) Minor headache and/or 20 to 40 mm.Hg increase in systolic BP occurred in a few patients (autonomic dysreflexia)
Pryor et al. (1995)	Vibration Case 1: ephedrine, imipramine, sodium bicarb. Case 2: ephedrine and sodium bicarb, imipramine and sodium bicarb Case 3: Case 4: ephedrine and sodium bicarb Case 5: Case 6: intra-uterine insemination	6/6	Case 1: headaches and spasticity due to ephedrine, switched to imipramine Case 2: NR (not recorded) Case 3: NR Case 4: NR Case 5: NR Case 6: NR
Lim et al. (1994)	Electroejaculation Vibration	12/12	"No incidence of severe hypertension due to autonomic dysreflexia" "Post-electroejaculation proctoscopy showed no damage to the rectal mucosa of any patient" "1 patient had significant problems with recurrent urinary tract infections" "1 pt complained of severe stomach cramps during electroejaculation"

Summary Table 3 (cont'd): Success rates and complications observed with electroejaculation and/or vibration

Author/Year	Procedure	Success Ratio*	Complications
VerVoort et al. (1988)	Electroejaculation	7/7	"All patients complained of headache/blurred vision/sweating/flushing and increased BP with no nifedipine" "Autonomic hyperreflexia effects reduced during electroejaculation with nifedipine"
Sonksen et al. (1994)	Vibration Population I – 25 pts.(Vibrator A, no nifedipine) Population II – 41pts.(Vibrator B, nifedipine sublingual prophylactically)	58/66	"Population I: 4 pts had light headache/no increase in BP;1 pt had glycerine nitrate sublingual" "Population II – no discomfort"
Heruti et al. (2001)	Electroejaculation	14/14	Abdominal pain or spasm in 17 stimulations raised BP in 15 stimulations 3 cases of increased spasm 1 case of syncope occurred in total of 16 patients, no tx needed, no further complications
Brindley (1981)	Electroejaculation	50/84	7 pts experienced intolerable pain – procedure stopped
Halstead et al. (1987)	Electroejaculation	10/12	Mild dysreflexia (3pts) disruption of normal bowel program (1 pt)
Rawicki & Hill (1991)	Electroejaculation Vibration Subcutaneous physostigmine 24 pt total (3 pt had electroejaculation under general anaesthetic due to pain) pts with lesions above C7 treated with labetolol 100mg or nifedipine 10mg	24/38	Electroejaculation: autonomic hyperreflexia in pts with high lesions; pain in pts with low lesions Vibration: autonomic hyperreflexia in pts with high lesions; 1pt with superficial ulcer; 2 pts with superficial trauma to the glans resulting in bruising Subcutaneous physostigmine: blurring vision (4/5); nausea and vomiting (2/5); marijuana-like highs (2/5)
*success of ejaculation			

To Improve Fertility Rates, When Should Invasive Techniques Such as Testicular Biopsy or Intracytoplasmic Sperm Injection be Used?

Invasive techniques to enhance fertility (advanced fertility [AF] techniques) such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) have been used more in recent studies. By grouping the 18 studies above that reported either pregnancies or live births (Figures 2 and 3) according to whether they used or did not use AF techniques, one can assess how using AF techniques impacts fertility rates (Summary Table 4). In doing so, one easily observes that to achieve pregnancy and birth rates approaching 50% or greater SCI couples need to use an AF technique.

Summary Table 4: Pregnancy and live birth rates for studies that used AF techniques compared with those that did not.

Study	N	AF vs non-AF	Pregnancies	Live births
Brackett 1995	23	AF	11/23 (48%)	8/23
Brinsden, 1997	35	AF	18/35 (51%)	14/35
Dahlberg, 1995	35	AF	18/35 (51%)	14/35
Elliot, 2002	73	AF	NR	45/73
Heruti, 2001	33	AF	18/33 (55%)	18/33
Hultling, 1997	25	AF	16/25 (64%)	11/25
Nehra, 1996	33	AF	17/33 (52%)	17/33
Pryor, 1995	6	AF	5/6 (83%)	NR
Pryor, 2001	11	AF	8/11 (73%)	NR
Taylor, 1999	19	AF	14/19 (74%)	NR
Beretta, 1996	6	non-AF	3/6 (50%)	NR
Buch, 1993	6	non-AF	NR	2/6
Chung, 1997	27	non-AF	7/27 (26%)	4/27
Halstead, 1987	10	non-AF	0/11 (0%)	NR
Hultling, 1994	12	non-AF	6/12 (50%)	2/10
Leduc, 1992	6	non-AF	3/6 (50%)	3/6
Lucas, 1991	10	non-AF	1/10 (10%)	1/7
Sonksen, 1997	28	non-AF	10/28 (36%)	9/28
NR=not reported				

Are There Pregnancy Complications and Prospective Obstetric Management Issues for SCI Females?

We did not find any reports that provided the necessary data for us to project the number and frequency of complications and other obstetric issues in females with SCI. There are numerous case reports, however, without the larger sample size obtained with a case-series study, it is difficult to conduct further research or inform practice or policy regarding this important health issue.

Question 2. How has the Availability of Viagra® and Other Remediation Affected Sexual Dysfunction and Adjustment After SCI?

By far, the majority of articles regarding sexual dysfunction after SCI are either opinion pieces or review articles (Appendix C; List of Excluded Studies). The only RCTs that were identified examined Viagra® for the treatment of erectile dysfunction. However, we did identify multiple case-series studies that had similar outcome measures, allowing their data to be pooled.

Interventions for Female Sexual Dysfunction

We found six articles that used a case-control design[6,100-104] and one article that used a RCT design[105] to examine the phenomena of sexual arousal in response to physical and cognitive stimulation in women with SCI (Summary Table 5).

The studies by Komisaruk et al.[103] and Whipple et al.,[104] appear to be separate reports on the same cohort of 16 women with SCI (n = 6 with upper SCI, n = 10 with lower SCI). In a case-

control study published in 1997, Komisaruk and colleagues[103] measured altered pain thresholds with genital stimulation in 16 SCI and five non-SCI females. The authors found that similar to their able-bodied counterparts, pain thresholds were increased with genital self-stimulation even in women with complete SCI. This finding led the authors to postulate that in the women with upper SCI, genitospinal visceral afferent pathways function (although unrecognized by the American Spinal Injury Association criteria) and/or there exists a functional genital afferent pathway that bypasses the spinal cord and projects directly to the brain. Whipple and colleagues[104] studied the 16 SCI females in the laboratory during self-stimulation and reported that only those with lesions below T-10 experienced increases in blood pressure; no SCI subjects had alterations in heart rate. Three females with complete SCI experienced orgasm with genital self-stimulation.

Sipski has published four case-control studies examining this topic in the most detail.[6,100-102] It is unknown, however, whether all of these patients represent new or restudied patients, although the outcome measures are different between the studies as the author is examining different phenomena. In 1996, Sipski et al.[102] demonstrated that even in females with supposedly complete SCI (n = 10), manual genital stimulation increased their sexual arousal, although requiring a higher level of concentration than able-bodied controls (n = 10). In a later study, Sipski et al.[6] demonstrated that with manual and audiovisual stimulation combined, greater than 50% of SCI women (n = 68) experienced orgasms that could not be differentiated from able-bodied controls (n = 21). Those with complete lower motor neuron dysfunction affecting S2-S5 had the lowest orgasm rate, and those with preservation of sensory function in dermatomes T11-L2 had greatest preservation of psychogenic-mediated sexual function. In another study, Sipski et al.[101] found similar orgasm rates among SCI women, with higher orgasm rates observed among women stimulated with a vibrator and among women who reportedly had higher sexual drive and greater awareness of their anatomic sexual function. Finally, Sipski et al.[100] demonstrated that women with complete SCI could respond with audiovisual stimulation in those physiologic functions that are controlled above the level of their injuries, whereas genital physiologic response could only be achieved by stimulation below the level of the injury. Overall, Sipski advocates using these data for behavioral counselling in SCI women, to help them achieve a higher level of sexual satisfaction by learning how their body works sexually after SCI.

The six case-control studies that addressed interventions for female sexual dysfunction all scored equal to, or above five on the NOS, with the highest score of seven obtained by Sipski et al.[102]

Summary Table 5. Studies examining various interventions for female sexual dysfunction

Author, Year	Study Design	Number of Patients	Quality Score
Whipple, 1996	Case-control	21 (16 SCI/5 controls)	6* (NOS)
Komisaruk et al., 1997	Case-control	21 (16 SCI/5 controls)	6* (NOS)
Sipski et al., 1995a	Case-control	21 (13 SCI/8 controls)	6* (NOS)
Sipski et al., 1995b	Case-control	35 (25 SCI/10 controls)	5* (NOS)
Sipski et al., 1996	Case-control	20 (10 SCI/10 controls)	7* (NOS)
Sipski et al., 2001	Case-control	89 (68 SCI/21 controls)	5* (NOS)
Sipski et al., 2000	RCT	19	2/5 (Jadad)

In addition, Sipski et al. performed a preliminary RCT study that evaluated Viagra® for sexual dysfunction in 19 women with SCI.[105] The authors found a modest physiologic effect, and the results of this study launched a large multicenter trial. The RCT received a quality score of 2 on the Jadad scale (Summary Table 8).

Male Sexual Dysfunction

Aside from a number of RCTs evaluating Viagra®, all of the studies that we identified which addressed this topic were case-series studies. The most common problems faced when trying to analyze this literature is that many authors chose different outcome measures. For example, some authors use a validated erectile grading system such as Schramek's, whereas others used their own grading system; some authors used all or parts of the IEFF sexual satisfaction rating scale, whereas others designed their own scales. When authors use either an on/off grading system or a common question on the IEFF, we have pooled the data when appropriate.

Behavioral interventions. We found only one study, a case-series study, that examined behavioral interventions.[132] Courtois et al.[132] demonstrated improvement in penile rigidity in ten SCI males before and after biofeedback followed by home perineal muscle training exercises. No measurements of sexual satisfaction were incorporated into the study. The quality score was 11/19.

Topical agents. An attractive alternative to either systemic medication or injected medication is the use of a topical vasoactive agent absorbed into the penis to stimulate erection in SCI males. We identified three noncomparative case-series studies[106-108] and one placebo-controlled clinical trial[109] that evaluated these agents (Summary Table 6). Sonsken et al.[108] evaluated the effect of applying transcutaneous nitroglycerin to the penis in 17 males with SCI, and found that five had a complete (full rigidity) response, seven had a partial response, and five failed to respond to the treatment. Six participants experienced headache with the treatment but no other serious side effects developed. Beretta et al.[106] performed a similar study using transcutaneous minoxidil in 15 males with SCI, and found that only four males had sufficient erection for vaginal penetration, while the others had an incomplete or no response. Only one patient reported experiencing headache. Kim and colleagues have studied both topical papaverine[109] and topical prostaglandin E1[107] in SCI males. Both agents appeared to be quite safe, with no symptoms reported and only a slight drop in blood pressure reported for the papaverine group. Kim et al.[107,109] reported that cavernous artery diameter was significantly increased for both papaverine and prostaglandin E1 as assessed by color flow Doppler ultrasound, although only approximately a quarter of both groups sustained a clinical erection with the treatment and there are no reports of using the medication during sexual activity.

Summary Table 6. Evidence for the use of vasoactive agents to stimulate erection in men with SCI

Author, Year	Topical Substance	Response	Quality Assessment
Beretta, 1993	Transcutaneous Minoxidil	4/15 had full erections	8/19
Kim & McVary, 1995	Topical prostaglandin	2/9 had clinical erections	10/19
Kim et al, 1995	Topical papaverine gel	3/12 had full erections	Not applicable (non-RCT)
Sonsken, 1992	Nitroglycerine patch	5/17 had full erections	7/19

Intraurethral Alprosatadil. We identified two case-series studies that evaluated intraurethral Alprostadil (prostaglandin) in males with SCI (Summary Table 7). Bodner[133,151] evaluated intraurethral Alprostadil in 15 males with SCI who had all responded to intracavernous injections of prostaglandin in the past, as measured by achieving a 5 out of 5 score on the Scrameks's erectile response grading system. Patients required the addition of a penile ring in order to prevent systemic hypotension. Only three achieved a grade 4 erection sufficient for intercourse, and all three patients were dissatisfied with the quality of the erection and did not continue to use the medication at home. Waldbaum[134] found similar results, and once again noted that the penile ring was necessary to prevent systemic hypotension.

Summary Table 7. Evidence for the use of intraurethral Alprostadil to stimulate erection in men with SCI

Author, Year	N	Results	Quality Assessment
Bodner, 1999	15	3/15 achieved erections sufficient for intercourse	8/19
Waldbaum, 1998	15	4/15 achieved erections sufficient for intercourse	Not applicable (abstract)

Intracavernous injections. Intracavernous (penile) injections of vasoactive substances have reported to treat SCI male impotence in the literature for several decades. Injected substances include papaverine, phentolamine, prostaglandin E1, or combinations of two or three of the above. Many clinics use combination therapy (papaverine, phentolamine, prostaglandin E1) for economic reasons, and there is no clear difference in efficacy between these substances.

Using "satisfactory erection" as a common outcome measure we were able to pool data from eight noncomparative case-series studies performed from 1987 to 1999, and involving a total of 263 patients (Figure 4).[110-117] These studies took place in the US, Australia, Italy, India, China and France. Overall these interventions resulted in a 90% satisfactory erection response rate (random effects pooled estimate: 0.90 [95% C.I. 0.83, 0.97]). One notes the very high success rates for these injections in males with SCI alone as a cause for their erectile dysfunction.

The studies by Zaslau et al.[115] and by Sidi et al.[116] were performed in individuals with SCI and either hypertension or diabetes. These studies found that the combination of SCI and another comorbidity decreases the efficacy of the injections.

The quality of these studies ranged from 6/19 to 13/19. Thirty-eight percent of the intracavernous injection studies met 11 of 19 (58%) quality criteria, with the highest score obtained by Sidi et al.[116]

Figure 4: Meta-Analysis—Intracavernous Injections

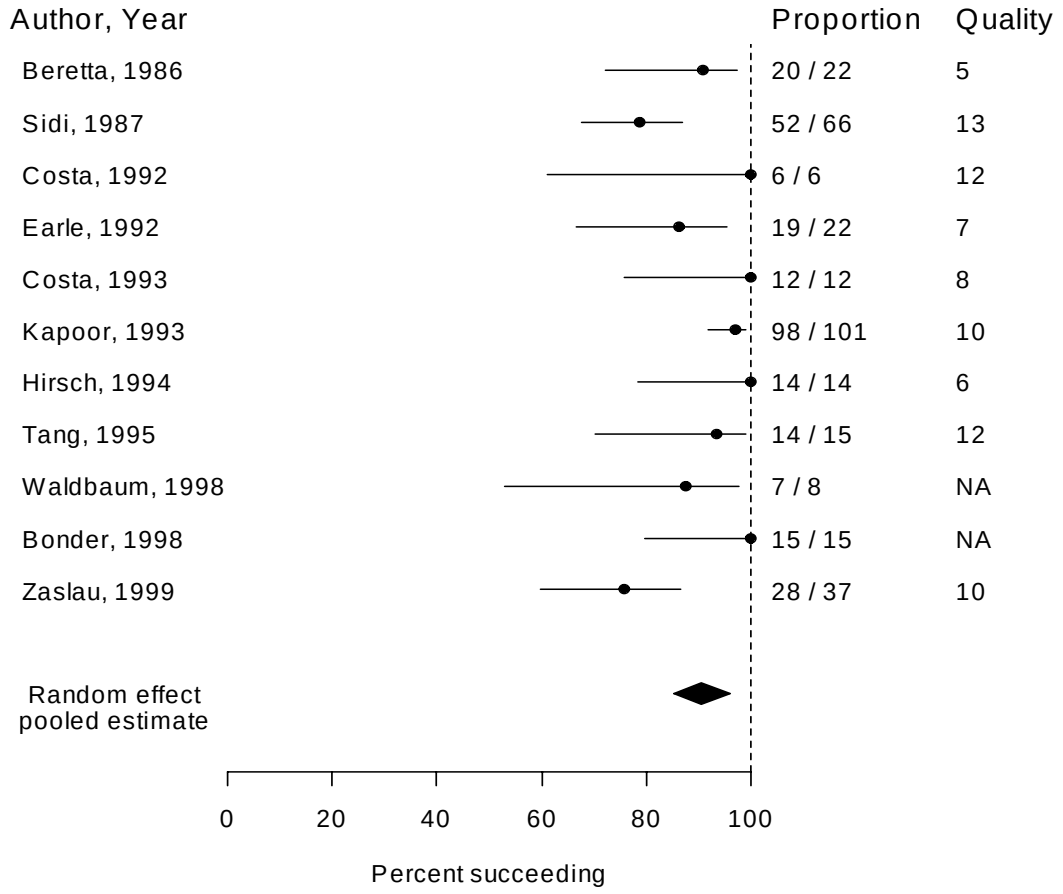

Figure 4: Forest plot of the success rate of intracavernous injections in noncomparative case-series studies that reported satisfactory erections as an outcome. The data was pooled and the overall estimate and its confidence interval was calculated using the random effects estimator of Laird & Mosteller.[36] Quality scores are out of a possible 19.

Vacuum tumescence devices. We found only two case-series studies that examined external vacuum pump devices for erectile dysfunction in males with SCI.[135,136]

In 1989, Zasler et al.[135] studied a novel vacuum pump system (Synergist) that uses a silicon sheath in 20 males with SCI, and reported that patient and partner assessments of the device efficacy and sex-life satisfaction with the device were very good to excellent. Although the device was required to stay on during intercourse, all patients in the study had complete SCI and therefore diminished sensation was not an issue. However, the silicon sheath did provide some protection for the partner. No side effects were reported. This report received a 13/19 quality assessment score. It is not known whether this device is still marketed.

In 1992, Heller et al.[136] studied two similar commercially available vacuum-pump systems in 30 males with SCI. All 30 subjects were trained on how to use the device in the clinic, and then 17 opted to purchase the device and use it at home. All 17 couples were satisfied with using the device during sexual activity. Some patients experienced transient testicle swelling (n = 3) and some experienced transient petechial hemorrhages (n = 5), although all of these side effects were resolved within 1 hour of use. This report received a quality assessment score of 8/19.

Penile implants. Now considered as one of the oldest treatments for erectile dysfunction, penile implants have been used in SCI males for decades, although with decreasing frequency. While this topic has been frequently discussed in opinion pieces, we found only five case-series studies that examined penile implants for either erectile dysfunction or erectile dysfunction plus urinary incontinence (Summary Table 8).[118-122] These case-series studies took place in the US, Germany and Japan, and involved a total of over 360 SCI males. A variety of different prostheses were used including inflatable, semirigid, semiflexible and flexible devices. Complications included infections, extrusions of the devices, perforations, pain, and mechanical device failure. The quality scores for these studies ranged from 5/19 to 7/19.

Summary Table 8. Case-series evidence for the use of penile implants for erectile dysfunction in men with SCI

Author, Year	N Implants	Complications	Quality Score
Golji, 1979	30	2 cases infection causing extrusion 2 cases wound infections treated conservatively	7/19
Green & Sloan, 1986	40	3 cases extruded rods 1 case penile erosion	7/19
Gross et al., 1996	209	14 cases requiring removal of implant 21 cases rod perforation	5/19
Iwatsubo et al., 1986	37	2 cases infection causing extrusion 1 case severe pain 1 case mechanical failure	5/19
Montague, 1994	47	2 cases infection requiring removal 1 case penile erosion requiring removal 2 cases mechanical failure	6/19

Sacral stimulators. Sacral stimulators have been championed by Brindley and others as a method of achieving continence with low voiding pressures in patients with complete SCI In general, the procedure is reserved for complete injuries since it necessitates a sacral rhizotomy with loss of a reflex erection, reflex voiding, or defecation; Brindley describes the stimulator as a way of voluntarily controlling these functions. We identified a single case-series study[137] that reported erection rates in SCI males treated with sacral stimulators for bladder control. van der

Aa et al.[137,152] reported that 29 of 33 subjects with implants could achieve a full sustainable erection by stimulating the S2 or S3 anterior routes. The report of this case-series study did not, however, state how the stimulator-induced erection impacted sexual function, or if there were side effects such as bladder or bowel incontinence during sexual activity. The study by van der Aa et al.[137] received a 5/19 quality assessment score.

Viagra® (sildafenil), RCTs. Although we originally identified nine reports of RCTs that examined Viagra® in males with SCI,[123,124,138-141,153-155] careful analysis revealed that only two of these reports were separate trials;[123,124] the remaining studies were repeat reports in separate journals. Data from these trials come from the UK, France and Australia., and involve a total of 205 male subjects with SCI (Summary Table 9). Different types of randomized trial designs, such as crossover and parallel, and different outcome measures were used in these studies, and the results were not poolable for meta-analysis. Both of these studies received a quality rating of 3/5 on the Jadad scale.

Summary Table 9: RCT evidence for the use of Viagra® for sexual dysfunction in men with SCI

Author, Year, Location	Number of subjects (N); Number of dropouts (D)	Results	Adverse Events	Quality Score
Giuliano et al., 1999 France, U.K., Australia	N=178 D=7	76% improved erections and a preference for Viagra® vs 4% for placebo	Headache: Viagra®=30, placebo=8 Flushing: Viagra®=12, placebo=2 Dyspepsia: Viagra®=5, placebo=0 Visual effects: Viagra®=4, placebo=0 Rhinitis: Viagra®=3, placebo=0	3/5 (Jadad)
Maytom et al., 1999, UK	N=27 D= 0	Erections in clinic >60% at base: Viagra®=65%; placebo=8% Global Efficacy Question (did treatment improve erections?): Viagra®=75%; placebo=7%	Headache: Viagra®=4, placebo=1 Dyspepsia: Viagra®=1, placebo=0 Vomiting: Viagra®=1, placebo=0 Dizziness: Viagra®=1, placebo=0 Rash: Viagra®=2, placebo=3	3/5 (Jadad)

Viagra (sildafenil), case series. Many of the case-series studies also used a variety of outcome measures, however, we were able to identify seven studies that assessed the subject's report of the drug improving erectile function for sexual intercourse when the drug was used at home.[125-131] These studies took place from 1999 to 2001 in the US, Germany, Spain, Switzerland and Japan. Overall, Viagra® resulted in a 79% successful erectile function (random effects pooled estimate: 0.79 [95% C.I. 0.68, 0.90]) (Figure 4). The analysis of these noncomparative case-series studies shows a high level of heterogeneity which is best explained by the subjective assessment of the outcome measure, with no standardized questionnaires being used across studies, and the fact that measurements were not obtained in the clinic, but rather secondhand from the patients "personal experience." For the studies where quality could be assessed (i.e. full reports), the quality ranged from 9/19 to 16/19. The Gans et al. study,[125] which met 16 of 19

(84%) quality criteria, was the only study identified by this systematic review to achieve such a high rating.

Figure 5: Meta-Analysis—Viagra®

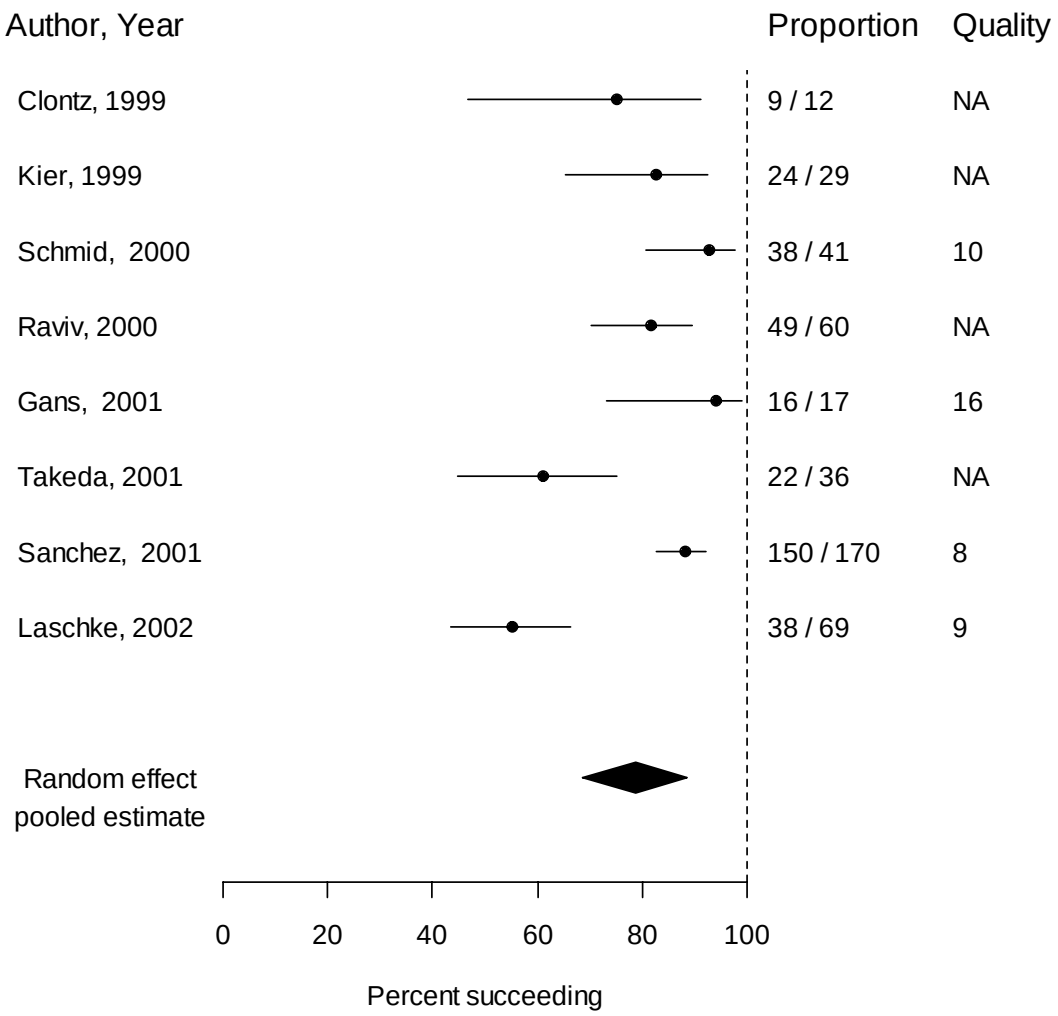

Figure 5: Forest plot of the use of Viagra® in noncomparative case-series studies that reported improved erectile function as an outcome. The data was pooled and the overall estimate and its confidence interval was calculated using the random effects estimator of Laird & Mosteller.[36]

Is Viagra Really More Benign Than Intracavernous Injections?

Intracavernous injections have a significantly higher efficacy than Viagra® (90% versus 79%). To compare the side-effect profile of intracavernous injections with that of Viagra®, we extracted data from the studies described above that reported side effects. Ten studies from the US, Europe and Japan conducted from 1998 to 2002 and including a total of over 600 patients

reported that the most common side effects observed with Viagra® were short-lived, and included headache, flushing and infrequent dizziness (Summary Table 10).[123,126-128,130,131,138-141] Note that all of these studies excluded patients on nitrate medications and that there were no reported sudden deaths. With regards to intracavernal injections, eight studies carried out from 1986 to 1999 in the US, Australia, Italy, India, China and France and studying a total of 263 patients reported transient local side effects, such as pain and swelling at the injection site.[112-117,142,143] The most serious was priapism (prolonged erection), which can be avoided by doing doseage adjustments in the clinic with a reliable subject.

Summary Table 10. Side effects associated with the use of intracavernous injection or Viagra® for sexual dysfunction in men with SCI

Author, Year	Intervention (number of pts)	Side Effects (number of pts)
Anonymous, (1999)	Viagra® (26)	2 pts with dyspepsia and respiratory disorder
Clontz et al., 1999 (abstract)	Viagra® (12)	visual changes (1) and headache (3)
Derry FA et al., (1998)	Viagra® (27), vibration	headache (4) dyspepsia (1) dizziness (1) anxiety (1)
Giuliano et al., (1999)	Viagra® (178)	headache (30) flushing(12) dyspepsia(5) rhinitis (3) abnormal vision (4) discontinued treatment (6)
Kier et al., 1999	Viagra® (29)	visual change (3%) headache (17%) dizziness (3%) flushing (3%)
Laschke et al., (abstract, 2002)	Viagra® (69)	headaches and flushing (25%)
Sanchez et al., 2001	Viagra® (170)	headache (10) flushing (15) GI discomfort (7) nasal congestion (8) visual disturbances (7) restlessness, palpitations, hiccup, dry mouth (9) unbearable abdominal pain (1)

Summary Table 10 (cont'd). Side effects associated with the use of intracavernous injection or Viagra® for sexual dysfunction in men with SCI

Author, Year	Intervention (number of pts)	Side Effects (number of pts)
Schmid et al., 2000	Viagra® (41)	headache(3) or dizziness(2) flushing (2) dyspepsia (1) blurred vision (1) 2 withdrew because of adverse events
Shenot et al., 1999 (abstract)	Viagra® (29)	headache (7%) flushing (7%)
Takeda et al., 2000 (abstract)	Viagra® (36)	headache, facial flush, chest strangled feeling
Beretta et al., 1986	Papaverine (22)	7 pts with prolonged erections
Earle et al., 1992	Papaverine, papaverine & phentolamine, prostaglandin E1 (22)	pain with 2 pts, one using papaverine one using papaverine and phentolamine
Hirsch et al., 1994	Prostaglandin E1 (14)	2 pts with subclinical corporal fibrosis
Kapoor et al., 1993	Papaverine: 101 volunteers, 65 papaplegics, 36 tetraplegics	3 subcutaneous haematoma, 2 cavernosal fibrosis, 3 prolonged erection, 1 systemic effects
Renganathan et al., 1997	Transdermal nitroglycerin vs papaverine (28)	9 pts complications with papaverine: 8 had mild edema, 1 pt with prolonged erection
Sidi et al., 1987	Papaverine HCl, or combo papaverine/phentolamine mesylate (66)	4 pts with sustained erections that required irrigation
Tang et al., 1995	Prostaglandin E1 (15)	2 pts pain at injection site
Zaslau et al., 1999	Fixed combo of prostaglandin E1 and papaverine (37)	2 pts stopped due to pain/ecchymosis at injection site

How Does the Morbidity of Prostaglandin Injections Compare With the Older, Less Expensive Papaverine or Phentolamine

Although similar in efficacy, prostaglandin E1 is less stable at room temperature and much more expensive than papaverine or phentolamine. Proponents cite a shorter half-life (less chance of priapism) and less injection-site pain and scarring as reasons to use this substance despite its expense. We identified six noncomparative case-series studies[112,113,115-117,142] and one RCT[143] that reported the numbers of side effects, and the adverse reactions are listed in Summary Table 11. The quality of the case-series studies ranged from 5/19 to 13/19. Thirty-three percent of the papaverine/prostaglandin intracavernous injection studies met 11 of 19 (58%) quality criteria. The RCT of Renganathan et al.[143] received a Jadad score of 0/5.

Summary Table 11. Side effects associated with intracavernous injections

Author, Year	N treated	Substance	Side Effects	Quality Score
Beretta et al. 1986	22	Papaverine	7 had priapism	5/19
Earle et al. 1992	22	Papaverine, papaverine & phentolamine, prostaglandin E1	pain with 2 pts, one using papaverine one using papaverine and phentolamine	7/19
Hirsch et al. 1994	27	Prostaglandin E1	2 had penile scarring detectable only on ultrasound after repeated use	6/19
Kapoor et al. 1993	101	Papaverine	3 had subcutaneous haematoma 2 had cavernosa fibrosis after 3 years use 1 had priapism 1 had a vasovagal reaction requiring dosage reduction	10/19
Renganathan et al. 1997	28	Papaverine	1 had priapism 8 had local swelling requiring no intervention	0/5 (Jadad)
Sidi et al. 1987	66	Papaverine or papaverine/phentolamine mixture	4 had priapism 3 had minor hematomas 1 had localized site induration requiring discontinuation	13/19
Tang et al. 1995	15	Prostaglandin E1	2 complained of pain at injection site	12/19
Zaslau et al. 1999	28	Papaverine and prostaglandin E1 mixture	2 complained of pain at injection site	10/19

What is the Morbidity of Vacuum Tumescence Devices?

As described above in the two identified reports of studies of vacuum tumescence devices,[135,136] when used with proper clinic instruction and according to the specifications of the manufacturers, these devices have a very low morbidity rate with no irreversible morbidity's noted. Although there are case reports of penile ischemia in the literature, these case reports serve only as a warning not to leave the device on too long and cannot help us with ascertaining a complication rate.

In a comparative cases series, Chancellor et al.[156] compared vacuum-pump devices with papaverine injections in 18 males with SCI. The injections and pumps were equally effective and neither group suffered any complications during the study. After trying both treatments, seven patients chose to remain with the pump and another seven chose the injections. A third arm of this study used topical minoxidil, but unfortunately no patients achieved satisfactory results with this treatment.

What Indications, if Any, Remain for Implantable Penile Prosthetic Devices?

See Summary Table 8 for the results of the five case-series studies that evaluated penile implants in patients with SCI. It is notable that although penile implants result in a high level of satisfaction for those clients who do not have complications, the serious complication rate is as high as 10%. Furthermore, patients who have an implant removed are no longer candidates for other treatment options as they are likely to have damage to the penile tissues that would make

them nonresponsive to intracavernous injections or vacuum devices. These devices are, however, useful to assist those who need them for external application of condom drainage systems. They also could be used in patients who failed to respond to oral or injectable medications and vacuum devices, or those who find these alternatives unacceptable.

Chapter 4. Discussion

Limitations

Much of the literature reviewed consisted of clinic reports in case-series format, describing a center's experience with a variety of treatment techniques. Although these descriptive experiences are valuable, they are often reported in variable formats with different outcome measures, providing little consistency for comparative purposesacross studies. Similarly, the quality of reporting, especially the earlier publications, is less than optimal.

As in all scientific fields, changes in technology tend to influence, and perhaps confound the effectiveness of interventions. We have tried to account for this "evolution" in technology by pooling results from the last decade, excluding early attempts that tended to have smaller numbers of patients, with lower success rates. We do not wish in any way to belittle the groundbreaking research of these earlier pioneers, without whose efforts we would still be counselling our patients to "forget about sex or having children," as was done only several decades ago. The pioneers encouraged us all to try to do "something," and our own early clinical experience reflects this; for example, we would inject intrathecal physostigmine into patients in the clinic with a kidney basin nearby to catch their vomit and a test tube to catch their semen—this before we knew that a simple modified vibrator could do the same. We hope this report accurately reflects the rapid evolution of this field, while respecting its history. Despite the somewhat high statistical heterogeneity in the pooled data, clinicians are familiar with discussing ranges of success with their patients, and saying that "this technique has a success rate of 80% to 90%" is not at all uncomfortable to those who deal with biologic uncertainties.

For fertility in males after SCI, one source of heterogeneity was a secular trend in success rates. For this reason, only studies from the last decade were pooled. Nevertheless, in each of the meta-analyses conducted in this evidence report, statistically significant heterogeneity remained. In the presence of statistical heterogeneity, confidence intervals for random effects pooled estimates are broadened to account for differences amongst the studies. However, these results should still be treated with caution, and we discuss other factors that may be contributing to the observed heterogeneity.

Fertility in Females After SCI

It is often stated, both in review articles and by clinician teachers at the bedside, that although there is an initial acute delay in the return of ovulation cycles in females following SCI, ultimately there is no impact on female fertility by the injury per se. Although this statement may be true, it is unfortunately not supported by studies comparing fertility of women with SCI with an uninjured cohort. There may well be unsuspected effects of SCI on the rate of miscarriages and live births in couples trying to have a child. A prospective, well-organized and

well-reported case-series or cohort study, potentially involving multiple centers, could provide valuable natural history information to answer this question.

Fertility in Males After SCI

In 1960, Bors and Comarr reported that males post-SCI had a fertility rate of less than 10%. Not surprisingly, since male reproduction is most obviously affected, the vast majority of fertility literature focuses on male reproduction post-SCI. In addition to this the vast majority of spinal cord injuries occur in men, most western nations approximately 80 percent of injured persons are male. Initial attempts to help infertile couples conceive a child were used to develop techniques to harvest sperm from the SCI male and inseminate the female partner, either using taught self-insemination or clinic intrauterine insemination. Although successful, these efforts were hampered by the low semen quality often found in SCI males. Later, IVF and ICSI techniques were used to overcome this problem, and now patients can typically expect a stepped approach in a fertility clinic, where couples start with the least invasive approach and progress to the most invasive techniques. Although these techniques improve the chances of a successful live birth by up over 50%, they are extremely expensive and somewhat invasive, with female partners often exposed to hormonal cycle manipulation and SCI males undergoing testicular biopsies and aspirations. Although these risks and expenses mirror those of other infertile couples, we must remember that those living with SCI have additional lifelong equipment and care expenses, as well as reduced employment opportunities, creating financial burdens that may not allow them to consider these options. This financial situation has imposed a new form of limitation on pregnancy success. There is therefore a need for research to improve semen quality in men with SCI so that pregnancy may be attempted at lower cost and less invasiveness in these couples. As a result of this combination of expense and invasiveness, most fertility clinics utilized a stepped approach, going from the most natural and inexpensive and least invasive methodology to the enhanced fertility option in a graduated approach. This may account for some of the heterogeneity in the data, nevertheless we felt that it was worthwhile to pool the fertility data to enable us to compare the results of this type of treatment for SCI males to the fertility treatment for the general population. It is also recognized that in the fertility literature in general, it is likely that this type of heterogeneity will also be present, again influenced by invasiveness as well as by cost.

Despite the fact that fertility clinic data is extremely valuable in understanding this subject area, many of the case-series studies published on fertility were rated low in quality. Since most fertility clinic data is reported in a similar fashion, the Spinal Consortium could improve the quality of future data by publishing guidelines on the reporting of case-series studies and case-control study designs.

Original articles recounting issues of fertility after SCI describe the problem of harvesting semen and the poor quality of the semen as factors inhibiting success. Our review demonstrates that by using vibration for upper motor neuron injuries and electroejaculation for the remaining lower motor neuron injuries, semen can be harvested in 80% to 90% of cases. Furthermore, testicular biopsy or vas deferens aspiration techniques, although expensive and invasive, are usually successful in the remaining patients. Partner pregnancy is achieved usually using a stepped approach, moving from intrauterine insemination to IVF techniques with success rates

for achieving a pregnancy of up to 50%. Sperm freezing probably does little to enhance this process unless the sperm is frozen almost immediately after injury, usually a difficult time to make such life decisions.

Sperm Quality in Males with SCI

There has been much discussion regarding the abnormal sperm found in the ejaculate of males with SCI including: decreased sperm counts,[87] decreased sperm motility,[82,87,94] increased reactive oxygen species formation,[94] sperm autoimmunity,[83] necrospermia,[91] the inhibitive effect of seminal plasma in SCI males,[90] and the presence of antisperm antibodies.[95] Methods used to counteract these negative effects include retrieving the semen more proximally through testicular biopsy or aspiration.[85,88] Medical factors can also be optimized in order to try to improve sperm quality. Chapelle et al.[157] studied 135 SCI males at various neurological levels using physostigmine and testicular volume, and found that damage to the T12-L2 region of the cord (T12 metamer) correlated with testicular atrophy and poor ability to ejaculate. Three studies examining the effects of bladder management on sperm quality found that those men managing their bladders with high-pressure reflex voiding had reduced sperm quality, whereas those men using intermittent catheterization had the best sperm parameters.[76-78] Two studies documented the effect of repeated ejaculation on sperm quality and demonstrated that repeated ejaculation improved sperm quality to a plateau, but that too frequent ejaculation (once per week) decreased sperm quality.[79,80] They also indicated that these procedures should be timed monthly with the female partner's cycle. Chen et al. compared the sperm counts in antegrade versus retrograde sperm samples, and found that although there was a non-statistical trend towards better sperm counts in antegrade specimens, retrograde ejaculation occurred more frequently.[56,89] Bracket et al. studied the effect of temperature on the semen of SCI males and found that although the semen of SCI males lose motility faster than the sperm of normal males, especially at higher (body as opposed to room) temperatures,[82] scrotal temperature and gonadotropin levels did not contribute to poor semen quality in SCI males.[81]

Although sperm motility and other aspects of fertility are seldom reported after acute SCI, studies show that in the chronically spinal cord injured individual (>1 year), there is no relationship between duration of injury and sperm quality.[77-79,87] However, Mallidus et al.[46] demonstrated that the sperm motility and viability first improve after the acute patient comes out of spinal shock then rapidly starts to deteriorate, reaching the levels observed in males with chronic SCI by Day 16 after injury.[46] Padron,[148] in a case-series study, and Green[37] in a case report, demonstrated that although sperm from SCI males freezes reliably, there is still a great reduction in sperm motility.

When these data are considered together, one can conclude that there is little to support the practice of freezing the sperm of SCI males after 16 days post-injury, and that even the advantages of early freezing (within the first 2 weeks) is outweighed by the loss of sperm motility during the procedure, since with modern techniques one is virtually certain of obtaining fresh sperm from the SCI male when he is ready to conceive a child in later years.

Sexual Dysfunction in Females with SCI

The studies done on female sexuality post-SCI, especially the thorough work done by Sipski, present fresh ideas and debunk old myths. Even without genital sensation, females with SCI have both reflex and cognitive pathways available to them to alow pleasurable experiences during sexual activities. Reflex pathways can be enhanced with increased stimulation (i.e. vibration) and cognitive behavioral therapy can enhance cognitive stimulation. Unfortunately, aside from a small RCT pilot with Viagra®, little has been done to study possible interventions along this line. Despite the early hope in the small Viagra® study, a large multicentre Viagra® study that has just been completed and not yet published, failed to reveal any benefit in SCI females with sexual arousal disorder (personal communication).

Cognitive/behavioral therapy is often used in clinical settings to help address female sexuality issues after SCI, yet there are no trials to support its use. These trials could be conducted, and it would be useful to describe protocols to help set practice standards in this important area. Given the complex biosocial issues described by Sipski, it is unlikely that pharmaceutical treatment alone will address the problems.

Male Sexual Dysfunction

Although attractive conceptually, topical and intraurethral pharmaceutical agents have not had much success in treating individuals with SCI erectile dysfunction. However, penile injections with a variety of medications have proven extrememly successful. It can be noted that careful dosage adjustment is necessary with the papaverine or papaverine/phentolamine combinations. When used alone, prostaglandin E1 has few side effects outside of its cost.

If subjects are reliable and if they have little sensation there seems to be few advantages of Viagra® over intracavernous injections aside from subject and partner preference.

Although other phosphodiesterase inhibitors have come to market since sildanefil, no SCI treatment data for these drugs were available at the time of this review.

Both vacuum pumps and intracavernous injections must be used with caution or not at all in anticoagulated patients because of the risk of hemorrhaging or bruising. Both treatment groups must also be monitored for priapism. Both of these complications appear to be quite rare if patients are first tested and instructed in the clinic before being sent home for self-treatment.

Research and Clinical Implications

Our review highlights some important issues in terms of how spinal cord clinical research is conducted. Like many other clinical content areas, there is a wide variation in the types of research designs used and measures used to assess similar outcomes. Although different approaches, particularly if they provide similar results, help to provide powerful evidence about the robustness of interventions, such as the use of Viagra®, there are important and often

debilitating consequences for such research development. Often, separate groups are so unique that the process of how their arrived at the results are disparate making it difficult to impossible to get a broad holistic view of the evidence base in the field.

To help overcome these problems groups are coming together and proposing more standardization when conducting clinical research. The rheumatology community provides an excellent example through the OMERACT initiative. For example, they have agreed upon standard methodologies and forms to collect specific outcomes. The advantage is that clinical trials conducted by various groups are 'similar' in terms of design features and outcomes. As such this information can be combined qualitatively and quantitatively providing the strongest possible evidence base regarding the merits of specific interventions. Such an approach might be beneficial for groups trying to advance this field of research and understanding.

Such actions are also happening for reporting clinical trials. The clinical trials community has moved towards a standard for reporting randomized trials. The CONSORT Statement, a 22-item checklist and flow diagram, is now required by most major medical journals when authors are submitting reports of randomized trials.

Finally, the female SCI literature describes biosocial holistic models of sexuality and, therefore, is ripe for trials involving multidimensional treatment modalities. The male SCI literature seems completely unidimensional (male sexuality + erection) and this focus deprives males from those same treatment options, the danger is that the clinician, when faced with a suffering patient, reaches into their drawer for the drug sample. Research must be driven by patient need—this literature is not.

As a final point, clinicians working in this area are confronted with issues from same sex couples, with absolutely no literature to guide them in this discussion. Well-conducted, qualitative analysis work would provide a great deal of clarity in these matters, but again this literature is absent.

Conclusions

There were two general themes in this review—sexuality and fertility after SCI. These reviewers often found the division between these two themes to be artificial, and overlap often occurred. Nevertheless, we attempted to discern between the two bodies of literature.

There is a great deal of literature in this area; however, much of the data was found to be repeat data (i.e., nonoriginal), and new data was incompletely reported, resulting in the evidence often being of poor quality. However, given these limitations and those outlined in the Discussion, we would like to answer the questions posed in as straightforward a manner as the evidence allows for:

1. Reproductive health: What is the current fertility rate for men and women after SCI?

   For women, fertility rate is likely unaffected but little is known beyond that. For example, is there a higher pregnancy failure rate, or are there more or less birth deformities?

   - Are fertility rates changed by freezing a new patient's sperm?

Unless done in the first one or two weeks after SCI, and even if done earlier, this intervention is unlikely to make a significant improvement in SCI fertility rates, and therefore is not widely practiced.

- Are there better fertility rates using electroejaculation or vibration? Does order of method influence outcome?

  The level of invasiveness is likely more of a factor than either the choice or the order. Vibration should be tried at least on all upper motor neuron injuries first, with electroejaculation reserved for those failures and the lower motor neuron injuries

- To improve fertility rates, when should invasive techniques such as testicular biopsy or aspiration or ICSI be pursued?

  Testicular biopsy or vas aspirations should be reserved for those patients who cannot achieve sperm harvesting or whose harvested sperm by the above techniques is of very low quality. ICSI can greatly enhance success in those individuals whose sperm quality is insufficient for intrauterine insemination (IUI).

- Are there pregnancy complications and prospective obstetric management issues for SCI females?

  Yes, but they are not described in the literature except in author opinion pieces and case reports. Comparative case series and cohort studies would add a great deal of information to this area.

2. Male sexuality: How has the availability of Viagra® and other remediation affected sexual function, frequency of activity, and adjustment after SCI?

   Penile injection, Viagra® and vacuum devices can help most problems in SCI males with erectile dysfunction, making the need for penile implants less common. These interventions positively affect sexual activity at least in the short-term. Long-term sexual adjustment has not been examined.

   - Is Viagra® really more benign than intracavernous injections?

     Not really, unless the patient has enough sensation that the injections are uncomfortable or if they find that the paraphernalia affects their sexual activity.

   - How does the morbidity of prostaglandin injections compare to the older (less expensive) papaverine?

     Although the efficacy of these two treatments is similar, priapism and discomfort are reported more frequently with papaverine.

   - What is the morbidity of vacuum tumescence devices?

There is a paucity of reports regarding the morbidity of these pumps. These devices are not recommended in patients on anticoagulants. Patients must take care to remove the device after sexual activity.

- What indications, if any, remain for implantable penile prosthetic devices?

  Very few patients will not respond to any of the more benign techniques. Penile implants still possess a significant morbidity risk, and in case-series studies, implants are often described with condom drainage systems.

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Search Strategy 1

1. comarr$.au.
2. (Female Sexual Function Index or FSFI).mp.
3. (Brief Index of Sexual Functioning or BISF-W).mp.
4. (Changes in Sexual Functioning Questionnaire or CSFQ).mp.
5. (Derogatis Interview for Sexual Functioning or DISF).mp.
6. (Golombok Rust Inventory of Sexual Satisfaction or GRISS).mp.
7. (International Index of Erectile Function or IIEF).mp.
8. (Brief Male Sexual Function Inventory or BMSFI).mp.
9. exp reproduction/
10. (reproducti$ or impoten$ or sex$ or ejaculat$ or erectile or menstruat$ or menopaus$ or hysterectom$ or infertil$ or orgasm$ or pregnanc$ or contracept$).mp.
11. (gay or lesbian or bisexual$ or transgender$ or homosexual$).mp.
12. or/2-11
13. Spinal Cord Injuries/
14. Paraplegia/
15. Quadriplegia/
16. Traumatic cord.mp.
17. post-traumatic myelopathy.mp.
18. (spinal cord inj$ or parapleg$ or quadripleg$ or tetrapleg$).mp.
19. meningomyelocele/ or spinal dysraphism/ or spina bifida cystica/ or spina bifida occulta/
20. (cerebral palsy not spinal cord).mp.
21. or/13-18
22. 21 not (19 or 20)
23. limit 22 to animal
24. limit 22 to human
25. 23 and 24
26. 22 not (23 not 25)
27. exp Sex Behavior/sn [Statistics & Numerical Data]
28. sexual$ activ$.mp.
29. sexual adjust$.mp.
30. sex$ counsel$.mp.
31. or/27-30
32. 12 and (sn or ep).fs.
33. (31 or 32) and 26
34. 12 and (1 or 26)
35. limit 34 to female
36. limit 34 to male
37. 34 and (35 not 36)
38. (menstruat$ or menopaus$ or hysterectom$ or pregnanc$).mp.
39. cesarean.mp.
40. obstetr$.ti.
41. obstetr$.mp.
42. or/38-41
43. 12 and 26 and (37 or 42)
44. 43 not 33
45. Fertility/
46. Birth Rate/
47. FERTILIZATION/
48. fertili$.mp.
49. conception.mp.
50. infertility.mp.
51. INFERTILITY, FEMALE/

52. infertility, male/
53. or/45-52
54. (53 and 26 and 34) not (33 or 44)
55. limit 54 to (adolescence <13 to 18 years> or adult)
56. viagra.mp.
57. Sildenafil citrate.mp.
58. Sildenafil.mp.
59. midodrine.mp.
60. Gutron.mp.
61. Electroejaculat$.mp.
62. Ultrex.mp.
63. Cialis$.mp.
64. Vasomax$.mp.
65. penile prosthesis.mp.
66. (prosthes#s adj2 (penis or penile)).mp.
67. (vacuum adj2 (constriction or device)).mp.
68. ((negative pressure or suction) adj device).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
69. negative pressure device$.mp.
70. vibromassage.mp.
71. massage.mp.
72. vibration.mp.
73. intracavernous.mp.
74. Alprostadil.mp.
75. PROSTAGLANDINS E, SYNTHETIC/ or PROSTAGLANDINS F/
76. Prostaglandin-e1.mp.
77. Papaverine.mp.
78. surgical collection.mp.
79. caverject.mp.
80. (MUSE and prostaglandin).mp.
81. Medicated Urethral System for Erection.mp.
82. vas aspiration.mp.
83. testicular biopsy.mp.
84. aspiration.mp.
85. or/56-84
86. 85 and 26
87. limit 86 to male
88. (Impoten$ or erectile).mp.
89. 86 and 88
90. ((87 or 89) and 34) not (33 or 44 or 45)
91. or/56-60
92. limit 91 to female
93. (92 and 26) not (33 or 44 or 55 or 90)
94. 34 not (33 or 44 or 55 or 90 or 93)

Search Strategy 2

1. comarr$.au.
2. (Female Sexual Function Index or FSFI).mp.
3. (Brief Index of Sexual Functioning or BISF-W).mp.
4. (Changes in Sexual Functioning Questionnaire or CSFQ).mp.
5. (Derogatis Interview for Sexual Functioning or DISF).mp.
6. (Golombok Rust Inventory of Sexual Satisfaction or GRISS).mp.
7. (International Index of Erectile Function or IIEF).mp.
8. (Brief Male Sexual Function Inventory or BMSFI).mp.
9. sexual satisfaction/
10. (reproducti$ or impoten$ or sex$ or ejaculat$ or erectile or menstruat$ or menopaus$ or hysterectom$ or infertil$ or orgasm$ or pregnanc$ or contracept$).mp.
11. (gay or lesbian or bisexual$ or transgender$ or homosexual$).mp.
12. or/2-11
13. Spinal Cord Injuries/
14. Paraplegia/
15. Quadriplegia/
16. Traumatic cord.mp.
17. post-traumatic myelopathy.mp.
18. (spinal cord inj$ or parapleg$ or quadripleg$ or tetrapleg$).mp.
19. meningomyelocele/ or spinal dysraphism/ or spina bifida cystica/ or spina bifida occulta/
20. (cerebral palsy not spinal cord).mp.
21. or/13-18
22. 21 not (19 or 20)
23. limit 22 to animal
24. limit 22 to human
25. 23 and 24
26. 22 not (23 not 25)
27. 12 and (1 or 26)

December 29, 2003

Director, Research & Development
Pfizer Global Research & Development
Canada Head Office
4747 Levy Street, Building B114
St-Laurent, Quebec
H4R 2P9

RE: ***Letter to Industry Representatives from the University of Ottawa Evidence-based Practice Center Investigating Sexuality and Reproductive Health Following Spinal Cord Injury***

Dear Sir or Madam:

I am writing on behalf of the University of Ottawa's Evidence-based Practice Center. We are conducting two systematic reviews concerning sexuality and reproductive health following spinal cord injury. They are as follows:

1. What is the current fertility rate for men and women after SCI?
2. How has the availability of Viagra and other remediation affected sexual function, frequency of activity, and adjustment after SCI?

These reviews are being conducted under a contract from the Agency for Healthcare Research and Quality (AHRQ). We are contacting you to see if there is any evidence, including unpublished studies, abstracts and other documentation, that you want considered for inclusion in the reviews.

For the **fertility rate** systematic review we will consider the following studies for possible inclusion:

- All **randomized or quasi-randomized** (i.e., trials in which the treatment allocation method was intended to be random but might have been biased, for example, allocation by day of the week), **studies or series** of any treatment intervention for fertility after spinal cord injury.

For the **remediation** systematic review we will consider the following types of studies for possible inclusion:

- All **randomized or quasi-randomized** (i.e., trials in which the treatment allocation method was intended to be random but might have been biased, for example, allocation by day of the week), **trials or series** of any treatment intervention for sexual dysfunction after spinal cord injury.

Our focus is on human studies reported in English and limited to conventional interventions, so animal, chemical, or complementary and alternative medicine intervention studies are not necessary.

The specific questions that the systematic review will address are detailed in the attachment. As well, we understand that we will require permission to cite any information provided to us and introduced into the public domain.

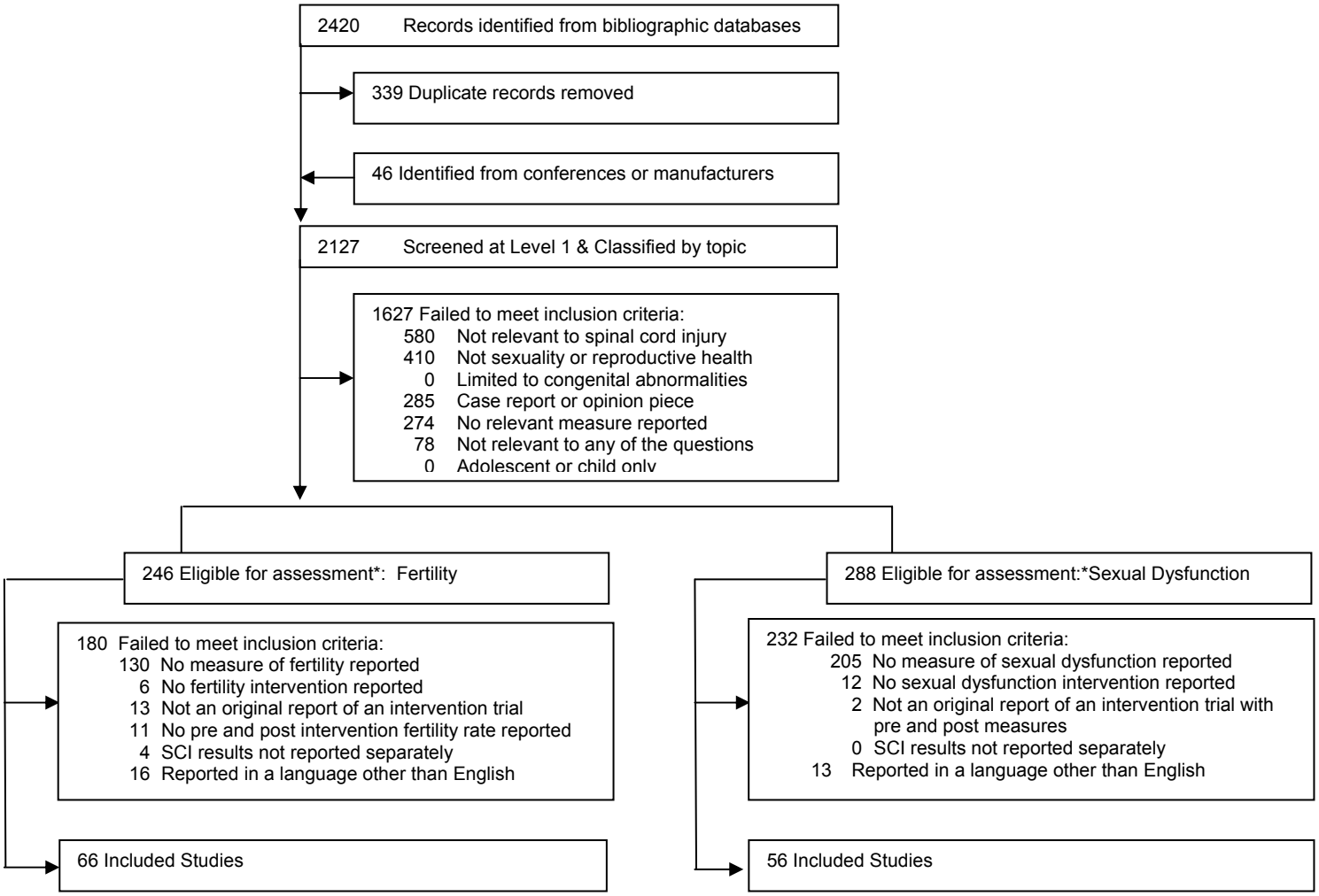
We look forward to receiving any information that you might have.

Best regards,

Dan Deforge, MD
Physiatrist-in-Chief, TRC
Chief, Division of PM&R
The Rehabilitation Centre
505 Smyth Road, Rm. 1104
Ottawa, Ontario, CANADA
K1H 8M2
Phone: +1 (613) 737-7350 x 5524
Email: ddeforge@ottawahospital.on.ca

c.c. David Moher,
Co-Director, University of Ottawa Evidence-based Practice Center
Director, Chalmers Research Group, Children's Hospital of Eastern Ontario Research Institute.

Modified QUOROM Flow Chart



*Note: some items were eligible for both reviews, therefore, the sum does not add up to the number of included studies.

Relevance Assessment Forms

Sexual Dysfunction Eligibility Criteria

Measures of sexual dysfunction under consideration:
A. Psychologic: Validated sexual function questionnaire for males and/or females, structured interviews with qualitative analysis, educational component, global efficiency, or patient logs.
B. Physiologic: Penile and/or clitoral engorgement, endocrine, ultrasound testing of testicular size.

1. Does the article contain an original report of a measure of sexual dysfunction? (see list above)
Yes
No
Can't Tell

Interventions under consideration for sexual dysfunction:
A. Cognitive/behavioral: Masturbation, intercourse
B. Device: Penile rings, vibrators, vacuum devices
C. Prescription medications: Intracavernous injections, oral, subcutaneous injections, intrameatal MUSE, creams
D. Surgical intervention; Penile implants, spinal cord stimulators or E. Hormonal interventions.

2. Does the article discuss an intervention for sexual dysfunction? (see list above)
Yes
No
Can't Tell

3. Does the article report an original intervention trial or series with a pre and post measure for sexual dysfunction after spinal cord injury?
Yes
No
Can't Tell

Fertility Eligibility Criteria

Measures of fertility rates under consideration:
Pregnancies, live birth rates, sperm motility, successful sperm harvesting, ejaculations, sperm count, % viable sperm, hormonal, ovulation rates, cycle function, other measures of sperm morphology, volume of ejaculation.

1. Does the article contain an original report of a measure of fertility rates in males, females or both?
Yes
No
Can't Tell

Fertility interventions under consideration:
1. Physical: masturbation, intercourse, or
2. Device: vibration, electrode ejaculation, home insemination or
3. Prescription medications: sympathetic agonists, physostigmine, etc.,
4. Surgical intervention; vas aspiration, testicular biopsy, ICSI, artificial insemination, spinal cord stimulators, or
5. Laboratory techniques.

2. Does the article discuss a fertility intervention?
Yes
No
Can't Tell

3. Does the article report an original intervention trial after spinal cord injury?
Yes
No
Can't Tell

4. Does the article include pre and post intervention fertility rates?
Yes
No
Can't Tell

5. Were results for SCI reported separately?
Yes
No

6. Is this a non-English language article?
Yes
No

Data Abstraction Forms

Sexual Dysfunction

1. Initials of reviewer:
2. Reference identification # (Refid):
3. Author, Year:
4. Number of review-relevant studies that this report describes
5. Publication status (select one):
6. If you answered 'Other' to the preceding question, specify:
7. If other included reports refer to this same study, provide the Refid(s)
8. Country in which the study was conducted (select all that apply):)
9. If you answered 'Other' to the preceding question, specify: Number of sites: (text)
10. Funding source type (select all that apply):
11. Specify the funding source(s):
12. Study design (select one): Other (Please specify)
13. If you answered 'Other' to the preceding question, specify:
14. Total # of individuals screened:
15. Full sample size (enrolled in study):
16. Full sample size (completing study):
17. Full sample's percentage of male participants:
18. Comments, including notable differences between study arms / cohorts re '% male participants':
19. Mean age (SD/SE; range) of all study participants:
20. Comments, including notable differences between study arms/cohorts re age:
21. Sample's percentage of married participants:
22. Comments, including notable differences between study arms/ cohorts re % of married participants:
23. From which racial groups were participant's drawn (select all that apply)?)
24. Specify each racial group's percentage/proportion of full sample:
25. Comments, including notable differences between study arms/cohorts re racial composition:
26. Specify each socioeconomic status group's percentage/proportion of full sample: Comments, including notable differences between study arms/cohorts re socioeconomic status:
27. Specify number of previous pregnancies:
28. Specify patient prescription drug history specific to SCI versus other:
29. Specify partner prescription drug history specific to SCI versus other:
30. Specify previous sexual dysfunction of patient:
31. Specify previous sexual dysfunction of partner:
32. Specify previous sexual dysfunction treatment of patient (Note: treatment type, duration, dose etc.):
33. Specify previous sexual dysfunction treatment of partner (Note: treatment type, duration, dose etc.):
34. Specify patient history of STD:

35. Specify partner history of STD:
36. Specify patient psychiatric/psychological history (e.g., depression):
37. Specify partner psychiatric/psychological history (e.g., depression):
38. Specify pre-existing cognitive impairments:
39. Specify previous patient drug and/or alcohol abuse:
40. Specify previous partner drug and/or alcohol abuse:
41. Specify patient general medical history including prior diseases, and/or conditions
    Specify partner general medical history including prior diseases, and/or conditions:
    Specify other causes of sexual dysfunction:
42. Concurrent conditions (list all that apply): (text)
43. Specify the type and severity (mean; SD/SE; range: with units) of each concurrent condition, as well as how it was defined and diagnosed:
44. Specify the percentage/proportion of the whole sample re each type of each concurrent condition:
45. Comments, including notable differences between study arms/cohorts re concurrent conditions:
46. Specify pre-study medications or treatments for each concurrent condition, with dose/frequency:
47. Comments, including notable differences between study arms / cohorts re pre-study medication(s) or treatments, including dose/frequency:
48. Specify cause of spinal cord injury:
49. Specify the level of spinal cord injury:
50. Specify ASIA Level:
51. Specify duration since spinal cord injury:
52. Please list general comments, including notable differences between arms/cohorts re participants' baseline control of condition? (e.g., do any red flags stand out between the groups?):
53. List of study's inclusion criteria:
54. List of study's exclusion criteria:
55. Intention of study (select all that apply)
56. Type of study (select one):
57. Data were analyzed according to which criterion (select one)?
58. Study duration, including units (includes run-in period protocol/duration, washout protocol/duration, etc.):
59. Specify product name used for pharmacologic, device and/or other intervention(s):
    Specify name of manufacturer of pharmacologic, device or other intervention product:
    Medications allowed or mandated during the study (dose/ frequency):
60. Comments, including notable differences between study arms/ cohorts re participants' medication:
61. Concurrent therapies (e.g., physiotherapy; occupational therapy; chiropractic; counseling etc.) allowed or mandated during the study (intensity; frequency; duration):
62. Comments, including notable differences between study arms/ cohorts re participants' concurrent therapies:
63. Permitted or required medications or treatments for concurrent conditions (specify dose/ frequency, and for which concurrent condition):
64. Outcomes assessed (e.g. efficacy, incidence, prevalence, etc):

65. Number of study arm/ cohorts (note: in a cross-over trial, each different phase is considered an exposure / intervention arm):
66. Define the study arms or cohorts of interest to the present review: (text Study arm number:
67. Sample size at study entry: (text)
68. Sample size of those who completed the study:
69. Intervention length (weeks, months):
70. Arm Type/Group Type (placebo, active, control):
71. Intervention/ exposure type (e.g. drug or placebo):
72. Dose / frequency:
73. Timing (AM, PM):
74. Study arm number (Click here if there is no more arm/cohort):
75. Sample size at study entry:
76. Sample size of those who completed the study:
77. Intervention length (weeks, months):
78. Arm type (placebo, active, control):
79. Intervention/ exposure type (e.g. drug or placebo):
80. Dose / frequency:
81. Timing (AM, PM):
82. Study arm number (Click here if there is no more arm/cohort):
83. Sample size at study entry:
84. Sample size of those who completed the study:
85. Intervention length (weeks, months):
86. Arm type (placebo, active, control):
87. Intervention/ exposure type (e.g. drug or placebo):
88. Dose / frequency:
89. Timing (AM, PM):
90. Study arm number:
91. Sample size at study entry:
92. Sample size of those who completed the study:
93. Intervention length (weeks, months):
94. Arm type (placebo, active, control):
95. Intervention/ exposure type (e.g. drug or placebo): Sexual Dysfunction: Quality Assessment
96. Dose / frequency:
97. Timing (AM, PM):
98. Anatomic/Physiologic (e.g., clitoral engorgement; errection; penile tumes. girth; EMG; vaginal lubrication):
99. Sexual satisfaction:
100. Psychological (e.g., sexual functioning questionnaires; depression scale & scores): Infection rates:
101. Divorce:
102. Additional Outcomes Not Covered Above - Other(s):
103. Specify Follow-up(s) (length; duration & results):
104. Adverse events/ side effects reported in the present study (including local (e.g., infection); systemic (e.g., hypotension, death, etc.);

105. Other (e.g., psychological etc.) per study arm/cohort:
106. General Study Comments (Identify any problems with the research design (e.g., definition of placebo/control(s); inappropriateness of run-in and washout periods), or its implementation):

Fertility

1. Initials of reviewer:
2. Reference identification # (Refid):
3. Author, Year:
4. Number of review-relevant studies that this report describes:
5. Publication status (select one):
6. If you answered 'Other' to the preceding question, specify:
7. If other included reports refer to this same study, provide the Refid(s):
8. Country in which the study was conducted (select all that apply): (check)
9. If you answered 'Other' to the preceding question, specify: (text)
10. Number of sites: (text)
11. Funding source type (select all that apply): (check
12. Specify the funding source(s): (text)
13. Study design (select one):
14. Other (Please specify)
15. If you answered 'Other' to the preceding question, specify: (text)
16. Total # of individuals screened: (text)
17. Full sample size (enrolled in study): (text)
18. Full sample size (completing study): (text)
19. Full sample's percentage of male participants: (text)
20. Comments, including notable differences between study arms / cohorts re '% male participants': (text)
21. Mean age (SD/SE; range) of all study participants: (text)
22. Comments, including notable differences between study arms/cohorts re age: (text)
23. Sample's percentage of married participants: (text)
24. Comments, including notable differences between study arms/ cohorts re % of married participants: (text)
25. From which racial groups were participants drawn (select all that apply)? (check)
    Specify each racial group's percentage/proportion of full sample: (text)
26. Comments, including notable differences between study arms/cohorts re racial composition:
27. Specify each socioeconomic status group's percentage/proportion of full sample: (text)
28. Comments, including notable differences between study arms/cohorts re socioeconomic status: (text)
29. Specify previous gynaecological/obstetric history of patient: (text)
30. Specify previous gynaecological/obstetric history of partner: (text)
31. Specify previous birth control use: (text)
32. Specify number of previous pregnancies: (text)
33. Specify complications of previous pregnancies: (text)
34. Specify previous abortions and list reasons if provided: (text)
35. Specify patient prescription drug history specific to SCI versus other: (text)
36. Specify partner prescription drug history specific to SCI versus other: (text)
37. Specify previous fertility treatment of patient (Note: note treatment type, duration, dose etc.): (text)

38. Specify previous fertility treatment of partner (Note: note treatment type, duration, dose etc.): (text)
39. Specify patient history of STD: (text)
40. Specify partner history of STD: (text)
41. Specify patient psychiatric/psychological history (e.g., depression): (text)
42. Specify partner psychiatric/psychological history (e.g., depression): (text)
43. Specify pre-existing cognitive impairments: (text)
44. Specify previous patient drug and/or alcohol abuse: (text)
45. Specify previous partner drug and/or alcohol abuse: (text)
46. Specify patient general medical history including prior diseases, and/or conditions: (text)
47. Specify partner general medical history including prior diseases, and/or conditions: (text)
48. Specify other causes of infertility: (text)
49. Concurrent conditions (list all that apply): (text)
50. Specify the type and severity (mean; SD/SE; range: with units) of each concurrent condition, as well as how it was defined and diagnosed: (text)
51. Specify the percentage/proportion of the whole sample re each type of each concurrent condition: (text)
52. Comments, including notable differences between study arms/cohorts re concurrent conditions: (text)
53. Specify pre-study medications or treatments for each concurrent condition, with dose/frequency: (text)
54. Comments, including notable differences between study arms / cohorts re pre-study medication(s) or treatments, including dose/frequency: (text)
55. Specify cause of spinal cord injury: (text)
56. Specify the level of spinal cord injury: (text)
57. Specify ASIA Level: (text)
58. Specify duration since spinal cord injury: (text)
59. Please list general comments, including notable differences between arms/cohorts re participants' baseline control of condition? (e.g., do any red flags stand out between the groups?): (text)
60. List of study's inclusion criteria: (text)
61. List of study's exclusion criteria: (text)
62. Intention of study (select all that apply) (check)
63. Type of study (select one): (mult)
64. Data were analyzed according to which criterion (select one)? (mult)
65. If you answered 'Other' to the preceding question, specify:
66. Study duration, including units (includes run-in period protocol/duration, washout protocol/duration, etc.): (text)
67. Specify product name used for pharmacologic, device and/or other intervention(s): (text) Specify name of manufacturer of pharmacologic, device or other intervention product: (text)
68. Medications allowed or mandated during the study (dose/ frequency): (text)
69. Comments, including notable differences between study arms/ cohorts re participants' medication: (text)
70. Concurrent therapies (e.g., physiotherapy; occupational therapy; chiropractic; counseling etc.) allowed or mandated during the study (intensity; frequency; duration): (text)

71. Comments, including notable differences between study arms/ cohorts re participants' concurrent therapies: (text)
72. Permitted or required medications or treatments for concurrent conditions (specify dose/ frequency, and for which concurrent condition): (text)
73. Outcomes assessed (e.g. efficacy, incidence, prevalence, etc): (text)
74. Timing of outcome assessments and when, relative to start of intervention (e.g. at week 4): (text)
75. Number of study arm/ cohorts (note: in a cross-over trial, each different phase is considered an exposure / intervention arm): (text)
76. Define the study arms or cohorts of interest to the present review: (text)
77. Study arm number: (text)
78. Sample size at study entry: (text)
79. Sample size of those who completed the study: (text)
80. Intervention length (weeks, months): (text)
81. Arm type (placebo, active, control): (text)
82. Intervention/ exposure type (e.g. drug or placebo): (text)
83. Dose / frequency: (text)
84. Timing (AM, PM): (text)
85. Study arm number (Click here if there is no more arm/cohort): (text)
86. Sample size at study entry: (text)
87. Sample size of those who completed the study: (text)
88. Intervention length (weeks, months): (text)
89. Arm type (placebo, active, control): (text)
90. Intervention/ exposure type (e.g. drug or placebo): (text)
91. Dose / frequency: (text
92. Timing (AM, PM): (text)
93. Study arm number (Click here if there is no more arm/cohort): (text)
94. Sample size at study entry: (text)
95. Sample size of those who completed the study: (text)
96. Intervention length (weeks, months): (text)
97. Arm type (placebo, active, control): (text)
98. Intervention/ exposure type (e.g. drug or placebo): (text)
99. Dose / frequency: (text)
100. Timing (AM, PM): (text)
101. Study arm number (Click here if there is no more arm/cohort): (text)
102. Sample size at study entry: (text)
103. Sample size of those who completed the study: (text)
104. Intervention length (weeks, months): (text)
105. Arm type (placebo, active, control): (text)
106. Intervention/ exposure type (e.g. drug or placebo): (text)
107. Dose / frequency: (text)
108. Timing (AM, PM): (text)
109. Seminal parameters (e.g., specify ejaculation volume; sperm concentration; sperm motility; morphology): (text)
110. Ejaculation rates (frequency): (text)
111. Cycle function: (text)

112. Ovulation rates (e.g., specify total # of ovulatory cycles of the female partner; state the # of cycles with fertilization; state the # of pregnancy rates per treatment cycle): (text)
113. Pregnancy rates (specify # reported): (
114. Miscarriage/ectopic pregnancy rates (genetic or other): (text)
115. Induced Abortion(s) (genetic or other): (text)
116. Live births (e.g., # of births and if singletons, twins or higher order): (text)
117. Psychological (e.g., sexual functioning questionnaires; depression scale & scores): (text)
118. Genetic abnormalities: (text)
119. Infection rates: (text)
120. Divorce: (text)
121. Additional Outcomes Not Covered Above:
122. Other(s): (text)
123. Specify Follow-up(s) (length; duration & results): (text)
124. Adverse events/ side effects reported in the present study (including local (e.g., infection); systemic (e.g., hypotension, death, etc.);
125. Other (e.g., psychological etc.) per study arm/cohort: (text)
126. General Study Comments (Identify any problems with the research design (e.g., definition of placebo/control(s); inappropriateness of run-in and washout periods), or its implementation): (text)

Quality Assessment Forms—RCTs

Jadad Scale

Descriptor			Yes	No
Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?				
The method used to generate the sequence of randomization was described and it was **appropriate** (table of random numbers, computer generated, etc)				
Was the report of allocation concealment:	Adequate ☐	Inadequate ☐	Unclear ☐	
Was the study described as double blind?				
The method of double blinding was described and it was **appropriate** (identical placebo, active placebo, dummy, etc)?				
Was there a description of withdrawals and dropouts?				

Allocation Concealment

Refers to the technique used to implement the randomization sequence, not to generate it.

Adequate

- Sequentially numbered, opaque, sealed envelopes (SNOSE)
- Pharmacy controlled
- Numbered or ordered containers
- Central randomization – for example by telephone to a trials office or other method whose description contained elements convincing of concealment – for example a secure computer assisted method.

Inadequate

- Alternation
- Reference to case record numbers or to dates of birth

Unclear

- No mention of an allocation concealment approach at all
- An approach that does not fall into either adequate or inadequate allocation concealment

Quality Assessment Forms—Case-Control and Cohort Studies

Newcastle-Ottawa Scale (NOS)

Descriptor	Yes	No	Can't tell
Was the therapeutic intervention reported?			
Were the inclusion/exclusion criteria reported?			
Was follow-up reported as an inclusion criterion?			
Was the sample size determination reported (cases accrued consecutively or non consecutively over a specified time period)?			
Were the sample size calculations (and any assumptions) reported?			
Was the time period for accrual of cases and whether they were accumulated prospectively or retrospectively reported?			
Were the sources of participants (same or different clinicians, one or more center) reported?			
Were how the outcome assessments made and who made them reported?			
Was blinding reported?			
Were the primary and secondary measures reported?			
Was the timing of the outcome measures reported?			
Was a follow-up schedule reported?			
Were efforts used to maintain follow-up with participants reported?			
Did the authors report on compliance with follow-up?			
Was the method of data collection reported?			
Were any participant exclusions from data analysis reported?			
Was the statistical approach for analyzing the data reported?			
Did the authors report any missing data and how it was handled in the data analysis?			
Did the authors report any adverse events?			

Quality Assessment Forms—Noncomparative Case-Series Studies

Quality assessment	yes	partial	no	n/a
1. Question / objective sufficiently described?				
2. Design evident and appropriate to answer study question?				
3. Subject characteristics sufficiently described?				
4. Subjects appropriate to the study question?				
5. Controls used and appropriate? **(if no control, check no)**				
6. Method of subject selection described and appropriate?				
7. If random allocation to treatment groups was possible, is it described? (if not possible, check n/a)				
8. If blinding of investigators to intervention was possible, is it reported? (If not possible, n/a)				
9. If blinding of subjects to intervention was possible, is it reported? (If not possible, n/a)[1]				
10. Outcome measure well defined and robust to measurement bias? Means of assessment reported?				
11. Confounding accounted for?				
12. Sample size adequate?				
13. Post hoc power calculations or confidence intervals reported for statistically non significant results?				
14. Statistical analyses appropriate?				
15. Statistical tests stated?				
16. Exact p-values or confidence intervals stated?				
17. Attrition of subjects and reason for attrition recorded?				
18. Results reported in sufficient detail?				
19. Do the results support the conclusions?				
Sum (items 1-19)				

Quality Assessment Forms—Abstracts

Abstract (conference proceeding) quality assessment
Study design
Human
interventional:

- parallel controlled trial ☐
- Randomization reported? ☐
- cross over trial ☐
- time series trial (before-after) ☐
- non-concurrent / historic controls ☐
- natural experiment ☐

observational:

- cohort, prospective ☐
- cohort, retrospective ☐
- cross-sectional ☐
- case-control ☐

descript., case report/series ☐

Appendix E. Evidence Tables

Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/ Quality Assessment	Intervention (e.g.,Pharmacological/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Bensman 1966, US (Ref ID 1627)	• Enrolled/ evaluated: N=5/N=5 • % males: 100% • Race/ethnicity: NR • Age: 24.2 (21-32) y • Level of Injury: C4-L2 • ASIA Level: NR • Duration since injury: (0.5-13) y • Previous fertility: NR • Drop-outs: n=0 • Lost in follow-up: n=0 • Number of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 4/19 (+) reported	• **Pharmacologic:** NR • **Device: Electrostimulator**(n=5) • Amplitude: sin current of 20-30 mA • Frequency: 2-10 cycle/m • Mode/Admin. Route: rectal probe; duration of ES maintained for 5-10 m • **Other Device:** NR • **Surgical:** NR • **Procedure:** NR • Bladder catheterization • -with/without alkalinization: not performed, urine acidic in all cases post ES • Epididymal aspiration (MESA/PESA): NR • Testicular biopsy: NR • **Behavioural:** NR • **Laboratory techniques:** NR	• **Outcomes:** • Seminal Parameters: sperm obtained in 3/5 pts; 1st pt SpC 410K sperm/ cm4 and 20-30% of sperm abnormal forms; 2nd pt SpC 1.3 mln sperm/ cm4, all non-motile; 3rd pt 14K sperm/cm4 obtained • EJ Rates: 0/5 AG; 3/5 RG • **Follow-up:** NR	• **A/E:** • Local: discomfort around area of electrode; sensation of voiding (n=3); bladder contraction (n=5) • Systemic: headache, rise in BP in 4/5

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde; BP = blood pressure

Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (continued)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/ Quality Assessment	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Beretta, 1989, Italy (Ref ID 695)	• Enrolled/evaluated : n=102/n=102 • % males: 100% • Race/ethnicity: NR • Age: 25.6 (NR) y • Level of Injury: (n=17) Cervical 7 complete, 10 Incomplete; (n=41) T1-T10 (22 complete, 19 Incomplete); (n=21) T11-L1; (n=15) L2-L5 3 complete, 12 Incomplete; (n=8) Sacral, 3 complete, 5 incomplete • ASIA Level: NR • Duration since injury: 6.1 y • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** 3 mo • **Eligibility Criteria:** • Inclusion: No secondary neurological sequelae, empty & not irritated rectum & bladder; (-) urine cultures; T12, L1 & L2 myelomeres must be intact • Exclusion: NR • **Quality Assessment:** 11/19 (+) reported	• **Pharmacologic:** NR • **Device: vibrator Le Vibrion** • Amplitude: NR • Frequency: 100 VS/ sec • Mode/Admin. Route: applied to penile surface for 10 m, some pts used vibrator at home • **Surgical:** (n=6) couples: • Penile Implants • **Procedural:** NR • **Behavioural:** NR • **Laboratory techniques** (n=6): AHI • If sperm quality good, female partners underwent fertility investigations, prolactin & progesterone assays in 2nd phase of menstrual cycle & cervical score determination. Homologous intracervical insemination performed during ovulation. • Intrauterine insemination: NR • IVF: NR • Intracytoplasmic sperm injection: NR • Embryo cryopreservation: NR • Sperm cryopreservation: NR - ejaculated -biopsy	• Outcomes: • Measures of Fertility Rates: • Seminal Parameters: S increase in sperm concentration over 3 mo ($p< 0.05$) with no correlation to increase in vol. S decrease in abnormal sperm (% of motility and morphology $P<0.01$), S increase in sperm concentration ($p<0.05$), no increase in volume. S increase in motility ($p<0.01$) • EJ Rates: Total EJs =78, AG = 68, RG = 20 • Pregnancy rates: (n=3) • Follow-up: (n=15) • Length: weekly follow-ups • Duration: NR • Results: abnormal spermatozoa steeple decreased over 3 m	• **A/E:** • Local: NR • Systemic: 2 reports of headache, 2 reports of increased BP

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde; AIH = artificial insemination from husband; BP = blood pressure

Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/ Quality Assessment	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Beretta, 1987, Italy (Ref ID 984)	• Enrolled/ evaluated: n=142/n=142 • % males: 100% • Race/ethnicity: NR • Age: 26.1 (NR) y • Level of Injury: n=79 > T11; n=48 thoraco-lumbar; n=15 sacral; n=59 complete & 83 incomplete • ASIA Level: NR • Duration since injury: mean 5.9 y • Previous fertility: NR • Drop-outs: NR • Lost to follow-up: NR • Number of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration**: NR • **Eligibility Criteria:** • Inclusion: no secondary neurology sequelae; empty & non-irritated rectum & bladder; negative urine cultures; no lesions of D12, L1, L2 • Exclusion: NR • **Quality Assessment:** 5/19 (+) reported	• **Pharmacologic:** NR • **Device:** Vibrator (n=142) • Amplitude: 30 Watts; 220 V • Frequency: 100Hz • Mode/Admin. Route: VS applied to penile surface for 10 m, wkly for 3 m • **Other Device**: NR • **Surgical:** NR • **Procedure:** NR • **Behavioural:** NR • **Laboratory techniques (n=21):** • Donor sperm insemination: NR • Sperm preparation: NR • Intrauterine insemination: NR • IVF: in 3/4 which resulted in pregnancy/ 1/4 used auto-insemination • Intracytoplasmic sperm injection: NR • Embryo cryopreservation: NR • Sperm cryopreservation: NR	• **Outcomes:** • EJ Rates: 99/142(69.7%) • Pregnancy rates: 4/21(19%) • **Follow-up:** (n=2) • Length: NR • Duration: 3 m • Results: before /after tx (wkly VS) study of seminal parameters in 2 pts: S increase in sperm concentration($p<0.05$); no Δ in semen volume; S decrease in abnormal spermatozoa ($p<0.05$); S (+) increase in motility & morphologic features over 3 m ($p<0.01$)	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde

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Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/ Quality Assessment	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Brackett, 1995, US (Ref ID 572)	• Enrolled/ evaluated: 23 SCI couples; 2 other couples 1 MS, 1 transverse myilitis/ n=23 couples • % males: 50% of couples • Race/ethnicity: NR • Age: SCI men 35.2±1.1; 26-42 y; female pts, 24-42 y, • Level of Injury: cervical in 7; thoracic in 12; lumbar in 2 • ASIA Level: NR • Duration since injury: 13.1 (5-28) y • Previous fertility: NR • Drop-outs: n=0 • Lost to follow-up: n=0 • Number of sites: 1 • Funding: Partially supported by NLB from the Miami Project to Cure Paralysis	• **Study Design:** NCS • **Duration:** May 1991-Sep 1994, retrospective study • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 10/19 (+) reported	• **Pharmacologic:** NR • **Device:** Oster Model 129-01A (n = 4) • Amplitude: NR • Frequency: NR • Mode/Admin. Route: mean time of stimulating frenulum until EJ, 2.5±0.7 m • **Other Device (n = 19):** Electrostimulator/ • Amplitude/voltage: 1 to max of 8V • Mode/Admin: anesthesia/ general anesthesia in 5 (4/5 SCI pts) • **Surgical:** NR • **Procedure** (n=23): • Bladder catheterization • -with/without alkalinization: sodium bicarbonate (20 g /6 hrs for 72 hrs) pre VS /ES • Epidydimal aspiration (MESA/PESA): NR • Testicular biopsy: NR • **Behavioural:** NR • **Laboratory techniques** (in 23 SCI couples): • Donor sperm insemination: NR • Sperm preparation: by all techniques in n=22- swim-up • Intrauterine insemination: 60 cycles of IUI in 22 couples with clomiplene Citrate (50-100 mg/d, orally for 5 ds)/ gondotropins (hMZG &/or FSH, 75-225IU/d, i.m.) • IVF/GIFT: IVF-ET in n=6 with embryo transfer @ 48 hr post retrieval; GIFT in n=4 with laparascopic gamete transfer • Intracytoplasmic sperm injection: NR • Embryo cryopreservation: NR	• **Outcomes:** • Measures of Fertility Rates: 13/22 conceptions • Seminal Parameters: normal sperm concentration (136± 32 mln/cc) but poor SpMot (12.6± 1.1%); SpMor within normal levels (50.2± 6.9%); all measures lower in RG vs. AG; NS dfs in sperm parameters of SCI vs. 2 other pts • Cycle Function: 21/23 females had 52 clomiphene citrate tx, 4 of them had 8 cycles of ovulation induction using hMG and /or FSH. • Pregnancy rates: 71% in IVF; 27% in IUI; total 11/22 • Miscarriage/ectopic: 1 case, medically treated • Induced abortion: 2 spontaneous abortions in pt with 3 pregnancies • Live Births: 8/23 • Singletons: 8/23 • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; MS = multiple sclerosis; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; ∆ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde; IUI = intra-uterine insemination

Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/ Quality Assessment	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Brackett, 1997, US (Ref ID 308)	• Enrolled/ evaluated: n=77/ n=77 • % males: 100% • Race/ethnicity: NR • Age: NR • Level of Injury: 45% cervical; 51% thoracic; 4% lumbar; 39% quadriplegic (all incomplete0; 61% paraplegic (43% complete) • ASIA Level: NR • Duration since injury: NR • Previous fertility: NR • Drop-outs: NR • Lost to follow-up: NR • Number of sites: 1 • Funding: grant from Miami Project to Cure Paralysis & State of Florida Specific Appropriation No. 224 for Spinal Cord Research	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 8/19 (+) reported	• **Pharmacologic:** NR • **Device:** Sunbeam Model 1850-1 Vibrator • Amplitude: NR • Frequency: NR • Mode/Admin. Route: 5 m VS & 1 m rest then resumed for 5 m; 1-3 trials of VS/ pt then assigned to 1/3 grps: VS only, ES only or VS+ES • **Other Device:** Electrical stimulator • Type: Seager Model 14 • Mode/Admin. Route: NR • **Surgical:** NR • **Procedure:** • Bladder catheterization • -with/without alkalinization: 41% intermittent catheterization, 36% external catheter, 14% voluntary voiding, & 8% suprapubic & 1% Foley catheter • Epididymal aspiration (MESA/PESA): NR • Testicular biopsy: NR • **Behavioural:** NR • **Laboratory techniques:** NR	• **Outcomes:** • Seminal Parameters: no Δ in SpC of vs. ES (155.0± 41.9 mln vs. 191.3± 50.0mln); in AG, S greater SpC with vs. ES (141.7± 24.4 mln vs. 89.9 ± 11.6 mln); in RG mean SpC greater in ES vs. VS (95.4± 9.1 vs. 38.1±6.3); mean percent motile sperm greater in vs. ES (18.5±2.5 vs. 10.1± 1.5%); mean % of sperm with rapid linear motion in VS S > vs. in ES in total ejaculate (12.8±2.1 vs. 5.7± 1.0%) & RG fraction (13.6± 1.3 vs. 6.2± 0.7%); within pt comparisons of vs. ES revealed NS Δ in total SpC in total EJ or AG or RG fractions between specimens obtained with 2 methods • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde

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Brackett 2000, US (Ref ID 950)	• Enrolled/ evaluated: n=26; n=12 SCI, n=14 ctrl/n=26 • % males: 100% • Race/ethnicity: NR • Age: SCI 37 (NR) y; ctrl 34.9 (20-40) y • Level of Injury: C4-L1 (n=9) data missing in (n=3) SCI • ASIA Level: NR • Duration since injury: 14.6 (5-23) y • Previous fertility: NR • Dropouts: n=5 • Lost in follow-up: n=20 • N of sites: 1 • Funding: NIH: Grant State of Florida Specific Appropriations & the Miami Project to Cure Paralysis	• **Study Design:** NCS • **Duration:** 3 mo • **Eligibility Criteria:** • Inclusion: No secondary neurological sequel, empty & not irritated rectum & bladder, negative urine culture, T12 & L1 & L2 myelomeres must be intact • Exclusion: NR • **Quality Assessment:** 7* (NOS)	• **Pharmacologic (n = x):** NR • **Device: (Vibrator Le Vibrion)** (n = 8) • Amplitude: NR • Frequency: NR • Mode/Admin. Route: NR • **Other Device** (n = 8): • Type Electroejaculator • Manufacturer: NR • **Surgical**: NR • **Procedure**: NR • **Behavioural** (n = 14): • masturbation in ctrl grp to obtain specimen • **Laboratory techniques**: (n = 26): • Donor sperm insemination: NR • Sperm preparation (vas deferens aspiration): Sperm removed by aspiration of vas deferens of normal ctrls (12/14) during standard vasectomy during local anesthesia. Epididymis milked & vas divided vas then lavaged & aspirated with 0.1 to 0.2 ml of sterile sperm buffering solution in 5 mg/ml Vas aspiration in SCI pts (9/12) obtained after anesthesia & hemisectioned mirosurgically. Cannulation, lavage & aspiration performed as in ctrls. Vas aspiration specimen then compared with AG EJ obtained from both grps.	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: % of motile & viable sperm in vas aspirated (VAS) vs. ejaculated specimen (EJ): S df between VAS of SCI < ctrls ($p < 0.001$), S between EJ of SCI < ctrls ($p < 0.0001$), S df between VAS > EJ in SCI ($p < 0.0001$), NS df between VAS & EJ of ctrls • Sperm viability: S df between VAS of SCI < VAS of ctrl ($p<0.02$), S df between EJ of SCI < EJ of ctrl ($p < 0.0001$), S between VAS > EJ in SCI ($p <0.0001$). • **Follow up:** EJ in (n=6) SCI 2-6 mo after vas aspiration revealed sperm parameters similar to ejaculates before aspiration.	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde; NIH = National Institute of Health

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Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/ Quality Assessment	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Brindley, 1981, UK (Ref ID 1830)	• Enrolled/ evaluated: n=37/ n=37 • % males: 100% • Race/ethnicity: NR • Age: NR • Level of Injury: lesions below, at or above L2. • ASIA Level: NR • Duration since injury: NR • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 2/19 (+) reported	• **Pharmacologic** (n=x): NR • **Device:** Electrostimulator (n =37) • Amplitude: NR • Frequency: Sinusoidal current of 15-35 Hz, or rectangular pulse for duration of 100 microseconds, resistant of 40 Ω on, 72-99 V for up to 30 sec. • Admin. Site: Obturator nerve • **Other Device:** NR • **Surgical:** NR • **Procedure:** NR • **Behavioural:** NR • **Laboratory techniques:** NR	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: Some motile spermatozoa seen in semen of 14/15 AG, & in urine of 2/9 RG. Motile spermatozoa range from 0-2.5 per mlns in (n=10), 2.5-5 in (n=2), 5-10 in (n=3), 10-20 in (n=5), 20-40 in (n=4), 40-80 in (n=5), & 80-100 in (n=2). Semen resulting in pregnancy in one 30 y old complete T6 contained 200 mlns spermatozoa per ml with 1% motility. • EJ Rates: AG EJ=12 on 1st attempt, 2 on 2nd & 1 on 3rd; RG EJ = 7 on 1st attempt & 2 on 2nd. No sperm in (n=7), 3 of them failed to produce urine specimen; in 4 of these semen contained no spermatozoa. • **Follow-up:** NR	• **A/E:** Pain preventing sufficient stimulation to produce EJ n=6

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde

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Brindley, 1981, UK (Ref ID 801)	• Enrolled/ evaluated: n=178: n=175 SCI; n=5 other/ n=NR • % males: 100% • Race/ethnicity: NR • Age: NR • Level of Injury: n=22 C6-T1; n=50 T2-T12; n=12 L1 or below; (n=17 incomplete, n=14 flaccid, n=53 complete) • ASIA Level: NR • Duration since injury: NR • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 5/19 (+) reported	• **Pharmacologic (n = x):** NR • **Device:** Electrostimulator (n=89) • **Amplitude:** Peak voltage up to 108v • **Frequency**: frequency of pulse 30, 15, 10 per sec, time between pulses 10ms • **Mode/Admin. Route:** NR • **Other Device:** NR • **Surgical:** NR • **Procedure:** NR • **Behavioural:** NR • **Laboratory techniques:** NR	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: • EJ Rates: In SCI pts external success in EEJ (n=36); RG success (n=14); Definite failure: (n=32) • In 7 pts electro stimulation intolerably painful. • Correlates of failure: In 9 of 20 definite failures EEJ seemed to have its proper effect on prostate, seminal vesicles, & vasa deferntia, but pts azoospermic from disease or injury of upper genital tract. • **Follow-up:** NR	• **A/E:** • Local: Contractions of striated muscles i.e. contraction of abdominal muscles in 6/146 AG EEJ without general anesthesia, & in 1/47 unsuccessful & in 1/44 RG EEJ. Bilateral contraction of adductors in 4 pts. After-effects on spasm: some have reported less spasm after EEJ. Mictuition: mixture of urine & semen in 10/37 AG. Erection: occurs in some but not all cases. Contraction of dartos muscle: more frequently in SCI with one complete T8 lesion. • Systemic: Rise in blood pressure BP

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde; EEJ = electro ejaculation; BP = blood pressure

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Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Brindley, 1984, UK (Ref ID 756)	• Enrolled/ evaluated: n=81/n=81 • % males: 100% • Race/ethnicity: NR • Age: NR • Level of Injury: 5-L1 or below • ASIA Level: NR • Duration since injury: (n=28) < 6 mo, (n=126) > 6 mo • Previous fertility: None • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 6/19 (+) reported	• **Pharmacologic:** NR • **Device:** The Ling 201 Vibrator (n=81) • Amplitude: about 2.5mm • Frequency: 80Hz • Mode/Admin. Route: NR • **Other Device:** NR • **Surgical:** NR • **Procedure:** NR • **Behavioural:** NR • **Laboratory techniques:** NR	• **Outcomes:** • Measures of Fertility Rates: • EJ Rates: (n=154): in SCI C5-T1 there 23 AG, 7 RG, 6 external failure, 0 pain (total (n=43); in SCI T2-12, 40 AG, 18 RG, 20 definite failure, 5 external failure, in 5 pain prevented EJ (total 88); in SCI L1 or below, 6 AG, 3 RG, 30 definite failure, 1 external failure & in 15 pain prevented EJ (total n=23). • With regard to time since injury, in pts with SCI< 6 mo post injury 14 AG, 2 RG, 3 definite failure, 5 external failure, & in 4 pain prevented EJ (n=28); in SCI> 6mo, 55 AG, 26 RG, 27 definite failure 5 external failure, & in 5 pain prevented EJ. • Pregnancy rates: n=11 • Live Births: n=9 • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde

Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/ Quality Assessment	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Brindley 1986, UK (Ref ID 729)	• Enrolled/evaluated: n=12/ n=12 • % males: 100% • Race/ethnicity: NR • Age: NR • Level of Injury: all paraplegic pts • ASIA Level: NR • Duration since injury: 0-10 y • Previous fertility: n=7 azospermia due to obstruction of abdominal part of vas deferens; n=2 cystectomy; n=1 ejaculatory cyst; n=1 imperforate anus, n=1 Panproctocolectomy; n=1 Tuberculosis, n=1bladder exstrophy • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** 36 mo • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 6/19 (+) reported	• **Pharmacologic:** NR • **Device:** NR • **Surgical** (n=12): Sperm Reservoir Implanted Sperm Reservoir for Obstructive (alumina & glass silicone rubber) • **Technique:** inserted via inguinal incisions. Prophylactic antibiotics given for 7d • **Behavioural:** NR • **Laboratory techniques** (n=12) • AIH: pts injected tissue culture medium into reservoirs & either provokes orgasm (SCI) or wait 1 h. Reaspiration yielded a mixture or culture & presumable fresh spermatozoa.	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: Sperm retrieval from right reservoir in paras: vol=0.2-1.0, Count=20-140, Motility=0-30%. Retrieval from left reservoir in paras: Vol=0.2- 0.8, Count=0-80, Motility=0-1%, • Sperm Retrieval from pt's with vasal obstruction, right reservoir: Vol=0.1-0.8, Count=0-233, Motility=0-30%; Left reservoir, Vol=0. 2-0.6, Count=0-30, Motility=0-30% • Pregnancy rates: (n=2) (17%) • Live Births: (n=2) • Singletons: (n=2) • **Follow-up:** • Length: monthly check up • Duration: • Results: aspirates examined microscopically. Upon identification of motile spermatozoa, instruction in artificial insemination given.	• **A/E:** • Systemic: (n=2) Infected reservoirs, (n=1) obstruction of reservoir requiring revision, 1 removed

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde; AIH = artificial insemination from husband

Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Brinsden, 1997, UK (Ref ID 528)	• Enrolled/ evaluated: n=35 couples/ n=35 couples • % male: 50% • Race/ethnicity: NR • Age: male 32.2 (24-47) y; female partner 29.4 (21-43) y • Level of Injury: C5-L1 • ASIA Level: NR • Duration since injury: 8.5 (1-27) y • Previous fertility: tubal factor infertility in 3/35 female; endometriosis in 2/35 • Dropouts: n=0 • Lost in Follow-up: N/A • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: other methods of assisted fertilization used • **Quality Assessment:** 9/19 (+) reported	• **Pharmacologic:** NR • **Device**: electrical stimulator/ Vibrator • Amplitude/Frequency: NR • **Laboratory techniques:** • AG: a two-step Percoll gradient, & resuspention in Earle's culture medium. Sperm concentration adjusted to 100 000/ml • RG: centrifuged at 200 g for 5 m resuspended in Earle's culture medium & centrifugation repeated. • Intrauterine insemination: NR • IVF: 71 cycle of IVF obtained by TREE. N of cycles to oocyte recover (%) 67(94.4); n of couples with complete failure of fertilization (%), 9 (13.4); n of embryo transfers cancelled: 2; n of fresh embryo transfer cycles: 54; n of fresh embryos transferred/cycle mean: 2.4; n of cycles with spare embryos cryopreserved (%): 22/54(40.7); n of spare embryos cryoprederved mean: 2.70. • Intracytoplasmic sperm injection • Embryo cryopreservation: n of couples with cryopreserve embryos: (n=11), n of thawed embryo transfer cycles 14, n of embryos transferred mean: 2.3; n of clinical pregnancies/ transfer (%): 4(28.6), n of live births / couple with frozen embryos (%), 4(36.4)	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: when fertilization occurred, initial mean total SpC 83 mln/ml; Initial mean total motile SpC 5.3 mln/ml; Initial mean motility 15%. Post sperm preparation mean SpC 3.8 mln/ml; mean motility 65%; n of cycles to acolyte recovery 67/71 (94.4%) • Pregnancy rates: 18 total; (n=14) fresh embryo transfers; (n=4) frozen embryo transfers; n of total delivered clinical pregnancies 14; pregnancy rate per tx cycle started: 21.2% (18/85); Clinical pregnancy rate per couple 51.4% (18/35) • Miscarriage/ectopic: (n=4) (3 in first trimester, 1 in a second trimester) • Live Births: (n=14) • Singletons: (n=13) • Multiples: 5 diagnosed as twins on early ultrasound, 2 of which delivered single babies • **Additional Outcomes**: Overall clinical pregnancy rate per stimulated IVF tx started 25.4% (18/71); Overall clinical pregnancy rate per fresh embryo transfer 25.9% (14/54); Overall clinical pregnancy rate per frozen-thawed embryo transfer cycle 28.6% (4/14) • **Follow-up:** NR	• **A/E:** NR

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Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Buch, 1993, US (Ref ID 624)	• Enrolled/evaluated: n=18/ n=18 • % males: 100% • Race/ethnicity: NR • Age: 31 (22-43) y • Level of Injury: Cervical C5-C6: 7,Thoracic T3-T12: 11(ASIA scores: A 12; B-D 6) • ASIA Level: NR • Duration since injury: 8.8 (2-22) y • Previous fertility: NR • Dropouts: n=2 • Lost in follow-up: NR • N of sites: 1 • Funding: Paralyzed Veterans of American Spinal Cord Injury Research Foundation	• **Study Design:** NCS • **Duration:** 2.5 • **Eligibility Criteria:** • Inclusion: men older than 19 Y with SCI for fertility evaluation • Exclusion: NR • **Quality Assessment:** 8/19 (+) reported	• **Pharmacologic:** • Drug name nifedipine (tx of hypertension) • Dose: 5-10 mg • Duration: NR • Schedule: at each session • Mode/Admin. Route: Sublingual (5-10 m pre-swallowing) • **Device:** rectal probe for EJ • Amplitude: up to 600 mA • Frequency: 60 Hz • Mode/Admin. Route: NR • **Other Device:** NR • **Surgical:** NR • **Procedure:** • Bladder catheterization -with/without alkalinization: Oral sodium bicarbonate 36 hr pre-tx (alkalization of urine)/Oral antibiotics 7-10 d pre-tx • protoscopy: ruling out rectal injury pre EEJ • **Behavioural:** NR • **Laboratory techniques:** • Sperm preparation: Std analysis on AG & RG specimens. (RG centrifuged @ 600 times gravity for 10 m, aspirated & resuspended over volume of 1-4ml. Bigger's Whitten & Wittingham solution then mixed with AG, frozen & thawed. • intrauterine insemination: in all couples; 2-4 cycles; with or without oral clomipene, nest 3 cycles with human menopausal gonadotropin ovarian stimulation & progress to IVF if IUI failed	**Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: average total SpC in both RG & AG EJs: 304 mln/ml; average total motile SpC 83 mln/ml; average % of motile sperm 21% • **EJ Rates**: total 89%; in quadriplegics 100% (7/7) & in paraplegics 82% (9/11) • Pregnancy rates: 50% (3/6) (one woman got pregnant twice) • Live Births: n=2 • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde; EEJ = electro ejaculation

Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Le Chapelain 1998, France (Ref ID 522)	• Enrolled/ evaluated: n=39/ n=10 evaluated for conception • % males: 100% of 39 SCI; 50% of 10 couples • Race/ethnicity: NR • Age: 28.5 (19-49) Y • Level of Injury: 17 tetraplagics C4-8 (8 complete, 9 incomplete); 15 paraplegic T1-T10 (all complete); 7 paraplegic pts T11-L2 (complete or incomplete)	• **Study Design:** NCS • **Duration:** 5 yr retrospective study • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 11/19 (+) reported	• **Pharmacologic** (n = 9): • Drug name: physostigmine • Dose: 2mg • Duration: NR • Schedule: 10 m post administration of Metoclopramide (10mg) • Mode/Admin. Route: injection of physostigmine followed by VS 10-15 m later • **Device:** Vibrion Vibrator (n=18) • Amplitude: 2-4.5 mm • Frequency: 100 Hz • Mode/Admin. Route: 3 m VS followed by 1 m pause for max of 3 cycles/session • Other Device: Electrostimulator (Stimed)(n=19) • Frequency: 50 Hz • Intensity: 125 mA • Duration: up to 10 m/session • Note: at least 2 distinct sessions with physostigmine/ VS or ES attempts conducted for each pt. • **Surgical:** NR • **Procedure:** NR	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: mean volume of sperm obtained by VS S higher (p=0.0136) vs. that of ES; % motile form S higher in vs. ES (p=0.0330); NS in number of spermatozoa & % of normal form in vs. ES • EJ Rates: 30/39 (77%) ejaculated • 12/18 (68%) ejaculated with VS; rate of success 86% in tetraplegic grp, 62% in T1-T10 paraplegic subgrp, & 33% in T11-L2 subgrp • 13/19 (68%) with ES ejaculated; rate of success 83% in tetraplegic grp, 66% in T1-T10 grp & 50% in T11-L2 grp • 6/9 (66%) ejaculated with	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Le Chapelain 1998, France (cont'd) (Ref ID 522)	• ASIA Level: NR • Duration since injury: NR • Previous fertility: NR • Drop-outs: n=0 • Lost to follow-up: NR • Number of sites: 1 • Funding: NR	• See above.	• Bladder catheterization: • without alkalinization after tx • Epididymal aspiration (MESA/PESA): NR • Testicular biopsy: NR • Behavioural: NR • **Laboratory techniques:** • Donor sperm insemination: NR • Sperm preparation: NR • Intrauterine insemination: n=3 • IVF: in one couple reported • Intracytoplasmic sperm injection: NR • Embryo cryopreservation: NR • Sperm cryopreservation: NR	• physostigmine injection; rate of success 100% in tetraplegic grp, 33% in T1-T10 grp & 0% in T11-L2 grp • Pregnancy rates: 3/10 • Miscarriage/ectopic: 1/10 spontaneous • Live Births: 2/10 • Singletons: 2/10 • **Follow-up:** NR	• See above

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde

Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/ Quality Assessment	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Chapelle, 1983, France (Ref ID 1404)	• Enrolled/ evaluated n=20/ n=20 • % males:100% • Race/ethnicity: NR • Age: NR • Level of Injury: NR • ASIA Level: NR • Duration since injury: NR • Previous fertility: NR • Dropouts: NR • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design**: NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 8/19 (+) reported	• **Pharmacologic** (n =20): • Drug name intervention: PSC injection, ISN • Dose: Baseline: PCS - 4 mg, average 2 mg 30 m after N-buthylhyocine 40 mg followed by masturbation 15 m later several wks ISN (following lumbar puncture) 0.25 or 0.5 mg mixed with cerebrospinal fluid, injected intrathecally. (Some pts received a supplementary injection of 1 mg PCS when no results obtained from first injection 30 m later. • Duration: NR • Schedule: NR • Mode/Admin. Route: injection of PSC or ISN test not performed if lesion affected T12, L1 or L2 & PSC test negative • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Procedure:** NR • **Behavioural** (n = 20): • Type: masturbation • Duration: NR • Frequency: 15 m post-injection • **Laboratory techniques**: NR	• **Outcomes:** • Measures of Fertility Rates: • Erectile function: erection easier to obtain & maintain after PSC test. Erection not affected in 60% of cases when PSC negative & improved in 40%. When PSC test positive, erection improved in 80% of cases. indication of PSC & ISN are identical but latter presents fewer disadvantages • **Follow-up:** • Pts used PSC at home without any medical supervision if they had experimented & responded to their test in hospital.	**A/E:** • Systemic: Orthostatic hypotension 15-60 m post injection, tachycardia<140 b/min, nausea in 33%, & vomiting in 3 pts, 3 times in one of them. Sense of well being, floating in space, & euphoria 10 m after injection of physostigmine, accompanied with tired feeling. Other side effects reported to be related to pre-study medication (i.e. anticholinergic agents)

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde; PCS = physostigmine; ISN = intrathecal neostigmine

Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/ Quality Assessment	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Chen, 1997, US (Ref ID 2069)	• Enrolled/ evaluated: n=14/ n=14 • % males: 100% • Race/ethnicity: NR • Age: 30.7 (25-41) y • Level of Injury: T6-L5 • ASIA Level: n=8 A; n=4 B; n=2 C • Duration since injury: 6.9 y; range, 1-16 y • Previous fertility: NR • Drop-outs: n=0 • Lost to follow-up: n=0 • Number of sites: 1 • Funding: US Dept. of Education; NIDRR Research; Rehabilitation Institute of Chicago	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: < 6 ms since SCI • **Quality Assessment:** 10/19 (+) reported	• **Pharmacologic:** NR • **Device:** Ling 201 Vibrator (n = 14) • Amplitude: 205 mm • Frequency: 80Hz • Mode/Admin. Route: VS to dorsal surface of penis near frenulum, in cycles of 3.5 on m-1.5 off; • Schedule: every 2-4 wk • **Other Device:** Vibrators • Type: panabrator; 4-in-1; Magic Wand; thrive Model 91 • Manufacturer: Panasonic Industrial NJ; Wahl Clipper Corp, IL; Hitachi Appliance Corp, GA; Daita Electronic Co, respectively • **Surgical:** NR • **Procedure:** NR • **Behavioural:** NR • **Laboratory techniques:** NR	• **Outcomes:** • Seminal Parameters: sperm in 43/51(84%) AG; & in 39/61(64%) RG; SpC in AG (mean 74.1 mln) > RG (mean, 40 mln) (NS); NS dfs between AG & RG in SpMot, progressive motility, or normal morphology, with motility being low & progressive motility being high in general • EJ Rates: AG in 51/61(84%) trials; AG in 1st cycle of VS in 41/61(80%) trials; RG in 100% of trials • **Follow-up:** NR	• **A/E**: • Systemic: rise in BP in 4/14 ; additional complications i.e. headache & increase in spasticity

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde; NIDRR = National Institute on Disability Research & Rehabilitation

Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Chen, 1999, US (Ref ID 952)	• Enrolled/ evaluated: n=14/ n=14 • % males: 100% • Race/ethnicity: NR • Age: 30 (25-41) y • Level of Injury: (n=8) Cervical, (n=6) Thoracic, n=8 Lumbar • ASIA Level: NR • Duration since injury: 6.9 (1-16) y • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: US Dept. Education; NIDRR; Rehabilitation Institute of Chicago	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: >6 m onset of SCI • Exclusion: NR • **Quality Assessment:** 9/19 (+) reported	• **Pharmacologic:** NR • **Device:** Vibrator Ling 201, Panabrator; 4-in-1; Magic W&; Thrive Model 91 (n = 14) • Amplitude: NR • Frequency: NR • Mode/Admin. Route: 3,5 m on & 1.5 m off until AG ejaculate obtained or until 4 cycles completed • **Other Device:** NR • **Surgical:** NR • **Procedure:** NR • **Behavioural:** NR • **Laboratory techniques** (n = 14): Sperm preparation: Std semen analysis for semen volume, sperm concentration, count, motility, progressive SpMot, & normal SpMor. Biochemical analysis using enzdymatic EJ.	• **Outcomes:** • **Measures of Fertility Rates:** • **Seminal Parameters:** sperm concentration: AG 81.4(101.4) mln/ml, range 0.03-473.0 mln/ml; SpMot: AG 37.0 (6.7)%, range 0-60%; RG 15.2 (30.8)%, range 0-63; sperm progressive motility: AG 58.1(23.1) %, range 0-92%; RG 57.0 (37.9) %, range 0-100%; normal morphology: AG 35.7 (11.0) %, range 8-52%; RG mean 31.1 (15.7) %; range 0-58% • NS between AG & RG samples with respect to SpC, SpMot, progressive motility & normal morphology • EJ Rates: AG EJ rate: 84% (51/61), RG ejaculate rate 100% (61/61) • **Follow-up:** NR	• **A/E:** • Systemic: 28.5% (n=4) increased blood pressure; 7.1% (n=1) headache; 7.1% (n=14) increased spasticity

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Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/ Quality Assessment	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Chung, 1997, US (Ref ID 547)	• Enrolled/ evaluated: n=27/ n=27 • % males: 100% • Race/ethnicity: NR • Age: (27-48) y • Level of Injury: NR • ASIA Level: NR • Duration since injury: NR (3-25) y • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS; retrospective observational study • **Duration:** NR • **Eligibility Criteria:** • Inclusion: unejaculatory men with SCI or retroperitoneal LND, who treated at Rehabilitation Center at Tampa General Hospital between September 1991 & October 1995 • Exclusion: NR • **Quality Assessment:** 9/19 (+) reported	• **Pharmacologic** (n = 27): nifidepine • Dose: 10 mg • Frequency: • Admin: 15 m pre-during & post procedure as prophylaxis for autonomic dysreflexia • **Device: Electrostimulator(n =27):** Amplitude : 2 V & increased progressively at 1- to 2-V increments per stimulation every 4 to 6 seconds until EJ occurred • **Other Device:** NR • **Surgical:** NR • **Procedure (n=x):** • Bladder catheterization: Alkalization of urine with a 24-hr regimen of sodium bicarbonate before EEJ • Epididymal aspiration (MESA/PESA) • Testicular biopsy • **Behavioural (n = x):** • **Laboratory techniques (n = x):** • Sperm preparation: • Both AG & RG with swim-up technique • Intrauterine insemination: specimen washed twice & centrifuged &resuspended in 0.2mL of medium, layered with same medium & incubated for 1h @ 37˚C & top layer collected for insemination • IVF • Intracytoplasmic sperm injection • Embryo cryopreservation • Sperm cryopreservation: -ejaculated: -biopsy	• **Outcomes:** • Seminal Parameters: • AG (mean, SD) (n=92): pH 7.4+-0.1; volume 16.5+-2.8 ml, SpC 64.6+-10.0 mln/ml; total SpC 578.5+-93.6 mln/ml; motility 16.7%+-1.5%; normal morphology 28.6%+-2.0% • RG (mean, SD) (n=34): pH 6.8+-0.1; volume 45.8+-6.4 ml; SpC 8.2+-2.7 mln/ml; total SpC 2.9.8+-69.6 mln/ml; motility 6.9%+-1.9%; normal morphology 26.7%+-3.7% • EJ Rates: sperm recovery rate: 93% (86/93); solely AG ejaculate in 63% (59/93); combination of AG & RG in 35% (33/93); 1 solely RG ejaculate • Pregnancy rates: 7 pregnancies in 13 couples with a total of 56 IUIs; pregnancy rate per IUI attempt 12.5% (7/56) • Induced abortion: 2 spontaneous abortions • Live Births: 4 term live births; 1 on-going twin pregnancy • **Follow-up:** NR	• **A/E:** NR

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Dahlberg, 1995, Finland (Ref ID 573)	• Enrolled/ evaluated: n=63 participated for fertility tx/ 35 couples evaluated for conception • % males: 100% of n=63; 50% of 35 couples • Race/ethnicity: NR • Age: NR • Level of Injury: NR • ASIA Level: NR • Duration since injury: NR • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment**: 7/19 (+) reported	• **Pharmacologic** (n=35): • Drug name: S/L Nifidepine • Dose: 10-30 mg • Duration: NR • Schedule: 30 m pre-procedure • Mode/Admin. Route: sublingually • **Device: Vibrator** (n=27): • Amplitude: NR • Frequency: NR • Mode/Admin. Route: NR • **Other Device:** Electrostimulator (n=13) • Brindley's technique / no anesthesia • **Surgical:** NR • **Behavioural:** • **Laboratory techniques:** • Sperm preparation: swim-up technique used followed by sperm discontinuous Percoll gradient (40/90%) • home insemination once per cycle • Intrauterine insemination: 4-6 cycles in all EEJ cases • IVF: 3rd choice of tx if 1st two did not result in pregnancy; down-regulation with intranasal buserelin acetate 1200 µg daily, started on 23rd d of previous cycle	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: concentration before preparation 87 mln/ml (range 1.2-200 mln); post preparation 32 mln/ ml. (range .6-88 mln). Sperm mobility before prep 18% (range 2-42) & after prep 25% (range 0-9). • EJ Rates: EJs obtained in 20 pts with VS & in 9 with ES; RG EJ in 8 pts(spermatozoa in n=2 • Pregnancy rates: (n=24) • Miscarriage/ectopic: (n=4) • Live Births: (n=24) • Singletons: (n=20) • Multiples: 2 sets of twins • **Follow-up:** NR	• **A/E:** NR

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de Lamirande 1995, Canada (Ref ID 960)	• Enrolled/ evaluated: n=207: n=20 healthy volunteers, n=166 non-SCI infertile, n=21 SCI/ n=207 • % males: 100% • Race/ethnicity: NR • Age: SCI 28.1(20-40) y; healthy volunteers (n=20) NR (23-43) y, Infertile grp: NR • Level of Injury: n=9 Cervical, n=12 Thoracic & Lumbar, (15 Complete, 6 incomplete) • ASIA Level: NR • Duration since injury: 5.8 (0.5-14) y • Previous fertility: NR • Dropouts: (n=21) failed to respond to vibratory stimulation to ejaculate • Lost in follow-up: NR • N of sites: 1 • Funding: MRC, Canada	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 8/19 (+) reported	• **Pharmacologic** (19/ 21 SCI): • Drug/ dose: name 40 mg of butylbromide at time 0. 1/2 h later, 2 mg of physostigmine SC following by semen collection (masturbation). In 2 other SCI men Nifedipine 5-10 mg sublingually pre electro stimulation to prevent Autonomic Dysreflexia • **Device:** Electrostimulation (EEJ probe modes) (n = 2 SCI) • Amplitude: NR • Frequency: NR • Mode/Admin. Route: NR • **Other Device:** NR • **Surgical:** NR • **Procedure:** NR • **Behavioural (SCI pts):** • Type : masturbation following injection of physostigmine • Duration: until EJ occurred • Frequency: NR • **Laboratory techniques:** • Sperm preparation: discontinuous Percoll gradients buffered with HEPES-balanced saline. • Reactive Oxygen Species Determination: ROS detected by luminescence during 10 s stirring analyzed sample following 10-fold dilution of Percoll-washed spermatozoa.	• **Outcomes**: • Seminal Parameters: SpMot in SCI men ranged from 0% to 20% in whole semen (23/32 samples), this measure did not Δ slightly after Percoll gradient centrifugation (20/32 samples). In 9 of 23 samples with poor motility a rise in ROS after Percoll washing observed, no increase in ROS noted after Percoll wash when same comparison made with semen with motility>20%. • **Additional outcomes:** ROS in normal pts are lower than those for infertile men ($p<0.05$) or those with SCI ($p<0.0001$). ROS levels lower in infertile men compare to SCI ($p<0.0001$). No df in level of ROS in SCI grp for level of lesion or duration of injury. • **Follow-up:** NR	• **A/E:** NR

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Halstead 1987, US (Ref ID 986)	• Enrolled/ evaluated: n=12 couples/ n=12 couples • % males: 50% of 12 couple • Race/ethnicity: NR • Age: NR (23-38) y • Level of Injury: n=4 C5-C6; n=7 T3-T12; n=1 L1 • ASIA Level: n=7 A; n=1 B; n=3 C; n=1 D • Duration since injury: 5mo to 18 y • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: • N of sites: 1 • Funding: Bob & Vivian Smith Foundation, Houston, & Model Rehabilitation Spinal Cord Injury System Grant, TIRR, funded by National Institute of Handicapped Research	• **Study Design:** NCS • **Duration: 18** mo • **Eligibility Criteria:** • Inclusion: Traumatic SCI, age>18 y, medically stable, with preference given towards married pts. • Exclusion: NR • **Quality Assessment:** 12/19 (+) reported	• **Pharmacologic:** NR • **Device:** (ES by rectal probe (38 occasion in 12 SCI) • Amplitude: 8-15 V & 200-400 MA • Frequency: Stimulation discontinued if BP>200 mm HG systolic or 130 mm Hg diastolic or for any other side effects/discomfort. • Mode/Admin. Route: max. of 25 stimulation/cycle (60 cycle/sec). • **Other Device:** NR • **Surgical:** NR • **Procedure:** • Bladder catheterization: prior to RPE with a sterile catheterisation technique. In/out sterile bladder irrigation with normal saline post EJ to assess RG. • Protoscopy: test of rectal mucosa • **Behavioural:** NR • **Laboratory techniques:** NR	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: Semen retrieval in 50% (6 of 12) of emissions, volume range=0.2-2.9cc; Sperm concentration range=7.5-678 mln/cc; %motility range=0-60%; %Normal morphology range=0-55%. Only 4 of 9 produced semen with live SpC adequate for AI. • EJ Rates: 10 of 12(83%) produced sperm on at least one occasion; Sperm obtained in 32 of 38 rectal probe EJs. • Pregnancy rates: Spouse of pts artificially inseminated but no pregnancy achieved • Live Births: n=0 • **Follow-up:** NR	• **A/E:** • Systemic: Mild autonomic dysreflexia in (n=3), disruption of normal bowel program in (n=1). Pain & discomfort in pts with incomplete lesions & some preservation of sensation (all cervical lesions & L1).

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Hellstrom, 1989, US (Ref ID 692)	• Enrolled/ evaluated: n=13: n=11 SCI, n=1 diabetic & n=1 MS/ n=13 • % males: 100% • Race/ethnicity: NR • Age: 32.1(26-45) y • Level of Injury: n=6 Cervical; n=5 Thoracic • ASIA Level: NR • Duration since injury: 7.7 (4-12) y • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: American Urological Association Scholarship & University of California	• **Study Design:** NCS • **Duration:** 14 mo • **Eligibility Criteria:** • Inclusion: all pts underwent physical exam, medical hx & lab work. No definite criteria listed. All pts included that attended EEJ clinic • Exclusion: NR • **Quality Assessment:** 8/19 (+) reported	• **Pharmacologic:** NR • **Device:** EEJ x 49 AI 2(All SCI pts) • Amplitude: NR • Frequency: 3 trial for each pt • Mode/Admin. Route: NR • **Other Device:** NR • **Surgical:** NR **Behavioural:** NR • **Procedure (All pts):** • Bladder catheterization with/without alkalinization: alkalization by admin. Of sodium bicarbonate orally for 36 hr. followed by rinse & instillation with tissue culture growth medium. • Epididymal aspiration (MESA/PESA) • Testicular biopsy: in all men testicular aspiration with a 23-gauge needle. DNA histograms collected within 4 d after aspiration. • **Laboratory techniques**: NR	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: (n=4) normal SpC & motilities (30% or greater); 3 pts had adequate sperms counts but low motilities (5% or less); 3 pts had mod abnormalities. Of 5 pts with markedly abnormal histograms, 4 remained azoospermic despite repeated attempts at EE • Ovulation rates: Ovulation problems in one partner are reported. • Pregnancy rates: 1 of 2 AI following EEJ. • **Additional Outcomes:** • Testicular biopsy results: 8 bilateral & 5 unilateral biopsies performed. In (n=5) normal histograms found, (n=3) mildly abnormal, & in (n=5) markedly abnormal. There no relationship with semen quality & level or completeness or duration of SCI • **Follow-up:** NR	• **A/E:** NR

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Heruti, 2001, Israel (Ref ID 454)	• Enrolled/evaluated: n=84 (including 49 couples)/ n=33 followed for pregnancy • % males: 100% of n=84 ; 50% of 33 couples • Race/ethnicity: NR • Age: 31.3 (19-45) y • Level of Injury: cervical 29 (34.5%), thoracic 50 (59.5%), lumbar 5 (5.9%), • ASIA Level: n=63 A; n=15 B; n=5 C; n=1 D • Duration since injury: 7.1 (4 mo-34) y • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 11/19 (+) reported	• **Pharmacologic:** NR • **Device:** • Amplitude: maximum voltage 20 V • Frequency: maximum current 300 mA • Mode/Admin. Route: following an anoscopic examination of rectal mucosa, lubricated probe inserted into rectum with pt in left lateral decubitus position. • **Other Device :** NR • **Surgical :** NR • **Procedure** (n=84): • Bladder catheterization -plastic catheter, used saline solution & 20cc Ham's F-10 solution • **Behavioural:** NR • **Laboratory techniques** (n = 84): • Donor sperm insemination • Sperm preparation: Sperms prepared by filtration with mini-percol in 3 gradients. Pentoxyl-phyllin & deoxy-adenosine to accelerate motility • Intrauterine insemination: IUI is first line of tx with sperm analysis > 10.mln/cc • IVF: If 3 cycles of tx have failed, pts are referred for IVF. IVF is primary tx for Pts with <10 mln sperm/cc or mechanical problems of female • Intracytoplasmic sperm injection: ICSI is used for all pts that reach IVF, as this method is more successful with low sperm rates	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: • AG EJ sperm parameters (77 pts), sperm volume (cc): mean 1.44+-1.3, range 0.1-8; sperm concentration (mln/cc): mean 31.5+-45.5, range 0-340; total SpC (mln/cc): mean 57.9+-86.3, range 0-1020; SpMot (%): mean 7.9+-13.9, range (0-70); total motile sperms (mln): mean 4.8+-14.6, range (0-111); motility grade (0-4): mean 2.1+-0.8, range (0-3.5); SpMor (% normal sperm) mean 10.5+-12.8, range 0-58. • RG EJ sperm parameters (77 pts): sperm volume NA, sperm concentration NA, total SpC (mln/cc): mean 12.3+-33.4, range 0-450; SpMot (%): mean 4.2+-11.8, range (0-84); total motile sperms (mln): mean 0.6+-2.7, range (0-36.3); motility grade (0-4): mean 1.9+-0.9, range (0-3.5); SpMor (% normal): mean 5.3+-8.0, range 0-55 • S dif. between AG & RG in all seminal parameters. • EJ Rates: successful EJ rate: 34.9% (124/350) of stimulations & 54.8% (46/84) pts; total EJ rate 98.6% (350/355); no S df found between pts with LMN & UMN • Pregnancy rates: overall rate/couple 69.2%; after IUI: 33.3% (5/15); after IVF: 70% (14/20) • Live Births: n=26 • **Follow-up:** NR	• **A/E:** • Local: 19.1% (16/84) pts, abdominal spasm, pain • Systemic: increased BP, syncope

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Hirsch 1992, US (Ref ID 974)	• Enrolled/ evaluated: n=9/n=7 • % male: 100% • Race/ethnicity: NR • Age: NR • Level of Injury: (n=2) L1&T3 (excluded from analysis) (n=7) C5-T12, n=5 complete, n=2 incomplete • ASIA Level: NR • Duration since injury: 6.8 (5-12) y • Previous	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 7/19 (+) reported	• **Pharmacologic:** • Drug name: nifedipine • Dose: 20 mg • Duration: NR • Schedule: NR • Mode/Admin. Route: sublingually • **Device:** Electrical stimulator • Amplitude: NR • Frequency: with sine wave of 60 Hz, with 1 V increments for max of 3 sec. & rest of 0.5 sec • Mode/Admin. Route: NR • **Other Device**: NR • **Surgical:** NR • **Procedure**: • Bladder catheterization • -with/without alkalinization: Pre tx Medication: 2-d oral sodium bicarbonate tore alkalinize urine • Epididymal aspiration (MESA/PESA) • **Behavioural:** NR	• **Outcomes:** • Measures of Fertility Rates: • Semen analysis: vol., 2.5±2.8mL; mean SpC 74.4±113.3 mln/mL; mean motile concentration: 28.6±54.0 mln/mL; No correlation between semen analysis parameters & severity of histopathologic defect observed on testicular biopsy. In seminal	• **A/E:** NR

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Hirsch 1992, US (cont'd) (Ref ID 974)	• fertility: NR • Dropouts: n=2 • Lost in follow-up: NR • N of sites: 1 • Funding: Regional Spinal Cord Injury Center of the Delaware Valley; NIDRR	• See above	• **Laboratory techniques**: • Sperm preparation: A-G ejaculates analyzed after liquefaction for 30 m at 370C. Seminal plasma separated by at centrifugation at 2,000 RPM for 10 m. Samples frozen at –200C until time of testing. ELISA performed on seminal plasma. Microtiter plates prepared by coating with 100ug/ml for 1 hr at 250C. Plates washed x 3 with PBS & coated overnight at 40C with sperm suspended in PBS at concentration of 2.5 x 10 sperm/well. To decrease non-specific binding plates washed x 3 with PBS coated with 200uL/well of blocking agent & left on plate x 15 m. After blocking step, each well filled with 100 uL of serial dilutions of test seminal plasma as well as (+) & (-) ctrls. Plate incubated for 1 hr at 370C. After incubation, 10-step wash with PBS Tween 1% N.G. Sperformed & plate coated with blocking agent. After this each well (apart from 1st row used for blanking) filled with 100 uL of alkaline phosphates conjugated, goat antihuman IgG, IgA & IgM, heavy &light chain specific secondarily antibody sol. Plate read for absorbance at wavelength of 405 nm on Titertek ELISA scanning spectrophotometer. • Background absorbance calculated by averaging secondary antibody row absorbance values. This value subtracted from observed absorbance values to obtain actual absorbance values. Values > than 0.100 indicative of (+) reaction	• plasma 71% (5/7) demonstrated (+) antisperm antibody response. • Additional Outcomes: • No relation found between level & degree of SCI, semen analysis (sperm concentration, %of motile spermatozoa & semen volume) & testicular biopsy (n=6); active sperm (n=1) • **Follow-up**: NR	• See above

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Hultling, 1994, Sweden (Ref ID 598)	• Enrolled/ evaluated: 12 couples/ n=12 couples • % males: 50% of 12 couples • Race/ethnicity: NR • Age: 34 (27-38) y • Level of Injury: cervical C4-C6: (n=4); thoracic T4-T12: (n=7); lumbar L3: 1 • ASIA Level: n=8 A; n= 2 C; n=2 D • Duration since injury: (4-33) y • Previous fertility: all spouses of SCI pts had regular menstrual cycles & healthy on routine gyn. Exam; 7 nulligravidae, 5 I-II gravidae; 3 had children from previous marriages • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: MRC, Sweden; Spinalis Foundation; Karolinska Institute	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: infertile male pts with SCI living in stable relationships with their female partners who express a strong wish for fatherhood & attending Solberga Spinal Cord Injury Project during January 1992 – November 1993 • Exclusion: NR • **Quality Assessment:** 6/19 (+) reported	• **Pharmacologic:** physostigmine in combination with vibration/ nifedipine (tx of autonomic dysreflexia**)** • **Device:** Vibrator & (n = 12) • Amplitude: NR • Frequency: NR • Mode/Admin. Route: VS used first in combination with physostigmine • **Other Device:** Electrical stimulator: • Mode/Admin. Route: transrectal ES usually under general anesthesia. • **Surgical:** NR • **Procedure:** NR • **Behavioural:** NR • **Laboratory techniques:** • IVF: GnRH-agonist (nafarelin/buserelin) intranasally starting d 1 or 21; HMG or Fertinorm HPR daily 10-12 ds (150-300 IU/d). Both partners received prophylactic antibiotic tx with metronodazol & doxycycline. • Oocyte retrieval: 37 hrs after vaginal ultrasound-guided follicular aspiration then percultured for 3-4 hrs pre-insemination	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: concentration (mln/ml): median 91; range 3.5-202; % of motile sperm: median 11; range 5-57; total motile SpC (mln/ml): median 73; range 11-442; concentration in prepared sperm (mln/ml): median 29.5; range 2.5-2.5; % of motile sperm in prepared sperm: median 27.5; range 0.2-99; total count of motile sperm in prepared sperm (mln/ml): median 2; range 0.16-32 • Ovulation rates: 23 ovulatory cycles in 12 women partners • Pregnancy rates: 7 pregnancies in 6 couples (2 pregnancies in 1 couple) • Miscarriage/ectopic: n=3 • Live Births: n=3 • Singletons: n=1 • Multiples: n=1 • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde; MRC = medical research council

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Hultling, 1997, Sweden (Ref ID 538)	• Enrolled/evaluated: 25couples/ n=25 couples • % male: 50% of 25 couples • Race/ethnicity: NR • Age: male: age 34 (25-51) y; women: age 31 (21-38) y • Level of Injury: range C2-L3 • ASIA Level: n=18 A; n=7: NR • Duration since injury: NR • Previous fertility: n=18 women nulligravidae; n=7 gravidae I-II; n=4 children born from previous relationship; n=2 women had a hx of endometriosis & n=2 PCOS; n of previous pregnancies: 7 gravidae I-II	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: stable relationship, motile spermatozoa in a diagnostic sample • Exclusion: NR • **Quality Assessment:** 9/19 (+) reported	• **Pharmacologic (n=25):** • Drug name: nifedipine • Dose: 10-25 mg • Duration: NR • Schedule: NR • Mode/Admin. Route: sublingually pre-ES or VS • **Device**: **Vibrator** • Amplitude: 2.5 mm • Frequency: 100 Hz • Mode/Admin. Route: duration of 204 m & repeated up to 8 times • Other Device: Electrical stimulator: • Type: • Manufacturer • Voltage: 7-35 V • Duration: 2-4 s • Mode/Admin. All pts with residual sensation in perineum &/or rectum underwent EEJ with general anesthesia: atropine prior to induction; alfentanyl 1-2 mg; 2-3 mg/kg propofol administered & supplemented with 5-15 mg/kg/h • **Surgical:** NR	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: total SpC: median 185.9 mln, range 0.01-978; motile SpC: median 32 mln, range 15-97.1 • Ovulation rates: total n of ovulatory cycles of female partner: 52 • Pregnancy rates: 16 clinical pregnancies (30.7%) • Miscarriage/ectopic: 4 in 1st or 2nd trimester & 1 case of intrauterine death in wk 31 of gestation • Fertilization rate (total n of fertilized eggs/total n of eggs): 52.3% (300/573); n of embryos (% of fertilized): 84.7%	• **A/E:** NR

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Hultling, 1997, Sweden (cont'd) (Ref ID 538)	• Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: MRC, Sweden; Spinalis Foundation; Karolinska Institute Funds; Norrbacka Eugenia Foundation	• See above	• **Behavioural:** NR • **Laboratory techniques** (25 couples): • Ovarian stimulation: Down-regulation with gonadotrophin-releasing hormone agonist, nafarelin, or buserelin, stating on cycle d 1 or 21. HMG, or purified FSH • IVF: antibiotic tx with metronidazole, 0.5 g 3x a d for 5 d & doxycycline, 0.1 g a d for 7 d, given prophylactic to all couples • Embryo transfer: n=47	• (254/300) • Live Births: (n=11) • Singletons: (n=9) • Multiples: 2 sets of twins • **Follow-up:** NR	• See above

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Kolettis, 2002, US (Ref ID 424)	• Enrolled/ evaluated: n=27(including 9 SCI with their partners)/ n=9 evaluated for conception • % males: 50% of couples • Race/ethnicity: NR • Age: NR • Level of Injury: n=10 cervical, n=16 thoracic, n=1 lumbar • ASIA Level: NR • Duration since injury: NR • Previous fertility: NR • Drop-outs: n=0 • Lost to follow-up: n=0 • Number of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** 1993-2001 • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 8/19(+) reported	• **Pharmacologic:** NR • **Device: Electrical stimulator(n=27)** • Amplitude: 12-18 V/ current of 400-600 mA • Frequency: NR • Mode/Admin. Route: 30 sec bursts of stimulation performed • **Other Device:** NR • **Surgical:** NR • **Procedure:** NR • **Behavioural:** NR • **Laboratory techniques:** • Donor sperm insemination: NR • Sperm preparation: NR • Intrauterine insemination: 25 cycles performed • IVF: 3 cycles of IVF • Intracytoplasmic sperm injection: 2 cycles of IVF-ICSI performed • Embryo cryopreservation: NR • Sperm cryopreservation: NR	• **Outcomes:** • Seminal Parameters: initial prep median total motile SpC & motility /procedure 6 mln & 7% respectively; 28 cycles(32%) yielded no motile sperm • EJ Rates: 112 EJ attempts made, 43/112(38%) AG; 24(21%) RG; 45(40%) AG+RG • Cycle Function: 25 cycles of IUI, 3 cycles of IVF & 3 cycles of IVF-ICSI • Pregnancy rates: 3/9 • Live Births: 2/9(both twins) • Multiples: 2 sets of twins • **Follow-up:** NR	• **A/E:** NR

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Leduc, 1992, Canada (Ref ID 2252)	• Enrolled/evaluated: n=37/n=3 evaluated for conception • % males: 100% of 37; 50% of couples • Race/ethnicity: NR • Age: 29.5 (19-61) y • Level of Injury: n=15 Cervical; n=22 Thoracic (29 complete; 8 incomplete) • ASIA Level: NR • Duration since injury: 3 mo-23 y mean 7.4 y • Previous fertility: NR • Dropouts: n=13 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 6/19 (+) reported	• **Pharmacologic**: • Drug name Butylbromure hyoscine, Interventional drug specified for this review: Physostigmine • Dose/admin: Butylbromure hyoscine injection: 40 mg subcutaneous 30 m prior to administration of physostignime: 2 mg subcutaneous & repeated (1-2 mg) if not EJ reached (n=7 up to 4mg); Nifedipine: 10 mg sublingual • **Device**: NR • **Other Device**: NR • **Procedure**: NR • **Behavioural**: NR • **Laboratory techniques**: • Donor sperm insemination • Sperm preparation: Semen collected for analysis post physostigmine induced EJ in a sterile container • Intrauterine insemination: 0.5 ml of unwashed fresh sperm inseminated into cervix. This procedure also done at home as well as in hospital • IVF in 6 couples • Intracytoplasmic sperm injection	• **Outcomes**: • Measures of Fertility Rates: • Seminal Parameters (n=46): Mean SpC: 134 mln/mL, Range: 2-285. Mean motility: 28%, range: 1-67% • Insemination rates: Insemination performed once in one of partners, 3 times in another & 15 times in other • Pregnancy rates: (n=3) in 3 couples • Live Births: (n=3) • **Follow-up**: NR	• **A/E:** • Systemic: (n=8) had autonomic dysreflexia: hypertension & headache following EJ, (n=2) autonomic dysreflexia with no EJ, (n=5) nausea with vomiting once, (n=1) hallucination, (n=1) dizziness

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Lim, 1994, Australia (Ref ID 333)	• Enrolled/evaluated: n=12/n=12 • % male: 100% • Race/ethnicity: NR • Age: 13 (21-36) y • Level of Injury: n=6 C4-C6; n=7 T10-T12; n=1 L2 • ASIA Level: NR • Duration since injury: 8 (1-24) y • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** 26 mo • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 10/19 (+) reported	• **Pharmacologic** (n=x): NR • **Device:** Electrical stimulator (n=12) • Amplitude: 500 mA • Frequency: sine wave currency 20 Hz at a maximum of 16 V • Mode/Admin. Route: • **Other Device** (n=12): • Type: vibrator @ 60 Hz • Manufacturer: Jeou Jen Electric Co. • **Surgical:** NR • **Procedure (n=12):** • Bladder catheterization: Foley catheter/no alkalization • SpMot /manual assessment of % of motile sperm & motility analysis • **Behavioural:** NR • **Laboratory techniques:** NR	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: • Sperm volume: range 0.1-8.5 ml; sperm concentration: 0-500 mln/ml; SpMot: 0-80%; normal forms: 6-46% • repeated stimulation had a + effect on semen quality • Volumes & concentration of sperm greater in EEJ vs. VE, but NS noted in SpMot • **Additional outcomes:** Silicone catheters had minimal effects on SpMot & viability. All lubricant gel found to adversely affect sperm quality • **Follow-up:** NR	• **A/E:** • Local: 8.3% (1/12) severe stomach cramps

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Lucas, 1991, UK (Ref ID 667)	• Enrolled/evaluated: n=14: n=12 SCI; n=2 diabetic/n=14 • % males: 100% • Race/ethnicity: NR • Age: 34.6 (25-46) y • Level of Injury: 92%, n=3 Cervical; n=9 thoracic (n=10 complete, n=2 incomplete) • ASIA Level: NR • Duration since injury: 9.9 (2-22) y • Previous fertility: secondary anorgasmy, due to diabetes (n=2) • Dropouts: (n=2) • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** 26 sessions • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 6/19 (+) reported	• **Pharmacologic** (n=12, SCI T6): • Drug name: glyceryltrinitrate or nifedipine • Dose: 20-40 mg • Duration: NR • Schedule: 20 m pre-procedure • Mode/Admin. Route: sublingually • **Device:** Electrical stimulator (n=14) • Amplitude: up to 35 V, current up to 900 mA • Frequency: 50 Hz • Mode/Admin. Route: rectal probe (PVC, 11/8 or 1¼ inches in diameter) with pressure to contact with ant. Rectal wall • **Other Device:** NR • **Surgical:** NR • **Procedure** (n=14): • Bladder catheterization - aseptically & washed with Ham's F 10 solution. Recatheterization after an AG EJ or 100% erection • Protoscopy: after procedure • Testicular biopsy: NR • **Behavioural:** NR • **Laboratory techniques** (n=14): • Donor sperm insemination • Sperm preparation: (n=8) centrifusion / & resuspension in a solution of 10% wife's serum supply. By Hams F 10 solution (swim up) to prepare for AIH • Embryo cryopreservation: • Sperm cryopreservation: (n=9) -ejaculated: Std technique with egg yolk & glycerol	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: Vol. range: drops to 5.5 ml; % of progressive motility: 0-60; Sperm concentration 0-260 • Pregnancy rates: (n=1) (AIH, RG ejaculate) • Live Births: (n=1) • Singletons: (n=1) • Multiples: none • Genetic abnormalities: none • **Follow-up:** NR	• **A/E:** NR

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Mallidis, 1994, Australia (Ref ID 966)	• Enrolled/evaluate: n=7/n=7 • % male: 100% • Race/ethnicity: NR • Age: NR (18-39) y • Level of Injury: n=6 C4 –6 , n=2 T4 –9 • ASIA Level: NR • Duration since injury: 2-15 d • Previous fertility: NR • Dropouts: n=2 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** EEJ performed every 2 d • **Eligibility Criteria:** • Inclusion: 2-15 d post-injury, Traumatic SCI, No known hx of testicular dysfunction • Exclusion: NR • **Quality Assessment:** 8/19 (+) reported	• **Pharmacologic:** NR • **Device:** Electrical stimulator (n=7) • Amplitude NR • Frequency: every 2 d; 2-13 EJ/pt • Mode/Admin. Route: insertion of rectal probe (CGS electroejaculator) • **Other Device:** NR • **Surgical:** NR • **Procedure:** • Bladder catheterization – suprapubic indwelling catheter, nasogastric tube & intravenous line for fluid & medication inserted & calf stimulator applied • **Behavioural:** NR • **Laboratory techniques** (n=7): • Donor sperm insemination • Sperm preparation: semen collected in warm, sterile plastic jar • Sperm cryopreservation: • -ejaculated: TEST egg-yolk buffer & vapour-frozen. Post-thaw motility after cryopreservation • Protoscopy: pre/post procedure	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: • Of 6 pts that started EEJ 2-3 d after injury, 5 had few sperms (<2-x10 mill/ml) & 1 had no sperm in first sample. • 3 pts who had EEJ 48 h later had no sperm in semen. • Samples collected from 4 men bet. 6-10 d after injury had normal sperm & motility. • Subsequent samples tended to have decreasing sperm viability & motility. • 5 pts produced samples suitable for cryopreservation. Post-thaw sperm-motility recovery (range 36%-74%, mean 55%) similar to that of normal-donor cryopreseved semen. 2 pts did not produce samples suitable for cryopreservation • EJ Rates: 46 EJs done (range 2-13 per pt) • Additional Outcomes: processes responsible for loss of semen quality appear to become established quickly after SCI. Post-thaw motility showed that cryopreserved samples as good as those stored from healthy men. collection of semen early after SCI can insure fertility • **Follow-up:** NR	• **A/E:** NR

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Mallidis, 2000, Australia US (Ref ID 472)	• Enrolled/evaluated: n=9/n=9 • % male: 100% • Race/ethnicity: NR • Age: 28 (22-36) y • Level of Injury: n=2 C5-C6; n=6 T4-T11; n=1 L2 • ASIA Level: NR • Duration since injury: 54 (8-103) mo • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** 4 consecutive d • **Eligibility Criteria:** • Inclusion: males 16-40 y; ≥6 mo duration of SCI; no known or suspected testicular dysfunction (past undescended tests or infertility) • Exclusion: NR • **Quality Assessment:** 8/19 (+) reported	• **Pharmacologic:** NR • **Device:** Electrical stimulation (n=9) • Amplitude: max 16 V • Frequency: sine-wave current 20 Hz • Mode/Admin. Route: daily EEJ for 4 consecutive d n=6; EEJ for 3 consecutive d n=2 & EEJ for 1 d n=1 • **Other Device:** NR • **Surgical:** NR • Penile Implants • **Procedure:** • Bladder catheterization: NR • Epididymal aspiration (MESA/PESA): NR • Testicular biopsy: fine needle tissue aspiration biopsy in (n=5) (>1mont pre EEJ n=2/ on last d of EEJ n=3) • **Behavioural:** NR • **Laboratory techniques** (n=9): • Electron Microscopy: in 15 semen samples	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: mean SpMot increase on d 2 vs. d 1 23 (6.9) %; mean sperm viability increase on d 2 vs. d 1 24.9 (6.8) %. • Overall, major gains in SpMot & viability achieved by d 2, although in 3 pts, improvement in motility & viability continued into d 3 • Testicular Biopsy: normal n=3; one-side normal n=1, other had moderately severe hypospermatogenesis; slight hypospermatogenesis n=1. • Additional Outcomes: Electron Microscopy: (n=9) all 9 d 1 samples showed marked degeneration of spermatozoa; samples after repeated EJ showed improved ultra structure with fewer degenerative features • **Follow-up:** NR	• **A/E:** NR

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Nehra, 1996, US (Ref ID 91)	• Enrolled/ evaluated: n=78; 33 couples for conception/ 27 couples evaluated for conception • % males: 100% • Race/ethnicity: NR • Age: 26.9 (23-40) y • Level of Injury: cervical 37; thoracic above T10 26; thoracic below T10 15 • ASIA Level: NR • Duration since injury: NR • Previous fertility: NR • Dropouts: 6/33 poor semen quality not candidates of assisted fertilization • Lost in follow-up: NR • N of sites: NR • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR (pts with poor semen quality not candidates of assisted fertilization) • **Quality Assessment:** 7/19 (+) reported	• **Pharmacologic:** • Drug name: clomiphene citrate daily (ovulatory enhancement) • Dose: 50 mg • Duration: on d 5-9 of cycle • Schedule: NR • **Device:** Electrical stimulator • Amplitude: 22 V, max of 420 mA • Frequency: 60 Hz • Mode/Admin. Route • **Other Device:** • Type: Vibrator oscillation rate of 1800 rmp • Manufacturer: NR • Admin: 3-4 m stimulation 3 x if necessary • **Surgical:** NR • **Procedure**: • Bladder catheterization: NR • Epididymal aspiration (MESA/PESA): NR • Testicular biopsy: in 3 pts revealed maturation arrest pattern. • **Behavioural:** NR • **Laboratory techniques:** • Donor sperm insemination • Sperm preparation: NR • Conception techniques: cervical self-insemination (n=5), IVF & gamete intrafallopian transfer (n=12) • IVF: for intrauterine insemination with human menopausal gonadotropins. IVF & gamete intrafallopian transfer combined with rectal probe EEJ (before laparoscopic oocyte harvesting or just after trasvaginal ultrasound guided oocyte retrieval. Fertilization assessed at 24 h & uterine transfer accomplished for max of 4 selected embryos 48-72 h post oocyte retrieval • Embryo cryopreservation: in all excess embryos • Sperm cryopreservation: ejaculated; biopsy	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: after EE: mean sperm concentration: 170 mln/cc; SpMot: 11.3%; • EJ Rates: overall EJ rate after vibratory stimulation: 44% (34/78); by level of injury: cervical 54% (20/37); thoracic above T10 54% (14/26); thoracic below T10 0% (0/15) • Pregnancy rates: overall pregnancy rate: 63% (17/27) • Miscarriage/ectopic (n=1) • Live Births: 20 live births in 14 couples (3 triplets, 2 twins & 9 singletons); one couple is expecting triplets & one - singleton • Singletons: (n=9) • Multiples: 2 twins, 3 triplets • **Follow-up:** NR	• **A/E**: NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; ∆ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde

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Matthews, 1996, US (Ref ID 563)	• Enrolled/evaluated: n=40: n=18 SCI; n= 9 retroperitoneal LND; n=9 idiopathic or psychogenic; n=4 diabetes mellitus/ n=33 couples evaluated for conception • % male: 100%of 40 SCI; 50% of 33 couples • Race/ethnicity: NR • Age: NR • Level of Injury: n=2 cervical; n=15 thoracic; n=1 lumbar • ASIA Level: NR • Duration since injury: NR • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: men with ejaculatory function • Exclusion: NR • **Quality Assessment:** 9/19 (+) reported	•**Pharmacologic:** NR •**Device:** Electrical stimulator •Amplitude: NR •Frequency: NR •Mode/Admin. Route: rectal probe insertion •**Other Device:** NR •**Surgical :** NR •**Procedure:** NR •**Behavioural:** NR •**Laboratory techniques:** •Sperm preparation; NR •Intrauterine insemination: 126 cycles in n=33 •IVF: n=7, total of 14 cycles •Intracytoplasmic sperm injection: NR	•**Outcomes:** •Measures of Fertility Rates: •Seminal Parameters: motile sperm recovery rate: 16/18 (89%); mean total motile sperm recovered per rectal probe EEJ (mln): total 360(73); AG 92(19); RG 351(54); RG ejaculate contained Sly more motile sperm ($p<0.05$); % motility: AG 25(3)%; RG 24(2)% •EJ Rates: 94% (17/18) •Cycle Function: mean total IUI cycles 3.2(0.6); mean intrauterine insemination cycles (pregnancy): 3.0(0.8); % IUI per cycle fecundity=14.3 •Pregnancy rates: 45% (5/11) •**Follow-up:** NR	•**A/E:** NR

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Odum, 1995, Denmark (Ref ID 1166)	• Enrolled/evaluated: n=12/ n=12 • % male: 100% • Race/ethnicity: NR • Age: NR (21-45) y • Level of Injury: C2-T12; n=9 complete, n=3 incomplete • ASIA Level: NR • Duration since injury: 7 (1-29) y • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: Gerda & Aage Haensch's Fond & Danish Biotechnology Center for Neuropeptide Research	• **Study Design:** NCS • **Duration:** 12 mo • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 7/19 (+) reported	• **Pharmacologic**: **NR** • **Device**: Vibrator (n=12) • Amplitude: peak to peak 2.5 mm • Frequency: 100 Hz • Mode/Admin. Route: once wkly for a period between 6-12 mo • **Other Device:** electrical stimulator • Dose/Frequency: NR • **Surgical:** NR • **Behavioural:** NR • **Laboratory techniques**: • Donor sperm insemination: NR • Sperm preparation: NR • Plasma extraction (frozen & thawed & proteinase inhibitors added to final concentrations: benxamidine 50 mM, EDTA 0.3 mM, leupeptin 1µM & PMSF 100µ & centrifuged at 2000 G for 20 m	• **Outcomes**: • Measures of Fertility Rates: • Seminal Parameters: (Seminal plasma Somatostatin Concentration: SSC): Marginal SD between SpMot rates in SCI below T6 (0%motile range: 0-30) & SCI at or above T6 (median=16%motile range: 10-37) (p=0.09). A trend towards lower motility in samples with SSC vs. samples without SSC (correlation coefficient =-0.66); normal SSC in lesions below T6; SSC did not correlate with semen volume, SpC, or morphology; type of stimulation (VS vs. ES) did not effect semen quality or SSC • **Follow-up:** every 3 mo for (n=5) resulted in no S dfs in SSC vs. baseline with repeated VE performed at home	• **A/E:** NR

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Ohl, 1989, US (Ref ID 385)	• Enrolled/evaluated: n=48 / n=48 • % male: 100% • Race/ethnicity: NR • Age: 31 (20-53) y • Level of Injury: n=15 cervical (31%); n=29 thoracic (61%); n=4 lumbar (8%); (56% complete; 44% incomplete) • ASIA Level: NR • Duration since injury: 8 y; (4 mo-34) • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: Supported in part by Eastern Paralyzed Veterans Association	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 4/19 (+) reported	• **Pharmacologic:** NR • **Device:** Electrical Stimulator • Amplitude: 500-600 mA • Frequency: NR • Mode/Admin. Route: NR • **Other Device:** NR • **Surgical:** NR • **Procedure:** • Bladder catheterization in (n=48) • -15-10 ccHamm's F 10 solution with 20 mm Hepes buffer in case of pH 6.5. • Methods: Intermittent catheterization in 28, Suprapubic tube in 2; Indwelling urethral catheter 2; Sphicterotomy in 8; Spontaneous voiding in8 • Epidydimal aspiration (MESA/PESA) • Testicular biopsy • **Behavioural:** NR • **Laboratory techniques**: NR	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: average total SpC =765 mln/ml & average total motile SpC =226 mln/ml; predominant forward progression 3+; average SpMot 25%; average N morphological forms 22%; successful EJ rate: 71% (34/48) • EJ Rates: Successful EJ rate by type of bladder management: intermittent catheterization: 85%; indwelling urethral catheter 50%; sphincterotomy 50%; spontaneous voiding 38%. Successful EJ rate by level of SCI: thoracic 90%; cervical 60%; lumbar 50%. Successful EJ rate by ASIA: A 77%; B-D 61% • **Follow-up:** NR	• **A/E:** NR

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Ohl, 1992, US (Ref ID 649)	• Enrolled/evaluated: n=38 Neurogenic bladder grps: n=28 SCI & n=1 MS; Normal bladder grp: n=7; Cancer; n=1 diabetic neuropathy; n=1 psychogenic/ n=33 evaluated for conception • % male: 100% of 38 SCI pts; 50% of couples • Race/ethnicity: NR • Age: 31.6 (23-47) y • Level of Injury: (n=9) cervical, (n=18) thoracic, (n=1) lumbar), • ASIA Level: NR • Duration since injury: NR • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: Eastern Paralyzed Veterans Association	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 6/19 (+) reported	• **Pharmacologic:** NR • **Device:** Electrical Stimulator (n=38) • Amplitude: up to 500 mA • Frequency: NR • Mode/Admin. Route: mean stimulation time, 7-8 m. (bulbous urethra massaged during stimulation) (n=16) underwent second EEJ trial with cultures • **Other Device**: NR • **Surgical:** NR • **Procedure** (n=29): • Bladder catheterization • Alkalization: sodium bicarbonate orally at 12 & 1 hr pre procedure to ctrl urinary acidity (EEJ). Type of bladder management: ISC in (n=12), sphincterotomy/condom in (n=5); reflex voiding in (n=8); indwelling urethral catheter in (n=1); suprapubic catheter in (n=2); Ileal loop in (n=1) • **Behavioural:** NR • **Laboratory techniques**: NR	• **Outcomes**: • Measures of Fertility Rates: • Seminal Parameters: Effect of bladder management on SpC in NGB grp: In AG of non-ISC grp average total SpC 50% lower but motility & total motile SpC slightly higher than ISC grp. In RG no Δ in SpMot, but average SpC & average total SpC substantially higher in ISC grp. In both AG&RG combined average total motile sperm slightly higher in • Infection rates: In first EEJ (n=5) semen & urine positive; In second EEJ 7 of 16 urine positive & 6 of 12 semen positive; All positive cultures in neurogenic bladder (NGB) grp • Pregnancy rates: (n=8); 5 in NGB grp (3 thoracic, 2 cervical, 1LMN, 4UMN) & 3 in non-NGB • **Follow-up**: (artificial insemination) • Length: 15-18 mo • Results: (n=24) in NGB & (n=9) in normal bladder • Pregnancy rate: 44% for ISC & 7% for other types of bladder management.	• **A/E:** NR

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Ohl, 1997, US (Ref ID 305)	• Enrolled/ evaluated: n=11/ n=11 • % males: 100% • Race/ethnicity: NR • Age: NR • Level of Injury: NR • ASIA Level: NR • Duration since injury: NR • Previous fertility: NR • Drop-outs: n=0 • Lost to follow-up: NR • Number of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 8/19 (+) reported	• **Pharmacologic:** NR • **Device:** FertiCareclinic Vibrator (n = 5) • Amplitude: 2.5 mm • Frequency: 100 Hz • Mode/Admin. Route: 3 m of VS or until EJ occurred • **Other Device** (n = 6): Electrostimulator • Type: Seager Model 11 (double dagger) with 1.25 inch probe • Manufacturer: NR • **Surgical:** NR • **Procedure:** • Bladder catheterization • -with/without alkalinization: without alkalization pre & post tx. • Epididymal aspiration (MESA/PESA): NR • Testicular biopsy: NR • **Behavioural:** NR • **Laboratory techniques:** NR	• **Outcomes:** • Seminal Parameters: NS in AG SpC in VS vs. ES; greater motility (26.0 vs. 10.7%), viability (25.2 vs. 9.7%) & motile SpC (185 mln vs. 97 mln) in VS; NS in immunobead test, cervical mucus penetration or sperm penetration assay; percent hamster egg penetration S (53.7% for VS vs. 22.1% ES, p=0.06); greater pain scores for ES vs. VS (5.2 vs. 1.7); all pts preferred VS. • **Follow-up:** NR	• **A/E:** NR

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Ohl, 2001, US (Ref ID 3059)	• Enrolled/ evaluated: n=87 (SCI) • males: 50% • Race/ethnicity: NR • Age: NR • Level of Injury: NR • ASIA Level: NR • Duration since NR • Previous fertility: NR • Drop-outs: n=NR • Lost to follow-up: NR • Number of sites:1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment**: 6/19 (+) reported	• **Pharmacologic:** sublingual nifedipine given to pts above T6 prone to dysrelexia • **Device:** electroejaculation with Seager machine • Amplitude: NR • Frequency: NR • Mode/Admin. Route: rectal • Schedule: NR • **Other Device:** • Type: catheter to obtain retrograde specimen • Manufacturer: NR • **Surgical:** female partners underwent hysterosalpingography & laparoscopies to exclude structural female infertility • **Behavioural:** NA • **Laboratory techniques:** artificial insemination enhanced with gonadotropin therapy, IVF was performed on those who could not conceive & who could afford associated costs	• **Outcomes:** 28/87 SCI couples achieved at least one pregnancy • Seminal Parameters: NR • EJ Rates: NR • **Follow-up:** followed to pregnancy or failure	• **A/E:** • Systemic: NR • Local: NR

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Perkash, 1985, US **(Ref ID** 989)	• Enrolled/evaluated: n=30/ n=30 • % male: 100% • Race/ethnicity: NR • Age: 32 (20-47) y • Level of Injury: n=27 T2-T12; n=3 L1-L3 • ASIA Level: NR • Duration since injury: 6.3 (0.3-21.7) y • Previous fertility: NR • Dropouts: n=8 • Lost in follow-up: NR • N of sites: 1 • Funding: NIMH; base grant from NIH to Yerkes Regional Primate Research Centre of Emory University; & grant from Spinal Cord Research Foundation of the paralyzed veterans of America	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 7/19 (+) reported	• **Pharmacologic:** NR • **Device:** Electrical stimulator (n=30) • Amplitude: (Current: stepwise from low to high currents every 2 sec enough to elicit penile tumescence &/or seminal emission0 • Frequency: 20 Hz • Mode/Admin. Route: • Other Device: NR • **Surgical:** NR • **Procedure:** • Bladder catheterization: irrigation with neomycin sulfate-polymyxin B sulfate solution/drainage • Epididymal aspiration (MESA/PESA): NR • Testicular biopsy: (n=13) volunteered with no anesthesia via std surgical procedure • Serum hormone analysis: (n=30) levels of estradiol-17ß/Follicle-stimulation & luteinizing hormones /Serum prolactin via radioimmunoassay • **Behavioural:** NR • **Laboratory techniques:** NR	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: SpC in (n=18)>40 mln. Total SpC in 22 pts>20 mln; SpMor: mean 55%, range 40-75%; Sperm progressive motility <20% in 27 of 35 specimens, no motile in 10 specimens & less than 10% motile in 13, 10-20% motile in 4 & more than 30%motile in 5. • Biopsy: Biopsy specimens (n=13) suggested normal testicular morphology, with tube atrophy & spermatogenesis activity only mildly reduced. • Serum testosterone & luteinizing hormone values Sly higher ($p<0.05$) in SCI than normal volunteers. • **Follow-up:** NR	• **A/E:** • Local: (n=8) intolerance of electro stimulation

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Pryor, 1995, US (Ref ID 591)	• Enrolled/evaluated: n=6/ n=6 • % male: 100% • Race/ethnicity: NR • Age: NR (30-36) y • Level of Injury: C4-C7 • ASIA Level: NR • Duration since injury: 6-18 y • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: hx & physical exam, preliminary lab evaluation, informed consent (1 trial of vibratory stimulation to determine seminal parameters, rule out infection & to determine need for sympathomietics) • Exclusion: NR • **Quality Assessment:** 5/19 (+) reported	• **Pharmacologic:** • Drug name: in cases 1, 2, & 4 ephedrine (& sodium bicarbonate) • Dose: 50 mg • Duration: 10 d • Schedule: NR • Mode/Admin. Route: NR • **Device:** Vibrator (Acuvibe 6002) • Amplitude: NR • Frequency: Vibrator speed range from 2,800rpm to 4, 29,000rpm • Mode/Admin. Route: Time from vibrator application to EJ varied from 5-45 m/ stimulation/ rest in 5 m increments for subsequent vibrations • **Other Device:** NR • **Surgical:** NR • **Behavioural:** NR • **Laboratory techniques** (n=6): • Sperm preparation • -swim-up technique • Intrauterine insemination: in all cases; case 2 partner: imipramine 25 mg t.i.d for 10 d, case 6 & 3 partners put on clomiphene citrate to regulate ovulation cycles	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: Case 1 ejaculatory vol. AG -1.1ml-3.0 ml, RG10-81 ml. SpC 30.5 mln/ml to 106 mln/ml. Motility<1%-30%, Morphology 16-52% normal; Case 2 AG =. 4-3.2 ml, RG =32.5-110ml.SpC .3 mln/ml to 2,800 mln/ml; Motility 0%-35%; Morphology - 6-10%normal. Case 3 AG 0.7-4.5 ml RG 1.8-78 ml. SpC 50.5 mln/ml; Motility 0-45%; Morphology 9-16% normal; Case 4 AG 0 ml RG 55-125 ml. SpC 0-600 mln/ml; Morphology 24% normal; Case 5 AG vol. 2-20ml RG 60-340ml; Count 1.28 mln/ml-30.5 mln/ml; Motility 25-35%; Morphology 3% normal; Case 6 AG vol. 1 unable to ejaculate 0-3.1 RG vol.28-55; Count .93 - 13 mln/ml; Motility <10%-70%. Morphology Not available • EJ Rates: Case 2 -4 EJ; Case 3 - 7 EJ; Case 4- 3 EJ; Case 5-2 EJ & Case 6-4 EJ reported • Ovulation rates: 6 case 1 conceived in 5th cycle, 5/6 normal ovulatory functions. 1/6 irregular ovulatory function • Infection rates: (n=1) UTI • Pregnancy rates: (n=5) • Miscarriage/ectopic: (n=1) at 9 wks gestation • Live Births: (n=5) • **Follow-up:** NR	• **A/E:** NR

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Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/ Follow-up	Adverse Events/ Complications
Pryor, 2001, US (Ref ID 439)	• Enrolled/evaluated: 11 couples/ n=11 couples • % male: 50% of couples • Race/ethnicity: NR • Age: NR • Level of Injury: NR • ASIA Level: NR • Duration since injury: NR • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: quadriplegic men with SCI presented at Abbott Injury Fertility Program over 3 y, who desired paternity • Exclusion: NR • **Quality Assessment:** 10/19 (+) reported	• **Pharmacologic:** • Drug name/Dose/ Admin: nifedipine to prevent headache & autonomic dysreflexia; 50 mg clomiphene citrate on d 5 through 9 of menstrual cycle to enhance female partner's ovulatory cycle; hCG, 10 000 IU, administered when dominant follicle 15-20 mm & estradiol range of each follicle 200-300 pg/ml)/ Oral sodium bicarbonate • **Device:** Electrical Stimulation • Amplitude: 0-10 V for 1st & 2nd stimulation, 15-29 V, 20-30 V, & 15-20 V for subsequent stimulations • Frequency: NR • Mode/Admin. Route: 30 sec stimulation followed by 45 sec rest. Repeated stimulations administered for second time. Following stimulations admin with higher voltages • **Other Device:** Vibrator • Type: Acuvibe 6002 • Manufacturer; Brookston • **Surgical:** NR • **Procedure**: • Bladder catheterization: irrigation with Ham's F-10 solution • -alkalinization by oral sodium bicarbonate solution for 36-48 h • Epididymal aspiration (MESA/PESA): NR	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: motile SpC affected by sperm prep technique. Mean no. of progressively motile sperm available for insemination S lower ($p<0.005$) in protocol 1 (3.3± 0.8), than in protocols 2 & 3 (17.5 ± 6.0 mln & 12.8 ± 5.8) mln).	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde

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Pryor, 2001, US (cont'd) (Ref ID 439)	• **See above**	• **See above**	• Testicular biopsy: NR • **Behavioural**: NR • **Laboratory techniques** (n=11 couples): • Donor sperm insemination: in protocol 2 :32-34 h after infection of hCG; in protocol 3: 38-40 h after injection of hCG • Sperm preparation: • -swim-up technique in (n=11) • -sperm WASH in (n=25) • -density gradient in (n=8) • -sperm incubation in (n=8) • Intrauterine insemination: In Protocol 1: 24 h after LG surge detection in non-stimulated cycles (self-monitored by pts); IVF in (n=1)	• Pregnancy rates: no pregnancy in protocol 1, 6 out of 10 pregnancies in protocol 2; 2 out of 4 pregnancies in protocol 3 • Live Births: (n=8/11) (73%) • **Follow-up:** NR	• **See above**

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde

Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Rawicki, 1991, Australia (Ref ID 655)	• Enrolled/evaluated: n=39 SCI (& their partners)/ n=38 • % male: 50% of couples • Race/ethnicity: NR • Age: NR • Level of Injury: n=35 C4-L5 • ASIA Level: NR • Duration since injury: NR • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** 5 y • **Eligibility Criteria:** • Inclusion: Pts recruited since 1985 • Exclusion: NR • **Quality Assessment:** 7/19 (+) reported	• **Pharmacologic:** • Drug name: physostigmine (SP) following admin. of an peripherally actin anticholinergic agent i.e. Buscopan (40 mg i.m.) tx of side effects: " Labetolol 100mg p.o. or Nifedipine 10 mg p.o. 30 m prior to EJ in event of autonomic dysreflexia (in all C7 or above when BP>40/30; systolic BP>150)" • Dose SP: NR • Duration: NR • Schedule: NR • Mode/Admin. Route: combined with ES/VS • **Device:** Electrical stimulator • Amplitude: 30 V • Frequency: 10 Hz • Mode/Admin. Route: through a rectal probe, to stimulate sympathetic nerves to seminal vesicles & ampulla of vas deferens causing semen emission • **Other Device:** Vibrator • Frequency: 80 Hz • application: glans of frenulum • Mode/Admin. Route: in combination with ES & SP • **Surgical:** NR • **Procedure**: NR • **Behavioural:** • Type: masturbation • Duration: NR • Frequency: NR • **Laboratory techniques:** • IVF & donor egg (n=1)	• **Outcomes:** • Measures of Fertility Rates: • EJ Rates: High chance of obtaining semen in men with lesions at T8 or above: AG in (n=18), RG in (n=3); in 3 of 10 SCI T10-12 semen also obtained • Pregnancy rates: 8 pregnancies in 6/15 couples • **Follow-up:** NR	• A/E: • Systemic: Autonomic Dysreflexia in pts with lesions at or above C7 following EEJ & VE. Superficial trauma resulting in bruising in one man & ulcer in another following VE. Following Superficial Physostigmine (SP) blurring of vision with Buscopan in 4 of 5, nausea & vomiting in 2 of 5, & in 2 of 5 marijuana like highs lasting up to 1 h

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde; EEJ = electro ejaculation

Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Rutkowski, 1995, Australia (Ref ID 959)	• Enrolled/evaluated: n=70/ n=70 • % male: 100 % • Race/ethnicity: NR • Age: 30 (19-59) y • Level of Injury: n=36 C1-C8; n=19 T1-T9; n=15 T10-L2 • ASIA Level: NR • Duration since injury: 6 (3 mo-2) y • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** data collection period: 1988-1994 • **Eligibility Criteria:** • Inclusion: SCI pts assessed between 1988-1994 at Royal North for enhancement/fertility issues • Exclusion: NR • **Quality Assessment:** 9/19 (+) reported	• **Pharmacologic:** NR • **Device:** Electrical stimulator (n=34) 9/34 failed to ejaculate with VS • Amplitude: voltage of 22-30 • Frequency: 10 or 50 Hz • Mode/Admin. Route: 3 cycle for duration of 45 s • **Other Device:** Vibrator (n=36) • Type: NR • Mode/Admin. Route: 3.5 m stimulation with 1 m rest repeated 3 times for lesions above T10 • **Surgical:** NR • **Procedure:** • Bladder catheterization: 3 techniques: Clean intermittent self-catheterization (CISC); indwelling urethral catheter (IDC) or suprapubic catheter (SPC); drainage without a catheter (i.e. voiding by reflex or staining) • **Behavioural:** NR • **Laboratory techniques:** NR	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: Neurological level ($p<0.0072$) & method of bladder management ($p<0.0115$) found to be S predictors of presence or absence of spermatozoa in samples. No df between catheters & non-catheter grp across 3 neurological levels (C1-8, T1-9, & T10 & below) • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde

Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Sarkarati, US, 1987 (Ref ID 985)	• Enrolled/evaluated: n=34/ n=34 • % male: 100 • Race/ethnicity: NR • Age: 16-36 y • Level of Injury: n=14 C5-6; n=13 T1-9; n =7 T10-L3 • ASIA Level: NR • Duration since injury: (n=11)<6 mo • Previous fertility: NR • Dropouts: n=5 • Lost in follow-up: • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** 5 y • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 10/19 (+) reported	• **Pharmacologic**: **NR** • **Device**: Vibrator (n=33) • Amplitude: 1.6-2.4 mm for 3.5 m on, 1.6-2.4 off • Frequency: 80Hz • Mode/Admin. Route: max of 3-4 cycles • **Other Device:** Electrostimulator (n=26) • Type: Soft silicone glove finger • Manufacturer: C.M. & rew 43 L&croft Rd, London, Engl. • Amplitude: 80-90 V • Frequency: 15/30 cycle/sec • Mode/Admin. Route: pain prevented ES in (n=4) (Brindley's technique) • **Surgical:** NR • **Procedure:** NR • **Behavioural:** NR • **Laboratory techniques:** NR	• **Outcomes**: • Measures of Fertility Rates: • Seminal Parameters: AG semen from VE in (n=7) & from EEJ in (n=8) : SpC range 0-250 mln/mL; Semen volume, range 1cc to 7cc in VE vs. 0.5-5 cc in EE; Normal Morphology ranges 7-250 mln in VE vs. 8-220 mln in EE • EJ Rates: VE (n=33) resulted in AG in 7 & RG in 1; EEJ resulted in AG in 8 & RG in 9 of 22. No response to VE or EEJ obtained in 5 of 34 & in 4 pain prohibited EEJ. • **Follow-up:** NR	• **A/E:** • Local: n=4 pain prohibited EEJ. • Systemic: Minor headache & /or Δ in BP 20-40 mm. Hg) observed n=10 with SCI<6 mo

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Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/ Quality Assessment	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Siösteen 1990, Sweden (Ref ID 979)	• Enrolled/ evaluated: n= 32/ n=33 • % males: 100% • Race/ethnicity: NR • Age (mean & range of male & partner) • Level of Injury: C4-L1 • ASIA Level: NR • Duration since injury: 2 (1-23) y • Previous fertility: NR • Drop-outs: n=6 • Lost to follow-up: NR • Number of sites: 1 • Funding: grants from Norrbacka-Eugenia Foundation; National Association of People Disabled by Road Accidents; Poliomeyelitis; Ted Söderlund Foundation; Greta & Einar Asker Foundation	• **Study Design:** NCS • **Duration:** 6 ms • **Eligibility Criteria:** • Inclusion: NR • Exclusion: injury <6 mo • **Quality Assessment:** 11/19 (+) reported	• **Pharmacologic:** NR • **Device:** Vibrator (Relax/Ling 201) (n = 29) • Amplitude: 1.5 mm/ 2.5 mm • Frequency: 100 Hz/ 80 Hz • Mode/Admin. Route: 3.5 m VS -1.5 m rest • **Other Device:** Electrostimulator (n=3) • Type: NR • Voltage: up to 80 V • Frequency: 15-30 Hz • Mode/Admin.: obturator nerve site , ES continued for up to 40 sec • **Surgical:** NR • **Procedure:** NR • **Behavioural:** NR • **Laboratory techniques:** NR	• **Outcomes:** • Seminal Parameters:4-6 ms of wkly VS in 16/22 pts with AG EJ resulted in a rise of semen volume & of fructose & acid phosphate levels in seminal plasma, suggesting improved function of seminal vesicles & prostate; sperm penetration capacity (SPC) showed strong evidence of long term stimulation effect (normal SPC in 4 pts pre- tx vs. 11 pts post-tx) • EJ Rates: AG in 22/32, RG in 7/32 ; no EJ in 3 pts • **Follow-up:** NR	• **A/E:** • Systemic: headache; rise in BP(tx: repositioning; 6.5 mg dihydralazine)

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Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Sonksen, 1994, Denmark (Ref ID 327)	• Enrolled/evaluated: n=66: Population I n=25; Population II n=41/ n=66 • % male: 100 % • Race/ethnicity: NR • Age: Population I: 27 (19-42) y, Population II: 29 (18-44) y • Level of Injury: Pop I - C3-L1, Pop II - C2-L1:(total of n=44 with complete lesion) • ASIA Level: NR • Duration since injury: Pop I: Range 0.6-39 y, Pop II: Range 0.2-27 y • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** NR • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 9/19 (+) reported	• **Pharmacologic** (n=9): • Drug name: glycerine nitrate • Dose: 0.5 mg • Duration: NR • Schedule: NR • Mode/Admin. Route: sublingually • **Device**: Vibrator A • Amplitude: 0-10 mm peak to peak • Frequency: 0-120 Hz • Mode/Admin. Route: vibrator held steady against frelunum for max of 3 m & 1 m rest. Cycle repeated for max of 6 times (6 cycle completed for all pts) • **Other Device**: Vibrator B • Amplitude: 1.5 mm peak to peak • Frequency: stationary at 100 Hz • Mode/Admin. Route: same as vibrator A • **Surgical:** NR • **Procedure:** NR • **Behavioural:** NR • **Laboratory techniques:** NR	• **Outcomes**: • Measures of Fertility Rates: • Seminal Parameters: • EJ Rates: in (n=58) of 66 (88%): AG response in PVS: 62%, RG response in PVS: 26%, no EJ in (n=8). No relation between level of cord lesion, completeness, & stimulation time required to obtain AG EJ. No relation between EJ response & completeness of cord lesion, age or y since lesion. • **Follow-up**: NR	• **A/E:** • Local: NR • Systemic: Light headache during AG EJ in (n=4)

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Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/ Follow-up	Adverse Events/ Complications
Sonksen, 1997, Denmark (Ref ID 531)	• Enrolled/evaluated: n=28 couples/ n=28 couples • % male: 50 % of couples • Race/ethnicity: NR • Age: men: 31(24-42) y, female partners: 29 (19-39) y • Level of Injury: C2-L4; (n=26 above T10) • ASIA Level: NR • Duration since injury: 8 (1-22) y • Previous fertility: NR • Dropouts: n=0	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 9/19 (+) reported	• **Pharmacologic**: • Drug name: (SCI >T6) nifedipine • Dose: 10 mg • Duration: NR • Schedule: 15 m pre PVS & EEJ • Mode/Admin. Route: 15 m prior to PVS or EEJ (prevention of autonomic dysreflexia) • **Device**: Electrostimulator • Amplitude: max voltage 30 V • Frequency: 600 mA • Mode/Admin. Route: median total n of 20 stimulation (range, 16-28) • **Other Device**: Vibrator • Frequency: NR • Mode/ Admin. Route: stimulation periods of up to 3 m & 2 m rest for up to 6 cycles • **Surgical**: NR • **Procedure**: • Bladder catheterization • with 10 mL of a sperm-friendly medium via a 14 F silicone catheter pre/post EEJ • Epididymal aspiration (MESA/PESA): NR • Testicular biopsy: NR • **Behavioural**: NR	• **Outcomes**: • Measures of Fertility Rates: • Seminal Parameters: total SpC: median 65 mln, range 0.1-480 mln; sperm concentration: median 43 mln, range 0.2-120 mln; SpMot: median 13%, range 1%-60%; Sperm normal morphology: median 34%, range 15-55% • EJ Rates: 79% with PVS & 21% with EEJ • Pregnancy rates: 35.7% (10/28) • Miscarriage/ectopic: none • Induced abortion: none • Live Births: (n=9) • Singletons: (n=7)	• **A/E:** NR

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Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/ Follow-up	Adverse Events/ Complications
Sonksen, 1997, Denmark (cont'd) (Ref ID 531)	• Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **See above**	• **Laboratory techniques:** • Donor sperm insemination • Sperm preparation: NR • Intrauterine insemination: in (n=3); 38 h following hCG injection. In these cases clomiphene citrate admin. 50-100 mg /d, on d 3 to 7 of cycle • IVF: in (n=1) treated with gonadotropin-releasing hormone (Gn-RG) analogue buserelin, followed by stimulation of human menopausal gonadotropins • Intracytoplasmic sperm injection; in 2 (drug admin. as IVF) • Self-insemination: in (n=4)	• Multiples: 1 set of twins • **Follow-up**: 16 couples performed home PVS & vaginal self-insemination. Four couples achieved pregnancy with delivery of four babies • Length: 2 y	• **See above**

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Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Taylor, 1999, Australia (Ref ID 500)	• Enrolled/evaluated: n=19 couples/ n=19 couples • % male: 50% of couples • Race/ethnicity: NR • Age: NR (24-44) y • Level of Injury: n=9 C4-C6; n=10 T4-T12/L1 • ASIA Level: NR • Duration since injury: 9.3 (1-24) y • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 7/19 (+) reported	• **Pharmacologic:** NR • **Device:** Vibrator (n=19) • Amplitude: NR • Frequency: NR • Mode/Admin. Route: NR • **Other Device:** Electrostimulator (n=10) • Type: NR • Manufacturer: NR • **Surgical:** NR • **Procedure:** • Bladder catheterization • -with instilling of 20 mL phosphate buffered Tyrode tissue culture medium pre EEJ • Epidydimal aspiration (MESA/PESA): NR • Testicular biopsy: NR • **Behavioural:** NR • **Laboratory techniques:** • Donor sperm insemination • Sperm preparation • - wash in (n=14) • - DG in 15 • Intrauterine insemination: (1st tx) in 15 couples by daily monitoring of serum LE hormone; multiple attempts in all but 1 • IVF & embryo transfer: in cases with poor SpC (n=1) • Intracytoplasmic sperm injection: in 8 couples other methods had failed due poor sperm quality. • GIFT: (2nd choice) in 7 couples	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: SpMot recorded as poor in SCI period of 1-24 y & consistently low 18 y post SCI • Pregnancy rates: per tx cycle in pts having; Intrauterine insemination 12% (11/92); gamete intra-Fallopian transfer 38.9% (8/18); intracytoplasmic sperm injection 19.2% (5/21). Success rate higher in SCI ≥ 10 y, 20/23 (87%) compare to rate of 22% in SCI ≤ 10 y • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde

Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
VerVoort, 1988, US (Ref ID 982)	• Enrolled/evaluated: n=7/ n=7 • % male: 100% • Race/ethnicity: NR • Age: 29 (21-38) y • Level of Injury: C4-C7 • ASIA Level: A-C(no designation) • Duration since injury: 8.8 (0.5-19) y • Previous fertility: NR • Dropouts: n=1 • Lost in follow-up: NR • N of sites: 1 • Funding: NIDRR & PMRERF	• **Study Design**: NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: BP elevation during EEJ • Exclusion: NR • **Quality Assessment:** 10/19 (+) reported	• **Pharmacologic** (n=6): • Drug name: Nifedipine • Dose: 10 mg • Duration: NR • Schedule: 10-15 m pre EEJ • Mode/Admin. Route: NR • **Device:** Electrostimulator (n=6) • Amplitude: without medication 125-300 mA; with medication: 175-500 mA • Frequency • Mode/Admin. Route • **Other Device:** NR • **Surgical:** NR • **Procedure:** NR • **Behavioural:** NR • **Laboratory techniques:** NR	• **Outcomes:** • Measures of Fertility Rates: • EJ Rates: Repeat EEJ attempts performed at least 2 wks apart. EEJ (AG or RG) in 3 of 9 (33%) without nifedipine, & 19 of 22 (86.4%) with nifedipine • Additional Outcome: S increase in mean maximum current delivered without nifedipine (367±112) mA vs. with nifedipine 172±69 mA, ($p<0.05$); Increase in current delivery resulted in greater success at sperm collection • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; ∆ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde; NIDRR = National Institute on Disability Research & Rehabilitation; EEJ = electro ejaculation; BP = blood pressure; PMRERF = Physical Medicine & Rehabilitation Education & Research Foundation

Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Wang, 1992 Taiwan (Ref ID 973)	• Enrolled/ evaluated: n=25/ n=25 • % males: 100% • Race/ethnicity: NR • Age : 31(19-43) y • Level of Injury: C5-T12 (all complete) • ASIA Level: NR • Duration since injury: 6 (0.3-14) y • Previous fertility: NR • Drop-outs: n=0 • Lost to follow-up: NR • Number of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** Aug 1990- May 1991, prospective study • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 11/19 (+) reported	• **Pharmacologic:** NR • **Device:** Electrostimulator(Seager Model) (n = 25) • Amplitude: 434±54 mA/ 21.7±2.7 V(15-25 V) • Frequency: max of 60 stimulations • Mode/Admin. Route: rectal probe; left lateral ducubitus position • **Other Device:** NR • **Surgical:** NR • **Procedure** (n=25): • Bladder catheterization • -with/without alkalinization: blastic catheter & instillation with 20 mL ham's F-10 solution • Epididymal aspiration (MESA/PESA): NR • Testicular biopsy: NR • **Behavioural:** NR • **Laboratory techniques:** NR	• **Outcomes:** • Seminal Parameters: SpMot <5% in most cases; no motile spermatozoa in 6/21; no S correlation in sperm quality & quantity with method of bladder management, age, level of injury or injury period; improved sperm analysis in 14/21 in later attempts of ES • EJ Rates: 21/25; RG in 12/21; pure AG in 9/21; • Infection rates: all pts had at least one episode/yr of UTI • **Follow-up:** • Length: wkly stimulation • Duration: NR • Results: in 19 occasions weekly ES resulted in deterioration of sperm quality (SpC reduction of 52±23%, total motile SpC reduced by 61± 27%)	• **A/E:** • Local: 4/25 (1, T11; 3, T12) local pain during ES • Systemic: autonomic dysreflexia in 2/25 (10 mg sulingual nifedipine) ; mild rectal edema in 2/25; petechia in 3/25

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde

Evidence Table 1: Non-comparative case series studies of fertility rates in pts with spinal cord injury (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/ Quality Assessment	Intervention (e.g., Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Warner, 1986, US (Ref ID 1339)	• Enrolled/ evaluated: n=31/n=31 • % males: 100% • Race/ethnicity: NR • Age: NR • Level of Injury: T2-L3 • ASIA Level: NR • Duration since injury: NR • Previous fertility: NR • Drop-outs: (n=9) intolerant to ES • Lost to follow-up: NR • Number of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 3/19 (+) reported	• **Pharmacologic:** NR • **Device**: Electrical stimulator Model 3(n = 31) • Amplitude: NR • Frequency: up to 100 Hz • Current: 160-200 mA (0.29-0.36 mA/mm2) • Mode/Admin. Route: rectal probe ES; semen collected by Foley catheter • **Other Device:** NR • **Surgical:** NR • **Procedure:** NR • **Behavioural:** NR • **Laboratory techniques:** NR	• **Outcomes:** • Measures of Fertility Rates: NR • Seminal Parameters: NR • EJ Rates: 22/31 tolerated current of 160-200 mA sufficient to induce erection; 14/22 AG; 7/22 RG only; 9/22 RG+AG (2/22 no emission) • Erection: 2/22 no erection with emission; 1/22 erection with no emission & 1/22 produced neither; 16/22 produced both erection& emission. • Pregnancy rates: NR • Live Births: NR • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mA = milliamphere; mg = milligrams; µg = microgram; V = volts; Hz = hertz; mln = millions; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; AG = antegrade; RG = retrograde

Evidence Table 2: Case-control studies of fertility rates in patients with SCI.

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/Device/ Behavioural/Surgical/Other)	Outcomes/Follow-up	Adverse Events/ Complications
Brackett, 1994, US (Ref ID 1208)	• Enrolled/ evaluated: total (n=107): SCI n=66; ctrl n=21, non-injured normospermic men; non-injured infertile n=20/ n=NR • % male: 100% • Race/ethnicity: NR • Age: SCI 30.8 (19-47) y; non-injured. normospermic 26.5 (19-40) y; non-injured. Infertile 34.2 (29-40) y • Level of Injury: 36% cervical, 56% thoracic, 8% lumbar, 39% quadriplegic (incomplete), 61% paraplegic (43% complete, 57% incomplete) • ASIA Level: NR • Duration since injury: 8.1 (1-25) y	• **Study Design:** Case-control Study • **Duration:** NR • **Eligibility Criteria:** • Inclusion: healthy • Exclusion: presence or absence of pyuria • **Quality Assessment:** 7 * (NOS)	• **Pharmacologic:** NR • **Device:** (Vibrator Oster) (SCI n=66) • Amplitude NR • Frequency NR • Mode/Admin. Route: 5 m vibration & 1 m rest; repeated if no EJ occurred • **Other Device** (SCI n = 66): • Type: Electroejaculator • Manufacturer: NR • **Surgical:** NR • **Procedure** (SCI n=66): • Bladder catheterization with/without alkalinization with 25-50 mL sperm washing medium added to bladder • Epididymal aspiration (MESA/PESA): NR • Testicular biopsy: NR • **Behavioural** (ctrls n=41): • Type: masterbation • Duration: NR • Frequency: NR	• **Outcomes:** • Measures of Fertility Rates: • Semen analysis: SpC, SpMot & % normal SpMor (AG & RG in SCI / AG in non-injured infertile & normospermic grps.). SpC: lower counts in IC (57.1: 0-75 mln) vs. SCI (231. 0-1 billion)($p < 0.01$), & to NC (231.7: 19 mln to 1 billion)($p < 0.02$). SpMot: S higher % of SpMot in NC (59.6: 4.6 %, range: 20-92 %) vs. SCI (27.2 +/- 3.7 %, range: 1-70 %)($p < 0.0002$), & also vs. IC (26.6 +/- 6.8 %, range: 20-90 %)($p < 0.0005$). SpMor: S dfs in SpMor in SCI & NC: SCI (60.7 +/- 3.5 %, range: 20-88 %) vs. NC (70.7 +/- 2.0 %, range: 56-89 %)($p < 0.05$). No S df between mean SpMor in SCI & IC or IC & NC	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; FSH = follicle-stimulating hormone; LH = luteinizing hormone; AG = antegrade; RG = retrograde; mln = millions; NOS = Newcastle Ottawa Scale

Evidence Table 2: Case-control studies of fertility rates in patients with SCI (cont'd).

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/Device/ Behavioural/Surgical/Other)	Outcomes/Follow-up	Adverse Events/ Complications
Brackett, 1994, US (cont'd) (Ref ID 1208)	• Previous fertility: infertile pts (n=20): abnormal semen analysis due to varicocele, testicular failure, ejaculatory dysfunction & idiopathic infertility. • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: Miami Project to Cure Paralysis	• See above	• **Laboratory techniques** (n=107): • Measurement of serum levels of hormones by radioimmunoassay using Amerlex LH radioimmunoassay kit or by micropartical enzyme immunoassay IMX system (ref range: 4-23 mIU/mL)	• **Additional outcomes:** Incidence of endocrine outliers: 42% of SCI had 1 or more hormone outliers. Incidence of outliers in SCI of T8 & T10 slightly > vs. SCI of other levels (C1 to C7 - $p < 0.01$, T1 to T7 - $p < 0.01$, & T11 to L5 - $p < 0.05$) - In SCI, SpC slightly & inversely correlated to levels of FSH ($r = -0.400$, $p < 0.02$) – IC pts with elevated FSH had SpCs ranging from 0 to 5 mln; Hormone levels: LH levels in SCI (22.1 +/- 2.8 %) slightly lower than IC (23.3 +/- 4.8 %)($p < 0.05$); in NC (33.0 +/- 4.5 %), mean did not differ from SCI & IC. • **Follow-up:** NR	• See above

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; FSH = follicle-stimulating hormone; LH = luteinizing hormone; AG = antegrade; RG = retrograde; mln = millions; NOS = Newcastle Ottawa Scale

Evidence Table 2: Case-control studies of fertility rates in patients with SCI (cont'd).

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/Device/ Behavioural/Surgical/Other)	Outcomes/Follow-up	Adverse Events/ Complications
Brackett, 1994, US (Ref ID 1185)	• Enrolled/ evaluated: n=87 (SCI n=66, non-SCI, ctrl n=21)/ n=87 • % male: 100% • Race/ethnicity: NR • Age: SCI 30.8 (19-47) y; ctrl 26.5 (19-40) y • Level of Injury: 36% cervical, 56% thoracic, & 81% lumbar • ASIA Level: NR • Duration since injury: 8.1 (1-25) y • Previous fertility: NR • Dropouts: (n=24) • Lost in follow-up: • N of sites: 1 • Funding: Miami Project to Cure Paralysis	• **Study Design:** Case-control Study • **Duration:** 25 mo • **Eligibility Criteria:** • Inclusion: good general health in SCI & ctrl no hx of fertility problem SCI >1y post-injury • Exclusion: NR • **Quality Assessment:** 8 * (NOS)	• **Pharmacologic:** NR • **Device:** (Vibrator & Electrostimulator in (n=66) • Amplitude: NR • Frequency: NR • Mode/Admin. Route: VS: in seated position, applied to penis for 5 m if no EJ, 1 m rest & resumed for additional 5 m • **Other Device** (n=87): • Type: Diatek Model 600/ digital oral & scrotal temperature measurements • Manufacturer: NR • **Surgical:** NR • **Procedure**: • Bladder catheterization • -with/out alkalinization in all SCI using 25-50 mL of sperm washing medium**.** • **Behavioural:** • Type: self-masturbation following 3-7 d of abstinence	• **Outcomes:** • Measures of Fertility Rates: • Semen analysis: Total SpC similar in SCI & ctrl (mean +/- SEM: 278.9 (67.4) (range: 19.2 mln - 1.1 mln) & 231.4 (53.9) (2.3 mln - 2.0 mln), respectively. Mean SpMot slightly lower in SCI (13.7) (0-55 %) vs. ctrl (61.3) (20-92%); % of normal forms per ejaculate. Slightly lower in SCI (47.2: 20-72%) vs. ctrl (72.4) (56-94%); NS dfs in SpC, SpMot, SpMor in To, Ts, Td (Oral minus Scrotal) of each grp. In each grp, To, Ts & Td each related to serum LH & FSH levels no S; Not generalized scrotal thermoregulatory dysfunction in SCI men, scrotal temperature not appear to contribute to poor semen quality in SCI men & elevated gonadotropin levels not related to elevated scrotal temperatures in SCI men, as reported in non-injured, infertile men. • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; ∆ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; FSH = follicle-stimulating hormone; LH = luteinizing hormone; AG = antegrade; RG = retrograde; mln = millions; NOS = Newcastle Ottawa Scale

Evidence Table 2: Case-control studies of fertility rates in patients with SCI (cont'd).

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/Device/ Behavioural/Surgical/Other)	Outcomes/Follow-up	Adverse Events/ Complications
Brackett, 1994, US (cont'd) (Ref ID 1185)	• See above	• See above	• **Laboratory techniques** (n=66): • Donor sperm insemination: NR • Sperm preparation: NR erum hormone measured by radioimmunoassay (RIA) using Amerlez LH RIA kit or microparticle enzyme immunoassay (MEIA) using IMx system.	• See above	• See above

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; ∆ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; FSH = follicle-stimulating hormone; LH = luteinizing hormone; AG = antegrade; RG = retrograde; mln = millions; NOS = Newcastle Ottawa Scale

Evidence Table 2: Case-control studies of fertility rates in patients with SCI (cont'd).

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/Device/ Behavioural/Surgical/Other)	Outcomes/Follow-up	Adverse Events/ Complications
Brackett, 1997 US (Ref ID 1135)	• Enrolled/ evaluated: total n=19; SCI n=10; ctrl n=9/ n=19 • % male: 100% • Race/ethnicity: NR • Age: SCI 33.1 (2.9) y; healthy ctrl 30.3 (1.8) y • Level of Injury: C4-C5 (n=5), T5-T6 (n=4), T12 (n=1) • ASIA Level: NR • Duration since injury: 1 (2.4) y • Previous fertility: no hx of infertility in ctrl grp • Dropouts: n=0 • Lost in follow-up: n=19 • N of sites: 1 • Funding: State of Florida Specific Appropriation No. 610 for Spinal Cord Research; Miami Project to Cure Paralysis	• **Study Design:** Case-control Study • **Duration:** NR • **Eligibility Criteria:** • Inclusion: no medication known to affect semen quality taken within 6 mo prior to study; SCI grp > 1 y post injury • Exclusion: NR • **Quality Assessment:** 8 * (NOS)	• **Pharmacologic:** NR • **Device:** Vibrator (n = 4) • Amplitude: NR • Frequency: NR • Mode/Admin. Route: NR • **Other Device** (n=6): • Type: Electrostimulator • Amplitude: starting at 1 V & increased to an average of 10 V • **Surgical (n = x):** NR • Penile Implants • **Procedure (n=x):** NR • Bladder catheterization • -with/without alkalinization: NR • Epidydimal aspiration (MESA/PESA): NR • Testicular biopsy: NR • **Behavioural (ctrl n=9):** • Type: masturbation following 3-7 d of abstinence • Duration: NR • Frequency: NR • **Laboratory techniques (n=19):** • Sperm preparation: 15-20 m liquification of semen at room temperature. SpMot & viability at time of 0. Specimens then divided into 2 aliquots, 1 at room temp. (23^{o}C) & 1 at body temp. (37^{o}C). SpMot & viability for each at 2, 4, 6 & 8 hrs after time 0)	• **Outcomes:** • Measures of Fertility Rates: Semen analysis**:** Effect of temperature on sperm characteristics baseline & % decrease in SpMot: S > decrease in SpMot in specimens from SCI vs. ctrls at 4, 6 & 8 hrs vs. time 0. S dfs at all time points at incubated temp. Heat did not affect rate of degradation in motility in ctrl specimens but hastened degradation in motility in specimens of SCI. % decrease in rapid linear SpMot: S > decrease in rapid linear motility in specimens from SCI vs. ctrls at 6 & 8 hrs after collection at room temp., & at all time points at incubated temp. Heat did not slightly affect rate of degradation in rapid linear motility in ctrl specimens. Heat had S effect on specimens from SCI. Decrease in rapid linear motility by 50% within first 2 hrs, & by 8 hrs 0% rapid linear SpMot • **Follow-up**: NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; FSH = follicle-stimulating hormone; LH = luteinizing hormone; AG = antegrade; RG = retrograde; mln = millions; NOS = Newcastle Ottawa Scale; V = volt

Evidence Table 2: Case-control studies of fertility rates in patients with SCI (cont'd).

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/Device/ Behavioural/Surgical/Other)	Outcomes/ Follow-up	Adverse Events/ Complications
Hirsch, 1991, US (Ref ID 976)	• Enrolled/ evaluated: n=29: SCI n=14; ctrl n=15/ n=29 • % males: 100% • Race/ethnicity: NR • Age: SCI 28.4 (17-42) y; ctrl 36 (29-51) y • Level of Injury: cervical, thoracic, lumbar (not specific) • ASIA Level: NR • Duration since injury: NR • Previous fertility: SCI 2/14 previous pregnancies pre-injury • Drop-outs: n=0 • Lost to follow-up: 0 • N of sites: 1 • Funding: Regional Spinal Cord Injury Center of the Delaware Valley; NIDRR	• **Study Design:** Case-control study • **Duration:** 4-6 mo • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 7 * (NOS)	• **Pharmacologic:** NR • **Device:** NR • **Other Device:** NR • **Surgical:** • Biopsy • **Procedure** (n=14): • Bladder catheterization; NR • Epididymal aspiration (MESA/PESA): NR • Testicular biopsy: in n=14 tubular diameter & tubular wall thickness measured by AO fialr micrometer eye pieces (Model 426B) • **Behavioural:** NR • **Laboratory techniques:** • Donor sperm insemination • Sperm preparation (swim-up & discontinuous gradient • Intrauterine insemination • IVF • Intracytoplasmic sperm injection • Embryo cryopreservation • Sperm cryopreservation: ejaculated & biopsy	• **Outcomes:** • Measures of Fertility Rates: • Seminal Parameters: SCI pts showed S lower mean SpC & higher Sertoli cell count vs. ctrls ($p<0.05$). No df in either mean internal tubular diameter or tubular wall thickness noted. No correlation between tubular wall thickness & mean sperm or Sertoli cell count for either grp. Sertoli cell-to-spermatid ratio S > for SCI grp ($p<0.0001$). Within SCI grp neither micrometric parameters nor Sertoli cell-to-sperm ratio showed any relationship to level, duration, or degree of injury. • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; FSH = follicle-stimulating hormone; LH = luteinizing hormone; AG = antegrade; RG = retrograde; mln = millions; NOS = Newcastle Ottawa Scale; NIDRR = National Institute of Disability Research & Rehabilitation

Evidence Table 2: Case-control studies of fertility rates in patients with SCI (cont'd).

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/Device/ Behavioural/Surgical/Other)	Outcomes/Follow-up	Adverse Events/ Complications
Hirsch, 1994, US (Ref ID 965)	• Enrolled/evaluated: n=16: SCI n=10,vasectomized men n=6/ n=16 • % male: 100% • Race/ethnicity: NR • Age: 30.1 (5.2) y; ctrl 37.2 (6.7) y • Level of Injury: NR • ASIA Level: NR • Duration since injury: 6-8 y • Previous fertility: n=6 vasactomized men (mean interval for vasectomy (8.8) y • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: Regional Spinal Cord Injury Center of the Delaware Valley; NIDRR	• **Study Design:** Case-control Study • **Duration:** NR • **Eligibility Criteria:** • Inclusion: ctrl grp: within range of age & duration since presence of outcome (infertility) to SCI grp, no hx of infertility • Exclusion: NR • **Quality Assessment:** 4 * (NOS)	• **Pharmacologic:** NR • **Device:** NR • **Other Device :** NR • **Surgical:** NR • **Procedure** (n=16): • Testicular biopsy: 10 randomly selected round seminiferous tubules analyzed, & mean tubular thickness measured from photomicrographs obtained after magnification with enlargement of print. • Histometric values: mean concentration of late spermatids /tubule; mean ratio of spermatids to Sertoli cells /tubule; tubular wall thickness • **Behavioural:** NR • **Laboratory techniques:** • DNA flow cytometric analysis	• **Outcomes:** • Measures of Fertility Rates: • Biopsy results**:** SpMot & viability measured at 0, 2, 4, 6 & 5 hrs after semen collection. Both anatomical & functional obstruction of male genital tract exerts similar spermatogenic insult. In both cause of neurogenic infertility is more likely to be at post-testicular level. Spermatid/Sertoli cell ratio no S df between grps. Similar values for tubular wall thickness noted in both grps. No S dfs between grps in % of haploid, diploid & tetraploid cells. Mean % of haploid cells in tissue of vasectomized (54.2%) & SCI (47.4%) men comparable • **Follow-up**: NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) = negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; FSH = follicle-stimulating hormone; LH = luteinizing hormone; AG = antegrade; RG = retrograde; mln = millions; NOS = Newcastle Ottawa Scale; NIDRR = National Institute of Disability Research & Rehabilitation

Evidence Table 2: Case-control studies of fertility rates in patients with SCI (cont'd).

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/Device/ Behavioural/Surgical/Other)	Outcomes/Follow-up	Adverse Events/ Complications
Hou 1995, US (Ref ID 1180)	• Enrolled/evaluated: n=116: SCI n=12; non-SCI n=104/ n=NR • % male: 100% • Race/ethnicity: NR • Age: NR • Level of Injury: NR • ASIA Level: NR • Duration since injury: NR • Previous fertility: NR • Dropouts: NR • Lost in follow-up: NR • N of sites: 1 • Funding: Dr. Ralph & Marion C. Falk Medical Trust	• **Study Design:** Case-control Study • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 5 * (NOS)	• **Pharmacologic:** NR • **Device:** Vibrator • Amplitude: NR • Frequency: NR • Mode/Admin. Route: NR • **Other Device:** NR • **Surgical:** NR • **Procedure:** NR • **Behavioural** (n = 104**):** • Type: self- masturbation • Duration: NR • Frequency: NR • **Laboratory techniques** (n=116**):** • Sperm preparation: Aniline Blue Staining	• **Outcomes:** • Measures of Fertility Rates: • Semen analysis: % SpMot & % normal SpMor from SCI (36.5 +/- 6.8, 44.0 +/- 2.4) men slightly poorer than those from non-SCI men 70.5 (1.2), 50.8 (0.7) ($p < 0.01$); % of spermatozoa unstained by Aniline Blue not slightly different in non-SCI men 83.4 (1.1 %) vs. SCI men 79.7 (4.8 %) • **Follow-up**: NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) = negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; FSH = follicle-stimulating hormone; LH = luteinizing hormone; AG = antegrade; RG = retrograde; mln = millions; NOS = Newcastle Ottawa Scale

Evidence Table 2: Case-control studies of fertility rates in patients with SCI (cont'd).

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/Device/ Behavioural/Surgical/other)	Outcomes/ Follow-up	Adverse Events/ Complications
Martin 1983, US (Ref ID 1406)	• Enrolled/evaluated: n=20: SCI n=8; ctrl n=12/ n=20 • % male: 100% • Race/ethnicity: NR • Age: SCI NR (24-41) y; ctrl NR (23-26) y • Level of Injury: T3-T12 (n=3) T12-L1 (n=2) L2 n=1 • ASIA Level: NR • Duration since injury: (1-20) y • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NIMH	• **Study Design:** Case-control Study • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 4 * (NOS)	• **Pharmocologic:** NR • **Device: Rectal Probe Electrostimulator** • Amplitude • Frequency: 60 Hz, 20 Hz, & 0.25 Hz • Mode/Admin. Route: dorsal lithotomy position (after bowel movement) intact subjects & 1st 5 pts controlled current delivery by themselves • **Other Device:** NR • **Surgical:** NR • **Procedure:** NR • **Behavioural:** NR • **Laboratory techniques:** NR	• **Outcomes:** • Measures of Fertility Rates: • Erection: Erection elicited repeatedly in only 1 of intact pts, & no seminal emissions or EJs occurred. Use of 60 Hz & 20 Hz currents ineffective in eliciting erection & mean maximally tolerable current level for these frequencies, respectively, 29mA & 29 mA. Repositioning of probe ineffective in initiation of erection during stimulation • **Follow-up**: NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) = negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; FSH = follicle-stimulating hormone; LH = luteinizing hormone; AG = antegrade; RG = retrograde; mln = millions; NOS = Newcastle Ottawa Scale; Hz = hertz; mA = milliamps; NIMH = National Institute of Mental Health

Evidence Table 2: Case-control studies of fertility rates in patients with SCI (cont'd).

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/Device/ Behavioural/Surgical/other)	Outcomes/ Follow-up	Adverse Events/ Complications
Monga, 2001, US (Ref ID 947)	• **Enrolled/evaluated:** 7 SCI; 5 ctrls/NR • % males: 100% male • Race/ethnicity: NR • Age: (27-54) y • Level of Injury: all cervical (n=5 incomplete lesion) • ASIA Level: NR • Duration since injury: (5-31) y • Previous fertility: NR • Drop-outs: n=0 • Lost to follow-up: 0 • N of sites: 1 • Funding: American Paraplegia Society grant	• **Study Design:** Case-control Study • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 5 * (NOS)	• **Pharmacologic:** NR • **Device:** FERTI CARE Vibrator (6/7 SCI) • Amplitude: 2.5 mm • Frequency: 100 Hz • Mode/Admin. Route: NR • **Other Device:** NR • **Surgical**: • Penile Implants • **Procedure** (n=7): • Bladder catheterization • - without alkalinization • **Behavioural** (n = 5 ctrl, n=1 SCI): • Type : masturbation • Duration: NR • Frequency: NR • **Laboratory techniques**: NR	• **Outcomes:** • Seminal Parameters: Semen samples from men with SCI showed azoospermia (n=3) & severe asthenospermia (n=2). Majority (65%) of sperm from asthenospermic samples showed degenerative Δs & S axonemal defects. Incubation of normal sperm with SCI seminal plasma induced concentration-dependent decrease in SpMot (43%) accompanied by S drop in intracellular ATP content (33%). • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) = negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; FSH = follicle-stimulating hormone; LH = luteinizing hormone; AG = antegrade; RG = retrograde; mln = millions; NOS = Newcastle Ottawa Scale; Hz = hertz

Evidence Table 2: Case-control studies of fertility rates in patients with SCI (cont'd).

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/Device/ Behavioural/Surgical/other)	Outcomes/ Follow-up	Adverse Events/ Complications
Padron 1994 US (Ref ID 1197)	• Enrolled/ evaluated: n= 19: SCI n=9; ctrl n=10/ n=19 • % male: 100% • Race/ethnicity: NR • Age: SCI 30.2 (1.2) y; ctrl 24.3 (3.6) y • Level of Injury: NR • ASIA Level: NR • Duration since injury: mean: 6.2 (1.1) y • Previous fertility: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: Miami Project to Cure Paralysis	• **Study Design:** Case-control Study • **Duration:** NR • **Eligibility Criteria:** • Inclusion: good health >1 y post injury • Exclusion: NR • **Quality Assessment:** 4 * (NOS)	• **Pharmacologic (in SCI grp):** • Drug name: nifedipine • Dose: 30-40 mg • Duration: NR • Schedule: 15 m pre EJ in SCI • Mode/Admin. Route: in SCI with hx or autonomic dysreflexia • **Device: Vibrostimulator (n=5)** • Amplitude: NR • Frequency: 5 m vibration, repeated if no EJ occurred for 2nd 5 m after 1 m rest period EJ • Mode/Admin. Route: on frenulum on dorsal aspect for 5 m • **Other Device: Electrical Stimulator (n=4)** • Type: Seager Model 12 • Manufacturer: National Rehab Hospital, Washington D.C. • **Surgical**: NR • **Procedure:** NR • **Behavioural** (n = 10): • Type: masturbation • Duration: NR • Frequency: NR • **Laboratory techniques (n = 19):** • Sperm cryopreservation: EJ done for all ejaculated samples / freezing using Vapor only; Vapor + liquid nitrogen & liquid nitrogen only.	• **Outcomes:** • Measures of Fertility Rates: • Semen analysis: Mean % SpMot in fresh & thawed samples for each method of freezing in SCI S lower vs. ctrl pts; mean % SpMot in SCI: 17+/-6.8 mln vs. 210+/-5.4 mln in ctrls (p, 0.05); % drop in SpMot after freezing not S different in SCI & ctrl pts. Freezing by Vapor only superior for retention of motility vs. other methods of freezing. For ctrl pts mean % drop in motility S less with Vapor only vs. two other methods (<p=0.05 & p<0.002). % of sperm with rapid linear motility (%RL) not S different between SCI & ctrl for fresh or thawed samples. • **Follow-up**: NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; (-) = negative; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; IVF = in vitro fertilization; FSH = follicle-stimulating hormone; LH = luteinizing hormone; AG = antegrade; RG = retrograde; mln = millions; NOS = Newcastle Ottawa Scale

Evidence Table 3: Evidence from conference proceedings of fertility rates in patients with SCI.

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Elliott, 2000, ND (Ref ID 3013)	• Enrolled/ evaluated: 57/57 • % males: 50% of couples • Race/ethnicity: NR • Age: NR • Level of Injury: above T10 • ASIA Level: NR • Duration since injury: NR • Previous fertility: NR • Dropouts: NR • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** Abstract from conference proceeding – interventional (time series before/after trial) • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** NA	• **Pharmacologic**: NR • **Device: Vibrator** (n=26) • Amplitude: NR • Frequency: NR • Mode/Admin. Route: NR • **Other Device** (n=29): **Electrostimulator** • Type: NR • Manufacturer: NR • **Surgical**: NR • **Procedure**: NR • **Behavioral**: NR • **Laboratory techniques** (n=26; VS grp): • Donor sperm insemination: NR • Sperm preparation: NR • Intrauterine insemination: in 20% with/ without medication • IVF: in 50% of VS cases • Intracytoplasmic sperm injection: in 30% of VS cases • Embryo cryopreservation: NR • Sperm cryopreservation: NR	• **Outcomes:** • Pregnancy rates: 18/26 (69.2%) in VS grp; 34% in ES grp • Miscarriage/ectopic: NR • Live Births: 17/26 in VS grp; 11/29(24%) in ES grp • Singletons: NR • **Follow-up**: NR	• **A/E**: NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; m = minute; ctrl = control(s); grp = group; pbo = placebo; µg = microgram; mg = milligrams; tx = treatment; hx = history; ∆ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; A/E = adverse event; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; mln = millions; AG = antegrade; RG = retrograde; IVF = in vitro fertilization

Evidence Table 3: Evidence from conference proceedings of fertility rates in patients with SCI (cont'd).

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/Quality Assessment	Intervention (e.g., Pharmacologic/Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Loecher-Ernst, 1998, Germany (Ref ID 3020)	• Enrolled/ evaluated: n=229/127 couples evaluated for conception • % males: 100% • Race/ethnicity: NR • Age: NR • Level of Injury: NR • ASIA Level: NR • Duration since injury: NR • Previous fertility: NR • Drop-outs: NR • Lost in follow-up: NR • N of sites: NR • Funding: NR	• **Study Design:** Abstract from conference proceeding – interventional (time series before/after trial) • **Duration:** NR • **Criteria Eligibility:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** NA	• **Pharmacologic**: NR • **Device: Vibrator** • Amplitude: NR • Frequency: NR • Mode/Admin. Route: NR • **Other Device:** Electrostimulator • Type: NR • Manufacturer: NR • **Surgical**: NR • **Procedure**: NR • **Behavioral**: NR • **Laboratory techniques:** • Donor sperm insemination: NR • Sperm preparation: NR • Intrauterine insemination+ VS at home: in 28 couples • IVF: 8 couples • Implantation of alloplastic spermatocele: 27 cases • Embryo cryopreservation: NR • Sperm cryopreservation: NR	• **Outcomes:** • Measures of Fertility Rates: NR • Seminal Parameters: reduced motility & divergence in sperm count in all ejaculates; quality not improved with repeated stimulation; ES resulted in lower quality semen • Ejaculation Rates: semen was retrieved in 168/229 (73%); 161/168(96%) with VS; 7/168(4%) with ES • Pregnancy rates: 52/127 (41%); (82/127 including 2nd pregnancies & twins) • Miscarriage/ectopic: 19/82 (1twin) • Induced abortion: NR • Live Births: rate NR; 63 healthy children including 2nd babies • Singletons: 63 including 2nd babies • Multiples: 5 sets of twins • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; m = minute; ctrl = control(s); grp = group; pbo = placebo; µg = microgram; mg = milligrams; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; A/E = adverse event; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; mln = millions; AG = antegrade; RG = retrograde; IVF = in vitro fertilization

Evidence Table 3: Evidence from conference proceedings of fertility rates in patients with SCI (cont'd).

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/ Quality Assessment	Intervention (e.g., Pharmacologic/Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Seager, 2000, ND (Ref ID 3012)	• Enrolled/ evaluated: total n=565:n=460 SCI; n=105 other& 2nd grp of 16 couples with SCI prior to puberty evaluated for conception/ n=565 & 16 couples • % males: 100% • Race/ethnicity: NR • Age 32.1 (16-61) y • Level of Injury: NR • ASIA Level: ANR • Duration since injury: NR • Previous fertility: NR • Dropouts: NR • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** Abstract from conference proceeding – interventional (time series before/after trial) • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** NA	• **Pharmacologic**: NR • **Device**: **Seager Electrostimulatror (n=460 SCI; n=105 other)** • Amplitude: 200 mamp; range 100-700 mamp/ 9 V • Frequency: NR • Mode/Admin. Route: NR • **Other Device**: NR • **Surgical**: NR • **Procedure**: NR • **Behavioral**: NR • **Laboratory techniques**: NR	• **Outcomes**: • Measures of Fertility Rates: 2nd grp of SCI, 15/16 had sperm in ejaculate & fertility potential similar to SCI post-puberty • Seminal Parameters: NR • Ejaculation Rates: success rate expectancy by authors, 100% • **Follow-up**: NR	• **A/E**: NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; m = minute; ctrl = control(s); grp = group; pbo = placebo; µg = microgram; mg = milligrams; tx = treatment; hx = history; ∆ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; A/E = adverse event; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; mln = millions; AG = antegrade; RG = retrograde; IVF = in vitro fertilization

Evidence Table 3: Evidence from conference proceedings of fertility rates in patients with SCI (cont'd).

Author, Year, Location	Study Characteristics	Study Design & Duration/Eligibility Criteria/ Quality Assessment	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/ Follow-up	Adverse Events/Complications
Park, 1999, Korea (Ref ID 3002)	• Enrolled/ evaluated: n=17/ n=17 • % males: 100% • Race/ethnicity: NR • Age: NR • Level of Injury: above & below T10 • ASIA Level: NR • Duration since injury: NR • Previous fertility: NR • Dropouts: NR • Lost in follow-up: NR • N of sites:1 • Funding: NR	• **Study Design:** Abstract from conference proceeding – interventional (time series before/after trial) • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** NA	• **Pharmacologic**: NR • **Device**: Ferticare Vibrator (n=17) • Amplitude: NR • **Frequency**: NR • Mode/Admin. Route: 3 times/ wk • **Other Device** (n = 17): Electrostimulator • Type: Seager • Manufacturer: NR • Mode/Admin. Route: 3 times/ wk • **Surgical**: NR • **Procedure**: NR • **Behavioral**: NR • **Laboratory techniques**: NR	• **Outcomes:** • Measures of Fertility Rates: rate of adequate sperm quality in lesions above T10 81.8% in vs. & 66.7% in ES; in lesions T10 & below, 82.6% in ES (rate for VS is NR) • Seminal Parameters: Sperm quality not improved with repeated EJ. • Ejaculation Rates: 100% in ES, in lesions above T10 91.7%, in lesions at or below T10, NR • Pregnancy rates: NR • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; m = minute; ctrl = control(s); grp = group; pbo = placebo; µg = microgram; mg = milligrams; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; A/E = adverse event; EJ = ejaculation; SpC = sperm count; SpMot = sperm motility; SpMor = sperm morphology; VS = vibratory stimulation; ES = electrical stimulation; mln = millions; AG = antegrade; RG = retrograde; IVF = in vitro fertilization

Evidence Table 4: RCT evidence of sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g.,Pharmacologic/ Device/Behavioral/ Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Derry, 1998, UK (Ref ID 58)	• Enrolled/ evaluated: n=27/n=27 • % males: 100% • Race/ethnicity: NR • Age: NR (21-49) y • Level of Injury: T6-L5 • ASIA Level: Sildenafil grp, A n=8; B n=2; C n=2; D n=1; pbo grp, A n=6; B n=1; C n=3; D n=4 • Duration since injury: ≥6 mo • Drop-outs: n=2 • Lost in Follow-up: NR • N of sites: 3 • Funding: Pfizer	• **Study Design:** Part 1:randomised, double-blind, 2 -way cross over design Part 2: randomized, double-blind, parallel-grp design • **Duration:** 28 d • **Eligibility Criteria:** • Inclusion: 1. documented hx of SCI ≥6 mo, 2. female partner, 3. ED solely attributable to SCI, 4. ability to achieve grade, reflexogenic erectile response, 5. pts must stop self intracavernous injections 1 wk pre screening • Exclusion: T5 level or above genital anatomic deformities causing penile ED hypotension <80/50, stroke, subarahnoid haemorrhage, bleeding disorder, peptic ulcer disorder, nitrate or anticoagulant use, excessive alcohol use, clinical depression • Quality Assessment: 3/5 Jadad scale	• **Pharmacologic** (n=27): • Drug name: sildenafil • Dose: 50 mg • Duration: 28 d • Schedule: NR • Mode/Admin. Route max 1 dose / d • **Device: Vibrator (n=27)** • Amplitude: NR • Frequency: NR • Mode/Admin. Route: NR • **Other Device**: NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: After 28 d of tx., 9/12 pts (75%) on sildenafil & 1/14 pts (7%) on pbo reported that tx improved erections (p=0.0043). 8/12 pts (67%) on sildenafil & 2/13 pts (15%) on pbo wanted to continue tx (p=0.018) • Psychological: questions assessing satisfaction with sex life demonstrated S df with pts receiving sildenafil > pbo (p=0.0122). • Sexual Satisfaction: S improvement in sexual satisfaction reported by pts taking sildenafil (p=0.012) • **Additional Outcomes**: oral sildenafil (not > 1 x d) S improves quality of erections & satisfaction with sex life in men with SCI & ED between T6 & L5 • **Follow-up**: NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; m = minute; cm = centimeters; sec = seconds; mg = milligrams; µg = microgram; ctrl = control(s); grp = group; pbo = placebo; RCT = randomized clinical trial; tx = treatment; hx = history; Δ = change; S = significant; df(s) = difference(s); NS = nonsignificant; pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; (+) = positive; A/E = Adverse Events; HR = heart rate; BP = blood pressure; t.i.d = three times daily; b.i.d = two times daily; ED = erectile dysfunction; IIEF = Index of Erectile Function

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Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g.,Pharmacologic/Device /Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Giuliano, 1999, UK (Ref ID 284)	• Enrolled/ evaluated: n=178/ n=NR • % males: 100% • Race/ethnicity: NR • Age: NR (19-63) y • Level of Injury: NR • ASIA Level: NR • Duration since injury: 0.7-38 y • Drop-outs: 2/178 active phase; 3/178 pbo phase; • Lost to follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** randomized double-blind pbo ctrl cross-over design • **Duration:** 20 wk • **Eligibility Criteria:** • Inclusion: SCI men >18 with ED (cause by SCI); SCI >6 mo • Exclusion: NR • **Quality Assessment:** 2/5 Jadad scale	• **Pharmacologic (n=178):** • Drug name: sildenafil/ pbo • Dose: 25, 50 or 100 mg of drug/ pbo • Duration: 6 wk with 2 wk wash out period • Schedule: approximately 1 hr pre-sex activity • Mode/Admin. Route: oral • **Device:** NR • **Other Device**: NR • **Surgical**: NR • **Behavioral**: NR	• **Outcomes**: • IIEF: 83% (168/178) reported improved erections with sildenafil vs. 12% on pbo (p<0.0001) • GEQ2: ability to achieve intercourse improved in (132/166) 80% on sildenafil vs. 10% on pbo • Ability to achieve (p<0.0001)& maintain an erection for intercourse (p<0.0001); satisfaction with sexual intercourse (p<0.0001); frequency of ejaculation (p=0.0012; satisfaction with sexual relationship with partner (p<0.0001) all improved vs. pbo **Follow-up**: NR	• **A/E:** • Systemic: headache mild or moderate in 25/178 & severe in 5/178; facial flushing in 7%; dyspepsia in 3% & mild & transient visual abnormalities in 2%; 1 withdrawal post-pbo reported due to A/E

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Hultling, 1999, Sweden (Ref ID 285)	• Enrolled/ evaluated: n=329/ n=178 • % males: 100% • Race/ethnicity: NR • Age : NR (19-81) y • Level of Injury: C5-L1 • ASIA Level: A-D, no designation • Duration since injury: NR • Drop-outs: n=0 • Lost in Follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** Part 1: RCT parallel design Part 2: RCT cross-over design • **Duration:** 12 wk study duration; washout - 4 wk, done after first 6 wk • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 3/5 Jadad scale	• **Pharmacologic (n=209):** • Drug name: sildenafil • Dose: 25-100 mg on demand • Duration: 4 wk • Schedule: NR • Mode/Admin. Route: NR • **Device**: NR • **Other Device** : NR • **Surgical**: NR • **Behavioral** : NR	• **Outcomes:** • Anatomic/Physiologic: erection: S improvement perceived by partners both in ability to achieve & to maintain erections when taking sildenafil vs. pbo. • Sexual Satisfaction: ability to have intercourse assessed by SCI pts considered improved by 80% of those on sildenafil vs. pbo (effect of 10%). # of attempts at intercourse also much improved in both grp taking sildenafil • **Follow-up**: • Length: NR • Duration: NR • Results: other results not covered above. sildenafil S improved erectile function in pts with ED of broad-spectrum aetiology & those with ED due to SCI	• **A/E:** NR

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Giuliano, 1999, France (Ref ID 49/2049)	• Enrolled/ evaluated: n=178/ n=170 • % males: 100% • Race/ethnicity: NR • Age: 38 (NR) y • Level of Injury: NR • ASIA Level: A n=95 (53%); B n=20; C n=12; D n=27; n=24 not categorized by ASIA scale • Duration since injury: pbo/sildenafil grp = 10.3 (0.70-35) y; sildenafil/pbo grp 11.7 (0.74-38) y • Drop-outs: n=8 • Lost in Follow-up: NR • N of sites: 19 • Funding: Pfizer	• **Study Design**: randomized double blind cross over • **Duration:** 20 wk: 4 wk run-in phase with no tx, two 6-wk, double-blind, cross over tx separated by 2-wk washout, & 2-wk f/u • **Eligibility Criteria:** • Inclusion: Men ≥18 y who sustained traumatic SCI at least 6 mo pre screening & with ED solely attributed to SCI. Stable relationship with female partner for 6 mo • Exclusion: 1. genital /anatomical deformities impeding ED; 2. hx of stroke/ MI or any S CVD within last 6 mo; 3. diabetes, 4.major haematological, renal, or hepatic abnormalities; 5. unwillingness to forego use of vacuum devices, intracavernous injection tx, or other tx for ED during study; 6. concomitant tx with nitrates • **Quality Assessment:** 3/5 Jadad scale	• **Pharmacologic:** • Drug name: sildenafil (n=89, n=85 completed tx)/ pbo (n=89, n=86 completed tx) • Dose: initial dose 50 mg of sildenafil up to 100 mg (4 tablets) or adjusted downward to 1 tablet (25 mg). After 6 wk of tx, 4.6%, 36.8%, & 58.6% of pts receiving 25 mg, 50 mg & 100 mg of sildenafil, respectively/or matching pbo. • Duration: 38 d for each tx period • Schedule: 1 hr pre-sex. activity • Mode/Admin. Route: • **Device:** NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: 111/143 SCI with ED (78%) reported improved erections & preferred sildenafil to pbo. 127/168 (76%) including those with no residual erectile function at baseline, showed improved erections. (+) drug effect in 132/166 (80%), pbo effect in 17/166 men (10%). In n= 25 pts with no residual sexual function 16 (64%) had (+) drug effect & all preferred sildenafil to pbo ($p<0.001$). • Psychological: S drug effect in erection (to achieve & maintain) in reports of IIEF & pts log activity vs. pbo ($p<.005$). Median proportion of successful intercourse in pts log=55% with sildenafil vs. 0% in pbo ($p<0.001$) • Sexual Satisfaction: discontinuation rate of sildenafil 2% vs. 1% for pbo. When data for all pts (including those with no residual erectile function at baseline) analyzed, at baseline 127/168 (76%) reported improved erections & preference for sildenafil vs. 7/168 (4%) with improved erections & preference for pbo ($p<0.001$). • **Follow-up:** NR	• **A/E:** • Systemic: pbo grp: n=8 headaches; n=2 flushing; n=1 tx related A/E; n=1 lab test abnormality. sildenafil grp: n=30 headache; n=12 flushing; n=5 dyspepsia; n=5 rhinitis; n=4 abnormal vision; n=3 tx related A/E

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Hultling, 2000, Australia (Ref ID 281)	•Enrolled/ evaluated: n=178/ n=178 •% males: 100% •Race/ethnicity: NR •Age : 38 (19-63) y •Level of Injury: NR • ASIA Level: NR •Duration since injury: 11.7 (0.78) y •Drop-outs: n=0 •Lost in Follow-up: NR •N of sites: 19 •Funding: Pfizer	•**Study Design:** RCT cross-over design •**Duration:** run-in-period: 2-4 wk protocol: 6 wk for each pbo or sildenafil washout period: 2 wk •**Eligibility Criteria:** •Inclusion: ≥ 18 y, traumatic SCI at least 6 mo pre screening, clinical diagnosis of ED caused only by SCI, & involvement in stable relationship with female for at least past 6 mo •Exclusion: laboratory abnormalities, genital anatomical deformities, primary sexual disorder other than ED, major psychiatric or psychological disorder, including major depression, diabetes mellitus, hx of stroke or MI within last 6 mo •**Quality Assessment:** 2/5 Jadad scale	•**Pharmacologic (n=178):** •Drug name: sildenafil •Dose: upward & downward titration flexible dose of 25 mg 1 hr pre sexual activity (not > 1 x d), increased to maximum of 100 mg, & adjusted 25 mg, respectively for each period. •Duration: pts randomized to 2 homogeneous grp receiving pbo & sildenafil in random order. Active, 2-4 wk of run-in-period + 14 wk intervention length (6wk+2wk+6wk); pbo, flexible dose matching dose of sildenafil •Schedule •Mode/Admin. Route •**Device**: NR •**Other Device**: NR •**Surgical**: NR •**Behavioral**: NR	•**Outcomes:** •Anatomic/Physiologic: NR •Psychological: statistically S ($p<0.05$) improvements in favour of sildenafil at end of tx seen in 4/10 pts for general mental, physical, & psychosocial parameters. No S dfs in end-of-tx scores between sildenafil & pbo grps for PGWB Index measure of self-ctrl, MOS Family Survey, health vs. 1 y ago, or MOS SF-12 physical summary score. •Sexual Satisfaction: S increase in overall satisfaction with sex life (increase of 49% over baseline) & sexual relationship with partner (34% improvement over baseline) with sildenafil > pbo ($p<0.0001$ for tx effect) •Pt logs/diaries/ Other: trend towards higher doses of pbo (4% at 25 mg to 81% at 100 mg) vs. sildenafil (5% at 25 mg to 59%at 100 mg). Erectile problem questionnaire: summary score improved S with sildenafil vs. pbo, percentage of Δ from baseline in pbo (4.5%), vs. 22.5% in sildenafil ($p<0.0001$) •**Follow-up**: NR	•**A/E:** NR

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Maytom, 1999, UK (Ref Id 55)	•Enrolled/ evaluated: n=27/ n=26 •% males: 100% •Race/ethnicity: NR •Age: NR (21-49) y •Level of Injury: T6-L5 •ASIA Level: NR •Duration since injury: NR •Drop-outs: NR •Lost in Follow-up: NR •N of sites: 3 •Funding: Pfizer	•**Study Design**: RCT: cross-over design •**Duration:** study has 2 parts: 1. RCT, double blind two-way cross over & assessed reflexogenic erectile response to PVS after single dose of sildenafil or pbo; 2. randomized, double-blind-pbo controlled parallel-grp evaluation of sildenafil in home setting •**Eligibility Criteria:** •Inclusion: 1. males aged 18-55 y; 2. documented hx of SCI (sustained at least 6 mo prior to screening); 3. female partner; 4. ED solely attributable to SCI; 5. ability to achieve at least grade 2 reflexogenic erectile response to PVS; 6. stable dose of drug therapy 1 mo pre screening •Exclusion: 1. pts with lesions at or above T5 level; 2. pts with genetic anatomical deformities causing ED; 3. vascular or endocrine causes of ED; 4. postural hypotension, BP <80/50 mmHg; 5. major haematological, renal, hepatic abnormalities; 6. diabetes; 7. hx of stroke, subarachnoid haemorrhage; 8. bleeding disorder; 9. active peptic ulceration; 10. use of nitrates or anticoagulant meds; 11. involvement with an experimental drug within last 3 mo; 12. alcohol use > than 28 units of alcohol per wk; 13. clinical depression •**Quality Assessment**: 3/5 Jadad scale	•**Pharmacologic (n=27):** •Drug name: sildenafil •Dose: 50 mg •Duration: 28 d •Schedule: •Mode/Admin. Route: 1 hr pre sexual activity (not to be taken > 1 x d), •**Device**: NR •**Other Device**: NR •**Surgical**: NR •**Behavioral**: NR	•**Outcomes:** •Anatomic/Physiologic: Part 1. 17/26 (65%) had erections of > than 60% rigidity at penile base; Part 2, 9/12 (75%) pts on sildenafil & 1/14 (7%) pts on pbo reported tx improved erections. •Psychological: analysis of diary data showed no df between grps with respect to mean # of erections hard enough for penetration (p=0.08). End of tx questionnaire indicated no S dfs between grps with respect to frequency of erections hard enough for sexual intercourse (p=0.47), or that lasted as long as pt would have liked (p=0.11) •Sexual Satisfaction: pts in sildenafil grp more satisfied with their sex life (p=0.001) •**Follow-up:** •Length: NR •Duration: RN •Results: 8/12 (67%) men on sildenafil & 2/13 (15%) on pbo indicated that they wished to continue tx (p<0.02). Mean proportion of successful attempts at sexual intercourse 30% & 15%, respectively (p=0.21).	•**A/E:** •Systemic: sildenafil /pbo: Headache 4/1, dyspepsia 1/0, rash 2/3; anxiety 1/0, dizziness 1/0, vomiting 1/0, rectal disorder 1/0, respiratory tract infection 4 /2, increased cough 0/1, asthenia 0 /1, malaise 0/ 1,fFlu 0/ 1, epididymitis 0/ 1, orchitis 0/ 1. Total events = 15/12.

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Potter, 1998, Canada, US (Ref Id 1097)	• Enrolled/ evaluated: n=29/ n=28 • % males: 97% • Race/ethnicity: NR • Age: Parkwood: 36.6 (26.9-46.4) y; VAMC hospital: 45.6 (37.5-53.7) y • Level of Injury: n=18 C4-7; n=11 T3-12 • ASIA Level: B n=6; C n=12; D n=11 • Duration since injury: Parkwood 99.9 (64.0) mo; VAMC: 217.7(111.8) mo • Drop-outs: n=1 SCI • Lost in Follow-up: NR • N of sites: 2 • Funding: NR	• **Study Design:** RCT cross-over design • **Duration:** 4 wk run-in-period; 2 wk drug/pbo; 1 wk washout period • **Eligibility Criteria:** • Inclusion: range 21-65 y, medical diagnosis of incomplete teraplegia/paraplegia made >2 y prior to study, neurological level of injury C4-T12, medically stable & able to breathe independently, & stable neurological deficits for >60 d prior to study. Also exhibition 5 or more of the following: paresis, sensory loss, pain, spasticity, bowel, & bladder of sexual dysfunction. If female, had to be post-menopausal or surgically sterile, or using an acceptable method of birth ctrl. • Exclusion: risk of epileptiform seizures, hx of CVD, cancer, diabetes, impaired hepatic or renal function, or S liver disease < 6 mo pre-study or total bilirubin > 2x upper limit of normal range; known allergy to pyridine-containing medicine, infections, neurologic, degenerative or psychiatric disorders to impair completion of protocol or provide informed consent or any illness or abnormality that may jeopardize their safety or interfere with conduct of study. Pts who had received any investigational drug < 30 d prior to study, had hx of substance abuse, unable to discontinue excluded concomitant medications, tx with an antispasticity compound & could not maintain stable daily dosage or had received any drug known to cause S major organ toxicity < 3 mo prior to study, or considered unlikely to complete study also excluded. Also, pregnancy/potential pregnancy, or lactation. • **Quality Assessment:** 3/5 Jadad scale	• **Pharmacologic (n=29):** • Drug name: Fampridine-SR • Dose: 12.5 mg b.i.d. for wk 1 & increased to 17.5 mg b.i.d on wk 2. Washout period of 7 d, & pbo with matching dose & titration pattern for next 2 wk • Duration: 5 wk • Schedule: NR • Mode/Admin. Route: random assignment to Fampridine-SR or pbo during first period followed by washout period & cross over to receive opposite tx • **Device**: NR • **Other Device**: NR • **Surgical**: NR • **Behavioral**: NR	• **Outcomes:** • Psychological: no statistically S benefits of drug on measures of pain or bowel, bladder & sexual function or functional independence. • Sexual Satisfaction: no S effects on sexual function as result of 4-ap. Some improvement in sexual function defined by stronger, more frequent, & more sustained penile erections reported in 5 (19%) following Fampridine-SR vs. 4 (15%) following pbo (p=0.739), • **Follow-up**: NR	• **A/E:** • Systemic: Mild & transient giddiness or light-headedness at onset of taking drug (n=5)

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Renganathan, 1997, India (Ref ID 307)	• Enrolled/ evaluated: n=28/ n=28 • % males: 100% • Race/ethnicity: NR • Age: NR (16-60) y • Level of Injury: NR • ASIA Level: NR • Duration since injury: > 3 mo post SCI • Drop-outs: n=0 • Lost in Follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** RCT cross-over design • **Duration:** NR • **Eligibility Criteria:** • Inclusion: SCI with ED • Exclusion: duration of lesion < 3 mo, age < 16 -> 60 y, active infection, hyposadias, impotence prior to injury • **Quality Assessment:** 0/5 Jadad scale	• **Pharmacologic** (n=28): • Drug name: transdermal nitro-glycerine vs. intracavernous injection of papaverine • Dose: NR • Duration: NR • Schedule: NR • Mode/Admin. Route: NR • **Device**: NR • **Other Device**: NR • **Surgical**: NR • **Behavioral**: NR	• **Outcomes:** • Anatomic/Physiologic: erectile index compared between 2 grps with statistically S df (p=0.045) in favour of papaverine. Erection occurred in 5 m & subsided after 30-40 m in most pts with injection of paparvarine of 10 mg. Higher doses (20, 40, & 60 mg) maintained erection for longer duration. • **Follow-up:** • Length: NR • Duration: NR • Results: Mean value for erectile index in papaverine grp 164.5 & in nitro-glycerine grp 106.	• **A/E:** • Systemic: mild oedema with papaverine injections; 2. mild headache with nitro-glycerine; 3. prolonged erection > 6 hr

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Evidence Table 4: RCT evidence of sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g., Pharmacologic/Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Sipski, 2000, US (Ref ID 475)	• Enrolled/ evaluated: n=19/ n=19 • % males: 0% (all female) • Race/ethnicity: NR • Age: NR (35-58) y • Level of Injury: 14 women had UMN & 5 had LMN injuries affecting sacral cord • ASIA Level: NR • Duration since injury: 131.47 (15-457) mo • Drop-outs: n=0 • Lost in Follow-up: NR • N of sites: 1 • Funding: NIH	• **Study Design:** RCT cross-over • **Duration:** 2 d • **Eligibility Criteria:** • Inclusion: 1. non-pregnant women between 7-14 d of last menses (pregnancy test done) • Exclusion: NR • **Quality Assessment:** 2/5 Jadad scale	• **Pharmacologic** (n=19): • Drug name: sildenafil • Dose: 50 mg • Duration: NR • Schedule: NR • Mode/Admin. Route: NR • **Device**: NR • **Other Device**: NR • **Surgical**: NR • **Behavioral (n=19)** • Type: video/visual stimulation • Duration: NR • Frequency: NR	• **Outcomes:** • Anatomic/Physiologic: • S ∆s in VPA (p<.02) with increasing levels of sexual stimulation. Borderline S effect of drug tx (p<0.07) observed, with markedly increased VPA on sildenafil vs. pbo in manual plus visual stimulation condition. Lesser increases observed in visual stimulation alone condition. • Psychological: S increases in Subjective Arousal (SA) observed with both drug (p<0.01) & sexual stimulation conditions (p=0.001), & borderline S (p<0.07) effect of drug administration on VPA noted. Maximal responses occurred when sildenafil combined with visual stimulation & manual stimulation. Cardiovascular data showed modest increases in HR (+/- 5 BPM) an mild decreases in BP (+/- 4 mmHg) across all stimulation conditions, consistent with peripheral vasodilatory mechanism of drug • **Follow-up**: NR	• **A/E:** • Systemic: 1. flushing 4/19 on sildenafil vs. 1/19 on pbo; 2. headache 2/19 on sildenafil vs. 1/19 on pbo; 3. mild vision ∆s 2/19 on sildenafil vs. 1/19 on pbo; 4. fatigue 3/19 on pbo vs. 1/19 sildenafil; 5. 1 pts. had pelvic pain on both d. All side effects self-limiting & of brief duration.

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; m = minute; cm = centimeters; sec = seconds; mg = milligrams; µg = microgram; ctrl = control(s); grp = group; pbo = placebo; RCT = randomized clinical trial; tx = treatment; hx = history; ∆ = change; S = significant; df(s) = difference(s); NS = nonsignificant; pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; (+) = positive; A/E = Adverse Events; HR = heart rate; BP = blood pressure; t.i.d = three times daily; b.i.d = two times daily; ED = erectile dysfunction; IIEF = Index of Erectile Function; UMN = upper motor neuron; LMN = lower motor neuron; NIH = Nation Institute of Health; VPA = vaginal pulse amplitude; BPM = beats per minute; mmHG = millimeters of mercury

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g.,Pharmacologic/ Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Beretta, 1986, Italy (Ref ID 402)	• Enrolled/ evaluated: n=22/ n=NR • % males: 100% • Race/ethnicity: NR • Age: NR (18-52) y • Level of Injury: n=7 above T10-T11; n=10 thoracolumbar; n=5 sacral; n=9 complete; n=13 incomplete lesion • ASIA Level: NR • Duration since injury: ≥ 1 y • Dropouts: n=0 • Lost to follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 5/19 (+) reported	• **Pharmacologic (n=22):** • Drug name: papaverine • Dose: 20-30 mg • Duration: NR • Schedule: NR • Mode/Admin. Route: injection into one of cavernous bodies • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: 20/22 obtained erection with complete rigidity, with mean duration of 4.1 hrs • Sexual Satisfaction: 20/22 successful intercourse • **Follow-up:** • Length: 3 mo • Duration: NR • Results: 20/22 offered training in self-injection; 10/20 accepted self-injection & had coitus 1 x wk for > 3 mo	• **A/E**: • Systemic: long lasting pulsatile erection in 7/22, lasting > 5 hrs (controlled by intraglandular injection of ethilefrine & aspirations of corpus)

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (continued)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g.,Pharmacologic/ Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Beretta, 1993, Italy (Ref ID 339)	• Enrolled/ evaluated: n=15/ n=NR • % Males: 100% • Race/ethnicity: NR • Age: 29.4 (20-38) y • Level of Injury: n=9 T2-7; n=2 T12-L1; n=4 L1-L5 (n=12 Complete n=3 Incomplete) • ASIA Level: NR • Duration since injury: 1.3 (1-2) y • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: Pts who achieved erection sufficient for vaginal penetration after Prostaglandin E1 injection included • Exclusion: NR • **Quality Assessment:** 8/19 (+) reported	• **Pharmacologic (n=x):** None • Drug name: Prostaglandin E1 injection -2% Minoxidil solution • Dose: 1 ml of 2.5-10 micrograms 1 ml 2% minoxidil solution (Regaine-Upjohn) up to 60 ml of 2% minoxidil solution • Duration: NR • Schedule: NR • Mode/Admin. Route: (2ml/d) to try at home if complete or partial response to minoxidil achieved • **Device:** NR • **Other Device:** • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: • n=9 (+) response: 4 with complete & 5 with partial response. n=6 no response, NR, NR, Complete response achieved only in paraplegics with dorsal lesion. No relation between level of lesion & results of minoxidil test • Psychological: NR • Sexual Satisfaction: NR • Pts logs/diaries: • Interviews: • **Follow-up:** • Length: NR • Duration: NR • Results: 9 pts with complete or partial response continued to use minoxidil (2ml/d) at home for 1 mo. Result of subjective evaluations based on questionnaires: 26.6%(4 of 9) obtained an erectile response to minoxidil solution sufficient for vaginal penetration. All paraplegic with complete dorsal level who had obtained a complete response during minoxidil test. 3 SCI men chose to use minoxidil vs. prostaglandin E1 injection.	• **A/E:** • Systemic: Headache following minoxidil application in 1 subject. No medication required

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g.,Pharmacologic/Device /Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Bodner, 1999, US (Ref ID 293)	• Enrolled/ evaluated: n=15/ n=NR • % Males: 100% • Race/ethnicity: NR • Age: 47 (30-70) y • Level of Injury: quadriplegia 7;paraplegia 8 (>sacral reflex arc) • ASIA Level: NR • Duration since injury: 7 y • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design**: NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: men with SCI at least 1 y after injury previously treated by intracavernous injection therapy for SD (Previous SD Treatments: n=15: either papaverine or in combination with phentolamine for intracavernous injection therapy) • Exclusion: NR • **Quality Assessment:** 8/19 (+) reported	• **Pharmacological (n=15):** • Drug name: intraurethral prostaglandin E1 – MUSE • Dose: 125 miug with escalation to 1000 miug • Duration: NR • Schedule: NR • Mode/Admin. Route: injection • **Device:** NR • **Other Device (n=12):** • Type: constricting band on penis with application of MUSE • Manufacturer: NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: all pts required max dose of alprostadil (MUSE, 1000 µg); with intracavernosal injection (papaverine with or without phentolamine) 12/15 achieved grade 1-3 erections, 3/15 achieved grade 4 erections, 15/15 achieved grade 5 erection • Psychological: NR • Sexual Satisfaction: complete satisfaction n=0 with quality of erection using MUSE; n=3 with grade 4 erection after MUSE returned to use of intracavernous injection therapy. • Pt logs/diaries: NR • Interviews: NR • **Follow-up:** NR	• **A/E:** • Systemic: n=3 who did not use constricting band experienced transient hypotensive episode of 5-10 m; n=1 transient episode of blood from urethral meatus after inserting MUSE

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; miµg/µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; SD = sexual dysfunction; IIEF = Index of Erectile Function

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g.,Pharmacologic/Device /Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Chancellor, 1994, US (Ref ID 335)	• Enrolled/ evaluated: n=18/ n=NR • % Males: 100% • Race/ethnicity: NR • Age: 29 (19-65) y • Level of Injury: C7-L3, n=15 thoracics • ASIA Level: NR • Duration since injury: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: No ED prior to SCI. Ability to achieve only poorly sustained reflex erection inadequate for intercourse, no hypertension, no previous use of antihypertensive meds & minoxidil orally or topicaly, no prior therapy for ED • Exclusion: hx of psychogenic impotence, diabetes mellitus, thyroid, renal, hepatic or vascular disease, myocardial infarction or use of organic nitrates or nitrites • **Quality Assessment:** 8/19 (+) reported	• **Pharmacologic (n=18):** • Drug name: 2% minoxidil solution, intracorporeal papaverine injection • Dose: 10 mg intracorporeal papaverine • Duration: NR • Schedule: sequential order for each pts, with 15 m interval (or to full detumscence) • Mode/Admin. Route: injection of papavarine/ 1 ml of 2% minoxidil solution sprayed onto glans penis • **Device:** NR • **Other Device:** NR • **Surgical** (n=18) • Type: VCD • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: Topical application of minoxidil caused minimun response subjectively & objectively. % of Δ in rigidity: minoxidil tx:0-15%, VCD therapy: 30-80%(median rigidity of 57%), intercorporeal papaverine injection: 30-100%(median 77%). Erectile rigidity S less ($p<0.05$) with topical minoxidil than with either VCD or papaverine. No S df in rigidity between VCD therapy & papaverine ($p=0.34$) • Psychological: NR • Sexual Satisfaction: Topical application of minoxidil caused minimum response subjectively & objectively.% of Δ in rigidity: minoxidil tx:0-15%, VCD therapy: 30-80%(median rigidity of 57%), intercorporeal papaverine injection: 30-100%(median 77%). Erectile rigidity S less ($p<0.05$) with topical minoxidil than with either VCD or papaverine. No S df in rigidity between VCD therapy & papaverine ($p=0.34$) • Pts logs/diaries: NR • Interviews: NR • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function; VCD = vacuum constriction device

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g.,Pharmacologic/ Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Chapelle, 1988, France (Ref ID 1318)	• Enrolled/ evaluated: n=135/ n=NR • % Males: 100% • Race/ethnicity : NR • Age: NR (18-47) y • Level of Injury: T12-L2 • ASIA Level: NR • Duration since injury: NR (0.5 -33) y • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: urological or medical causes of testicular damage (orchiepididymis, destructive functional tx of lower urinary tract, cryptorchidy & systemic lupus • **Quality Assessment:** 8/19 (+) reported	• **Pharmacological (n=135):** • Drug name: physostigimine+ N-\buthyigyoscine • Dose: 0.2 mg/ 40mg • Duration: NR • Schedule: NR • Mode/Admin. Route: intervention consisted of 3 physostigimine tests. Each test = 0.2mgs s/c (in association with 40 mgs N-buthyihyoscine) followed by masturbation • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Behavioral** (n=135**)** • type: masturbation post medication tx • Duration/Frequency: NR	• **Outcomes:** • Anatomic/Physiologic: relation between testicular vol & SCI in n=86 pts (45 from EJ grp & 41 from ANEJ grp): Mean testicular vol did not differ S from that of ctrl. Testicular vol. slightly lower in ANEJ grp than EJ grp (t= 1.8, not S) Mean testicular vol did not differ S from that of SCI pts & ctrl. The relation between testicular vol & SCI in n=86 pts (45 from EJ grp & 41 from ANEJ grp): Mean testicular vol did not differ S from that of Control. Testicular vol. slightly lower in ANEJ grp than EJ grp (t= 1.8, not S) Mean testicular vol did not differ S from that of SCI pts & ctrl • Psychological: NR • Sexual Satisfaction: NR • Pt logs/diaries: NR • Interviews: NR • **Follow-up:** NR	• **A/E:** • Systemic: Autonomic Dysreflexia

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; ∆ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g.,Pharmacologic/Device /Behavioral/Surgical/other)	Outcomes/ Follow-up	Adverse Events/Complications
Costa, 1992, France (Ref ID 353)	• Enrolled/ evaluated: n=26/ n=NR • % Males: 100% • Race/ethnicity: NR • Age: 31.2 (24-39) y • Level of Injury: all complete lesions with paraplegic - upper levels of spinal cord • ASIA Level: NR • Duration since injury: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: screening included haematology, urinalysis, liver function test (alkaline phosphatase, total bilirubin & lactic deshydrogenase), hx & physical exam. All had normal height (178.5 +/- 5.7cm) & weight (75.8 +/-12.5kg). No hx or allergies, no drugs of any kind in 2 wk pre-tx. No drugs of enzyme inducers or inhibitors in 3 mo pre study. • Exclusion: NR • **Quality Assessment:** 12/19 (+) reported	• **Pharmacologic (n=26):** • Drug name: moxisylyte, dissolved in 2 ml physiological saline • Dose: 30 mg • Duration: NR • Schedule: NR • Mode/Admin. Route: Intracavernous injection; blood sampling before dosing (20ml) & at 0.08, 0.17, 0.33, 0.55, 1, 1.5, 2, 2.5, 3, 3.5, 4 & 8h post dosing (10 ml) • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: successful erections (10-20 m) obtained in all pts. NS decrease of BP with admin of drug. NS df between screening lab tests performed pre & post tx. Metabolites found in plasma: Unconjugated DAM, glucuronide & sulpho derivates of DAM & MDAM. The elimination half-lives are 0.89 +/-0.35 h for unconjugated DAM, 2.16 +/-0.85 h for conjugated VAM, & 5.32 +/- 3.23 h for conjugated MDAM. • **Follow-up:** NR	• **A/E** • Systemic: 1 case of sleepiness

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; ∆ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function; PB = blood pressure

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g.,Pharmacologic/Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Costa, 1993, France (Ref ID 344)	• Enrolled/ evaluated: n=12/ n=NR • % Males: 100% • Race/ethnicity: NR • Age: 34 (25-43) y • Level of Injury: n=1 C6-7 n=7 T3-T12 n=2 T12-L1 n=1 L1 All complete SCI • ASIA Level: NR • Duration since injury: 3-26 y • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: Erectile impotence due to post-traumatic paraplegia • Exclusion: Peyronie's disease, impotence related to another etiology than SCI, unbalanced bladder, bedsores, cardiac, renal, hepatic or ventilatory failure, systolic blood pressure below 10 cm Hg • **Quality Assessment:** 8/19 (+) reported	• **Pharmacological (n=12):** • Drug name: moxisylyte • Dose: 20 mg • Duration: NR • Schedule: NR • Mode/Admin. Route: 4 different vols: 0.4, 0.8, 1.2 & 2 ml. 7 d interval between injections • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic : NS df between 4 injection vols. (0.4, 0.8,1.2 & 2 ml 20 mg moxisylyte) for mean max rigidity (2.8, 2.8, 2.3 & 2.3), abdominopenile angle (100,101,107 & 101 degrees), penile length increase (33,34,36 & 35 mm), penile circumference increase (31.5,32,31 & 29 mm), duration of erection (47,62.5,60,57 m). • **Follow-up:** NR	• **A/E**: NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g., Pharmacologic/Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Courtois, 2001, Canada (Ref ID 1657)	• Enrolled/ evaluated: n=10/ n=NR • % Males: 100% • Race/ethnicity: n=2 cervical, n=7 Thoracic, n=1 lumbar; all UMN lesions, n= 6 Incomplete, n=4 Complete • Age: 37.7 (25-52) y • Level of Injury: NR • ASIA Level: NR • Duration since injury: 7.1(1-23) y • Dropouts: n=0 • Lost in follow-up: n=2 • N of sites: 1 • Funding Source: FRSQ & Foundation Andre Senecal	• **Study Design:** NCS • **Duration:** 4 wk • **Eligibility Criteria**: • Inclusion: screening test included neurological examination to verify lesion level & perineal muscle activity. Sexual evaluation to confirm ED defined by plethsmographic recording, reflex responses within normal latency (i.e. under 40 msec) • Exclusion: NR • **Quality Assessment:** 11/19 (+) reported	• **Pharmacological:** NR • **Device:** NR • **Other Device** (n =10): • Type: Rigiscan Device (erectile measurements) • Manufacturer: NR • **Surgical:** NR • **Behavioral** (n=10): • Type: Perineal training to investigate role of these muscles in erection. Technique combined with biofeedback & home exercises.	• **Outcomes:** • Anatomic/Physiologic: SCI pts could achieve initial tumescence, revealed by an average increase in penile circumference of 2.01 cm at beginning of training program. Following 4 wk of training, tumescence improved & reached an average of 3.22cm increase in penile circumference. Post 4 wk of stopping tx average tumescence dropped to 2.66 cm. Penile rigidity moved from 43% pre training to 59% at end of training program & back to 47% following secession of tx. • **Follow-up:** NR	• **A/E**: NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function; UMN = upper motor neuron; FRSQ = Fonds de la Recherche en Sante du Quebec

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g., Pharmacologic/Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Earle, 1992, Australia (Ref ID 359)	• Enrolled/ evaluated: n=22/ n=NR • % Males: 100% • Race/ethnicity: NR • Age: 35.2 (20-45) y • Level of Injury: C5-7 n=3, T5-12 n=8, L1 n=2, S1 n=1 (n=3 tetraplegic & rest are paraplegic); 11 complete, 3 incomplete • ASIA Level: NR • Duration since injury: 27 (15-42) y • Dropouts: n=5 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 7/19 (+) reported	• **Pharmacologic (n=19):** • Drug name: Papaverin, /mixture of papaverine 40 mg & phentolamine, Prostaglandin E1 • Dose: initial injection of 2-5 mg; max 80 mg, mixture of papaverine 40 mg & phentolamine 0.5 mg, prostaglandin E1 1-2 microgram • Duration: NR • Schedule: range 1 x wk to 1-4 x wk • Mode/Admin. Route: mixture of papaverine 40 mg & phentolamine administered if pts failed to respond to papaverine alone • **Device:** NR • **Other Device: Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: 19/22 achieved full erection following injections.14 pts continued to use self injection, 8 used papaverine, 1 used combination of papaverine/ phentolamine & 3 used prostagl & in E1. 8 pts felt spontaneous erections improved with injections while 5 had unreliable spontaneous erections • Sexual Satisfaction: partner subjective responses towards injection tx: favorable in 9, 1 not willing, 1 apprehensive & 1 partner glad not required every time • **Follow-up:** NR	• **A/E**: • Local: bruising • Systemic: blood in urethra, & prolonged erections • Other: lack of confidence

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g.,Pharmacologic/ Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Gans, 2001, US (Ref ID 269)	• Enrolled/ evaluated: n=17/n=NR • % Males: 100% • Race/ethnicity: NR • Age: 40.3 (25-58) y • Level of Injury: cervical 4; thoracic 12; lumbar 1 • ASIA Level: NR • Duration since injury: 9.8 (3-21) y • Dropouts: n=1 • Lost in follow-up: 10 • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** Feb.- Sept. 1998 • **Eligibility Criteria:** • Inclusion: hx of organic ED, SCI, & a consistent sexual partner • Exclusion: unwillingness to participate in f/u appointments, use of organic nitrates or nitric oxide donor compounds, dependency on alcohol or drugs, or major, uncontrolled medical illness, previous hx of ischemic events (e.g., myocardial infarction or stroke), or abnormal baseline testosterone • **Quality Assessment:** 16/19 (+) reported	• **Pharmacologic (n=17):** • Drug name: sildenafil • Dose: starting dose 25 mg with increase of dose in 25 mg increments; mean dose 73.4+/-33.5 mg • Duration: NR • Schedule: NR • Mode/Admin. Route: oral (no ctrl wash-out period pre to tx) • **Device:** NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: mean duration of erection increased to 10 m post-tx. Scores from IIEF questionnaire (all p<0.05): mean scores of confidence that one could get & keep erection increased 1.6-3.8; mean score of frequency of erections hard enough for penetration increased from 1.1-3.8; mean scores of frequency of ability to maintain erection post penetration of partner increased 1.3-4.1; mean duration of erection increased from 8.4-10 m; difficulty maintaining erection to completion of intercourse improved 1.4-4.3. • Sexual Satisfaction: mean scores frequency of satisfaction with attempted sexual intercourse increased 1.3-4.1(p<0.05); mean scores of satisfaction with therapy increased 1.8 with previous therapy to 3.5 post sildenafil (p<0.05) • **Follow-up:** (n=6) • Length: NR • Duration: mean duration f/u 5.3 +/-2.2 mo • Results: NS in erectile function between early & long-term f/u except for an improvement in quality of erection. All 6 pts stated that they would recommend sildenafil therapy to a friend with ED SCI, no S Δ in frequency of successful intercourse between f/u periods	• **A/E**: • In n=1 hypotension resulting in dropout.

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g.,Pharmacologic/Device /Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Golji, 1979, US (Ref ID 414)	• Enrolled/ evaluated: n=30/ n=NR • % Males: 100% • Race/ethnicity: NR • Age: NR (25-60) y • Level of Injury: 36% cervical, 4% lumbar; 68% complete, 32% incomplete • ASIA Level: NR • Duration since injury: NR • Dropouts: n=5 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** 2 y • **Eligibility Criteria:** • Inclusion: impotence due to SCI • Exclusion: NR • **Quality Assessment:** 7/19 (+) reported	• **Pharmacologic (n=25):** • Drug name: Gentamicin (non interventional) • Dose: NR • Duration: 1 d preoperatively & 3-4 d postoperatively Schedule: NR • Mode/Admin. Route: orally; most underwent another wk of other antibiotic urinary antiseptic therapy. • **Device:** NR • **Surgical** (n=25): • Type: Small-Carrion penile prosthesis • **Behavioral:** NR	• **Outcomes:** • Psychological: 18/20 wished they had penile implant sooner & 2 indicated marriages could have been saved if penile implant earlier. • Sexual Satisfaction: 68% of pts with choice of oral sex pre-operation & remaining 42% with no specific pattern in sexual satisfaction result of operation : (+) Δ in sexual pleasure in intercourse & morale of pts & their partners • **Follow-up:** NR	• **A/E**: • Systemic: extrusion of penile prosthesis in 2 pts caused by infection

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Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g., Pharmacologic/Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Green, 1986, US (Ref ID 192)	• Enrolled/ evaluated: n=40/ n=NR • % Males: 100% • Race/ethnicity: NR • Age: 33 (21-60) y • Level of Injury: NR • ASIA Level: A n=31; B-D n=9 • Duration since injury: > 0.75 –1 y • Dropouts: n=4 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** 1981-1986 • **Eligibility Criteria:** • Inclusion: SCI pts suitable for penile prosthesis no less than 9-12 m post injury with: 1. stable bladder programs; 2. recent urologic X-ray evaluation; 3. sterile urine at time of implantation; 4. free of open skin lesions • Exclusion: NR • **Quality Assessment:** 7/19 (+) reported	• **Pharmacological:** NR • **Device:** NR • **Other Device:** NR • **Surgical** (n=36): • Type: penile implants: 1. semi-rigid penile implants; 2. inflatable penile implants • **Behavioral:** NR	• **Outcomes:** • Sexual Satisfaction: 86% (31/36) intercourse regularly & pleased with their decision for implants; partners confirmed satisfaction as well; 11% (4/36) dissatisfied: all had semi-rigid implants & stated rods not rigid enough to sustain vaginal penetration; 1 wife not satisfied; 1 pt died but wife stated they had regular intercourse. • **Follow-up:** • Result: 8.3% (3/36) pts had extruded rods, all happened >2 y post implantation; 1 pt had paraphimosis requiring circumcision; 1 pt with an inflatable prosthesis had minor erosion through fossa navicularis that spontaneously healed	• **A/E**: • Local: no immediate postoperative complications

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g.,Pharmacologic/Device /Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Gross, 1996, Germany (Ref ID 85)	• Enrolled/ evaluated: n=209/ n=NR • % Males: 100% • Race/ethnicity: NR • Age: 39.9 (16-72) y • Level of Injury: 77% paraplegic, 23% tetraplegic • ASIA Level: NR • Duration since injury: NR • Dropouts: n=37 • Lost in follow-up: n=17 • N of sites: 1 • Funding: NR	• **Study Design:** NCS (Retrospective study) • **Duration**: 1980-1992 • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 5/19 (+) reported	• **Pharmacological:** NR • **Device:** NR • **Other Device:** NR • **Surgical** (n=209): • Type: semi-rigid (Jonas) prosthesis (in 49 pts with ED, 113 pts with penile retraction & 47 with both); prosthesis implanted under strict aseptic conditions with antibiotic prophylaxis 3 d pre & 5 d post surgery. • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: n=179 evaluable. 234 operations in 209 pts with revision due to perforation, infection or malfunction. 143/209 initially received semi-rigid, 59 semi-flexible & 7 flexible penile prosthesis. After revisions, 127 still had a semi-rigid, 74 a semi-flexible & 8 a flexible prosthesis. • Sexual Satisfaction: Of pts treated for penile retraction, 92% satisfied with their sexual life, & of those treated for ED, 83% satisfied. • **Follow-up:** n=165 • Duration: mean of 5 y since implantation (range 0.6-11.4), • Results: 126/165 used penile prostheses for external condom drainage, 116(92%) succeeded; ED main indicator for penile prostheses in n=83 (11 tetra & 72 para). 70/83(84%) reported satisfactory sexual intercourse post-tx. Reasons for not using prostheses were: unsatisfactory surgical result in 5 pts, lack of stability in 2 pts, subcoronal ventral deviation in 3 pts, & lack of interest in rest.	• **A/E**: • Local: infection led to removal of implants in 14/179 (6.7%); bilateral perforation in n=6, repeated bilateral perforation in n=2 & unilateral perforation in 13: total 7% of 179 pts. perforation occurred with 9.4% of semi-rigid prostheses & 2.7% of semi-flexible prostheses. • Systemic: n=13 death

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g.,Pharmacologic/ Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Heller, Israel, 1992 (Ref ID 149)	• Enrolled/ evaluated: n=30 (neurological impotence)/ n=NR • % Males: 100% • Race/ethnicity: NR • Age: NR • Level of Injury: NR • ASIA Level: NR • Duration since injury: NR • Dropouts: n=13 • Lost in follow-up: NR • N of sites: 1 • Funding: NIDRR; US Dept. of Education; USIEF	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 8/19 (+) reported	• **Pharmacological:** NR • **Device:** NR • **Other Device** (n=30): • Type: vacuum tumescence • Manufacturer: 2 different VTCT devices: 1. Eracaid system, Osborn Medical Systems, Augusta, Georgia, USA; 2. Ved brand vacuum system, Mission Pharmaceuticals • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Psychological: questionnaires used but scales not given • Sexual Satisfaction: 83% of 17 pts reported very satisfied with sexual relationship after using VTCT; 100% of their partners reported very satisfied with present sexual relationship; this enhancement in satisfaction attributed to following: pts felt that they had a greater ability to give pleasure to sexual partners resulting in increased desire to engage in sexual activity; partners felt enhancement secondary to engaging in a more "natural" sexual relationship • **Follow-up:** NR	• **A/E**: • Local: 17% (3/17) complained of suction around testicles with VTCT use; 17% (3/17) reported occasional swelling of testicles; 33% reported petechial hemorrhages

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function; NIDRR = The National Institute on Disability &Rehabilitation Research; USIEF = US Israel Educational Foundation

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g.,Pharmacologic/Device /Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Hirsch, 1994, US (Ref ID 326)	• Enrolled/ evaluated: n=27: SCI n=14; MS n=7; discogenic disease n=6/NR • % Males: 100% • Race/ethnicity: NR • Age: 31.5 (22-39) y • Level of Injury: NR • ASIA Level: NR • Duration since injury: 8 y • Dropouts: n=15 (8 SCI; 4 MS; 3 discogenic disease) • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 6/19 (+) reported	• **Pharmacological (n=27):** • Drug name: intracavernous prostaglandin E1 - PGE-1 • Dose: 1 pts 2.5 miμg & increased 2.5 miμg increments to mean maintenance dose of 6.2 miμg • Duration: NR • Schedule: NR • Mode/Admin. Route: NR • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Sexual Satisfaction: all pts completing protocol reported excellent penile rigidity & duration of erection on standardized home assessment questionnaires; no objective data available from article • **Follow-up:** • Duration: quarterly f/u visits up to 28 mo • Results: NR	• **A/E**: NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; miμg/μg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; MS = multiple sclerosis; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g., Pharmacologic/Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Iwatsubo, 1986, Japan (Ref ID 404)	• Enrolled/ evaluated: n=37/n=NR • % Males: 100% • Race/ethnicity: NR • Age: 42 (21-63) y • Level of Injury: 10 tetraplegic 23 paraplegic 4 walking with cauda equine • ASIA Level: NR • Duration since injury: mean 5 y • Dropouts: n=2 • Lost in follow-up: n=2 implant removed due to infection • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** 5 y • **Eligibility Criteria:** • Inclusion: all SCI with urinary incontinence or impotence • Exclusion: NR • **Quality Assessment:** 5/19 (+) reported	• **Pharmacological:** NR • **Device:** NR • **Other Device:** NR • **Surgical** (n=37): • Type: Shirai-type Penile Implant • **Behavioral:** NR	• **Outcomes:** • Sexual Satisfaction: 15 pts (41%) reported improved marital life. 18 pts (48%) reported no benefit & 4 pts (11%) reported dissatisfaction. • Pt logs/diaries: questionnaire survey result in 37 pts: 32 pts (86%) reported satisfaction with regards to better condom fitting & easier intermittent catheterisation, 5 pts (14%) dissatisfied/ discontinued. • **Follow-up:** NR	• **A/E:** • Systemic: pain n=1; 46 y-old T12 complete: implant removed; irritation in a 29 y-old C7 complete: modification made

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Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g., Pharmacologic/Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Jaworski, 1992, US (Ref ID 150)	• Enrolled/ evaluated: n=80/n=56/ SCI n=30; DBT n=26 • % Males: 100% • Race/ethnicity: NR • Age: SCI 37.2 (NR) y; DBT; 51.4 (NR) y • Level of Injury: L-3 (10%) T-20 (67%) C-7 (23%), 63% motor & sensory complete • ASIA Level: NR • Duration since injury: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NIDRR; US Dept. of Education	• **Study Design:** Case-control Study • **Duration:** NR • **Eligibility Criteria:** • Inclusion: All pts screened for testosterone & prolactin levels, general physical exam & urinanalysis • Exclusion: NR • **Quality Assessment:** 3 * (NOS)	• **Pharmacological:** • Drug name: Papavarine/phentolamine injection & penile prosthesis implant • Dose: NR • Duration: NR • Schedule: NR • Mode/Admin. Route: NR • **Device:** NR • **Other Device** (n=56): • Type: snap gauge nocturnal penile tumescence monitoring • Manufacturer • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Sexual Satisfaction: vs. a normative sample both DBT & SCI males found to have better body image post-implant/injection. Also engaged in more sexual activities. • Pt logs/diaries: SCI men scored higher on sexual information & attitudes vs. DBT men; DBT men scored slightly higher on overall adjustment in relationship than SCI men ($p < 0.07$) • Measures of sexual satisfaction (sexual activities, frequency & 2 measures of satisfaction): pre-tx (implant/injection) S df between SCI > DTB ($p = 0.08$); SCI more satisfied overall in sexual encounters (frequency, variety, duration, interest, communication) vs. DBT; S time effect for all outcome measures, with S improvement for SCI & DBT males "on all measures" from pre to post procedure ($p = 0.0001$). • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; DBT = diabetics; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function; NIDRR = The National Institute on Disability &Rehabilitation Research

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g., Pharmacologic/Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Kapoor, 1993, India (Ref ID 341)	• Enrolled/ evaluated: n=101/n=NR • % Males: 100% • Race/ethnicity: NR • Age: NR (20-51) y • Level of Injury: C4-L4; n=9 complete, & n=27 incomplete tetraplegic; n=23 complete & n=42 incomplete paraplegic • ASIA Level: NR • Duration since injury: all>1 y • Dropouts: n=0 • Lost in follow-up: NR • n of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: baseline tests (urine, hemoglobin, liver function tests & ECG) • Exclusion: NR • **Quality Assessment:** 10/19 (+) reported	• **Pharmacologic (n=109):** • Drug name: papaverine • Dose: starting at 7.5 mg & increased according to status of erection • Duration: NR • Schedule: 2-3 x wk • Mode/Admin. Route: intracavernous injection to posterolateral aspecto of penis at base • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Behavioral:** NR	**Outcomes:** • Anatomic/Physiologic: Dose-erection relation: all pts in younger age grp (up to 30 y) required 7.5-15 mg of papaverine. Older age grps required a higher dosage. 78 pts had good erection within 10 m duration & 20 over 22 m. Duration of erection less than 1 h in 35, 1-2 h in 29, 2-4 h in 31 & more than 4 h in 3 pts. Lag period of erection onset 10 m in 78 pts, 20 m in 13 pts, & 30 m in 7 pts. • Sexual Satisfaction: 98 pts achieved good erections & enjoyed coitus with their spouse **Follow-up:** • Length: NR • Duration: monthly intervals • Results: NR	• **A/E:** • Systemic: Subcutaneous haematoma in 3 pts, Cavernosa fibrosis in 2 after prolonged use (over 36 mon), prolonged erection (more than 4 h) with 1 pts needing cavernosal wash with dopamine solution, & systematic effects in 1 so case dosage reduced.

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Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g., Pharmacologic/Device/Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Kim, 1995, US (Ref ID 318)	• Enrolled/ evaluated: n=10: SCI n=9; mild arterial insufficiency n=1 • % Males: 100% • Race/ethnicity: NR • Age: 33 (19-50) y • Level of Injury: n=4 cervical; n=5 thoracic • ASIA Level: NR • Duration since injury: NR • Dropouts: n=1 • Lost in follow-up: NR • N of sites: 1 • Funding: Pharmedic Company	• **Study Design:** NCS • **Duration:** 5 d (interventions & assessments done on d 1, 3 & 5) • **Eligibility Criteria:** • Inclusion: NR • Exclusion: if hormonal or yohimbine therapy used within 6 m • **Quality Assessment:** 10/19 (+) reported	• **Pharmacologic (n=10):** • Drug name: 0.04% prostaglandin E1 topical gel • Dose: NR • Duration: 1h • Schedule: d 3 • Mode/Admin. Route: medication applied to penis, scrotum &perineum • **Device:** NR • **Other Device** (n=10): • Type: color flow Doppler ultrasound, & L10-5 linear array transducer • Application: 10 m post –tx, to measure velocity & angle. • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: mean cavernous artery diameter (cm): pre-application 0.09 +/- 0.02 & post-application 0.11 +/- 0.04; ($p<0.05$) mean peak flow velocity (cm/sec): pre-application 15.4 +/-6.4 & post-application 22.8 +/-7.3 ($p<0.05$); clinical erection (grade 4 & 5) occurred in 2 pts who did not have erections with pbo gel; mean diastolic BP variations (mm Hg): pre-application 78, post-application 83 ($p<0.0001$); mean HR variation (beats/m): pre-application 59 & post-application 64 ($p<0.01$); NS Δ's in systolic & diastolic BP. • **Follow-up:** NR	• **A/E:** • Local: facial redness in 1 pts with a previous hx of psoriasis

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Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g.,Pharmacologic/Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Kim, 1995, US (Ref ID 322)	• Enrolled/ evaluated: n=20: n=13 SCI; n=7 other/ n=NR • % Males: 100% • Race/ethnicity: NR • Age: 40 (19-73) y • Level of Injury: n=8 cervical; n=5 thoracic • ASIA Level: NR • Duration since injury: 5.9 (0.6-27) y) • Dropouts: n=3 • Lost in follow-up: NR • N of sites: 1 • Funding: Pharmedic Company	• **Study Design:** non-RCT • **Duration:** each pts evaluated on 5 separate d for a 13-d period • **Eligibility Criteria:** • Inclusion: NR • Exclusion: pts excluded if hormonal therapy used within 6 mo • **Quality Assessment:** NA	• **Pharmacologic (n=x):** • Drug name: 5.5%, 7%, 15%, & 20% topical papaverin gel; color flow Doppler ultrasound with a L10-5 linear array transducer • Dose: papaverin gel: mean 295 mg; range 133-500 mg • Duration: NR • Schedule: NR • Mode/Admin. Route: NR • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: SCI pts grp (n=12): mean cavernous artery diameter increased 36% from 0.11-0.15 cm (p<0.001); mean peak systolic flow velocity increased 21% 13.8-17.5 cm/sec (p=0.06); after genital application of papaverin BP Δ's did not reach statistical S; mean HR decrease after application statistically S: from 68 beats/m to 63 beats/m at 30 m (p<0.0004); clinical erection of grade 5 noted in 3/17 pts (18%) with both papaverin & placebo gel applications, but in papaverin grp duration of erection longer: 38.7 +/-18.7 m vs 8.0 +/-4.6 m. (NS) • Pt logs/diaries/ Other: mean serum papaverin levels after genitalia application (ng/ml): 10.5 at time 0, 9.9 +/-3.3 at 15 m, 13.8 +/-4.4 at 30 m, & 15.1 +/-4.8 at 60 m. • **Follow-up:** NR	• **A/E:** • Local: forearm skin rash in 1 pts

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; m = minute; cm = centimeters; sec = seconds; mg = milligrams; µg = microgram; ctrl = control(s); grp = group; pbo = placebo; RCT = randomized clinical trial; tx = treatment; hx = history; Δ = change; S = significant; df(s) = difference(s); NS = nonsignificant; pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; (+) = positive; A/E = Adverse Events; HR = heart rate; BP = blood pressure; t.i.d = three times daily; b.i.d = two times daily; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g.,Pharmacologic/Device /Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Komisaruk, 1997, US (Ref ID 530)	• Enrolled/ evaluated: n=32: SCI n=16; ctrl n=16/ n=NR • % Males: 0%(all female) • Race/ethnicity: NR • Age: SCI 37.2 (25-55) y; ctrl 45.4 (35-56) y • Level of Injury: SCI T10 &/or above n=6; SCI T10 & below n=10 • ASIA Level: NR • Duration since injury: 12.4 (2-27 y) • Dropouts: n=1 SCI • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** Case-control Study • **Duration:** NR • **Eligibility Criteria:** • Inclusion: SCI: incomplete at least 1-y post injury, no hx of autonomic dysreflexia, minimum age 21 y. Uterus & cervix intact in all pts • Exclusion: psychosis or severe depression, cystocele or hysterectomy • **Quality Assessment:** 6 * (NOS)	• **Pharmacologic:** NR • **Device:** NR • **Other Device** (n=32): • Type Pain threshold measurement: Frey & Passive stimulator • **Surgical:** NR • **Behavioral** (n=32) • Type: self stimulation of vaginal, cervical, sensate region in random order • Duration: 90 m total consisting of 12 m stimulation for each experimental condition preceded & followed by resting, non-stimulation rest period. • Frequency: 1 x/ experimental condition	• **Outcomes:** • Anatomic/Physiologic: Ctrl Grp: vaginal self stimulation S increased PD threshold by 66.7 +/-18.5%(p<0.01), & PT by 42.5 +/-10.5%(p<0.01).Cervical self-stimulation S increased PD threshold by 34.9% +/-1% (p<0.05) & PT threshold by 28.3% +/-8.2% (p<0.01) over control resting condition. Cervical self-stimulation in grp with lower SCI S increased PD threshold by 33.8% +/-10.2% & PT(p<0.05) & PT threshold by 27.2+/-7.6%(p<0.01). In upper SCI, vaginal self stimulation S increased PD threshold by 91.6%+/-32.9%(p<0.01) & PT threshold by 46.1% +/-8.8%(p<0.01) over corresponding ctrl resting condition; cervical self stimulation in this grp increased PD threshold by 72. +/-34.6%(P<0.05), & PT threshold by 36.5% +/-9.6%(p<0.01); S higher increase in PD threshold by vaginal or cervical self stimulation in grp with upper SCI vs. grp with lower SCI (p<0.01 & p<0.05) • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; m = minute; cm = centimeters; sec = seconds; mg = milligrams; µg = microgram; ctrl = control(s); grp = group; pbo = placebo; tx = treatment; hx = history; Δ = change; S = significant; df(s) = difference(s); NS = nonsignificant; pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; (+) = positive; A/E = Adverse Events; t.i.d = three times daily; b.i.d = two times daily; NOS = Newcastle Ottawa Scale; ED = erectile dysfunction; IIEF = Index of Erectile Function; PD = pain detecting; PT = pain tolerance

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Martin, 1983, US (Ref ID 1406)	• Enrolled/ evaluated: n=20/ SCI n=12; healthy ctrl n=8 • % males: 100% • Race/ethnicity: NR • Age: healthy grp - NR (23-26) y; SCI NR (24-41) y; NR (24-39) y • Level of Injury: T3-T12 n=3; T12-L1 n=2; L2 n=1 • ASIA Level: NR • Duration since injury: NR • Drop-outs: n=0 • Lost to follow-up: NR • N of sites: 1 • Funding: NIMH	• **Study Design**: Case-control study • **Duration**: NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 4 * (NOS)	• **Pharmacologic**: NR • **Device:** Rectal Probe Electrostimulator • Amplitude: NR • Frequency: 60 Hz, 20 Hz, & 0.25 Hz • Mode/Admin. Route: dorsal lithotomy position (after bowel movement) intact subjects & 1st 5 pts controlled current delivery by themselves • **Other Device**: NR • **Surgical**: NR • **Behavioural**: NR	• **Outcomes:** • Anatomic/Physiologic: erections with max. tumescence in 1 ctrl pt, with no seminal emissions or ejaculations; 6/10 SCI achieved erection with 20 Hz stimulation; surface area & intensity of applied current directly affected extent of RPE-induced penile tumescence; use of 60 Hz & 20 Hz currents ineffective in eliciting erection • Interviews: verbalized descriptions of threshold current sensations included tenesmus, rectum burning sensation, testicular pain resembling intense pressure in rectum, bladder or bowel, suprabubic midline discomfort, pain at base of penis & sensation of gluteal muscle spasm. • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; m = minute; ctrl = control(s); grp = group; pbo = placebo; mg = milligrams; µg = microgram; tx = treatment; hx = history; ∆ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; NOS = Newcastle Ottawa Scale; ED = erectile dysfunction; IIEF = Index of Erectile Function; Hz = Hertz; NIMH = National Institute of Mental Health

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g., Pharmacologic/Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Montague, 1994, US (Ref ID 1736)	• Enrolled/ evaluated: n=47: SCI n=12, non-traumatic neurological disorders n=25, peripheral nerve injuries n=10/ n= NR • % of Males: 100% • Race/ethnicity: NR • Age: 48 (19-71) y • Level of Injury: NR • ASIA Level: NR • Duration since injury: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** July 1987 to July 1992 • **Eligibility Criteria:** • Inclusion: Neurogenic Impotence • Exclusion: NR • **Quality Assessment:** 6/19 (+) reported	• **Pharmacologic:** NR • **Device:** NR • **Other Device:** NR • **Surgical** (n=47): • Type: Prostheses implant: AMS 700CX (13) AMS Malleable 600 (10) AMS Ultrex (9) DuraPhase (9) Hydroflex (5) Dynaflex • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: 91% of pts implanted in study had functioning prosthesis. Penile prosthesis implants (SCI) increased incidence of infection & erosion, so considered alternative tx (e.g., vacuum devices/intracavernous injection therapy) • **Follow-up:** NR	• **A/E:** • Systemic: 2 pts had prosthesis removed 1 & 26 mo post implantation for infection. Of devices removed for infection, 1 semi-rigid device (AMS Malleable 600) & 1 inflatable device (AMS 700CX). 1 device removed for erosion post 6 wk implantation (device hydralic (hydroflex)), 2 devices mechanical failure, a DuraPhase cable fracture 34 mo post implant & a Duraflex hydraulic leak 24 mo post implant. Infection rate 4%, erosion rate 2%, mechanical failure 4%

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g., Pharmacologic/ Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Richards, 1993, US (Ref ID 1759)	• Enrolled/ evaluated: n=17/ n=NR • % Males: 100% • Race/ethnicity: 76% white • Age: NR • Level of Injury: NR (76.4% paraplegic; 74.6%complete) • ASIA Level: NR • Duration since injury: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NIDRR; US Dept. of Education, & MRRTC	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: SCI Diagnosed by urologist as having neurologically based impotence; steady sexual partner; couples with ongoing substance abuse, poor self-esteem, marked relationship instability/discord, or active partner opposition to procedure documented &referred for appropriate tx. If tx recommended followed & successful, couple then enrolled. • Exclusion: NR • **Quality Assessment:** 9/19 (+) reported	• **Pharmacologic (n=17):** • Drug name: Intracavernous injection of vasoactive (Not specified) • Dose: NR • Duration: NR • Schedule: NR • Mode/Admin. Route: NR • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Psychological: > overall satisfaction subsequent to tx implementation. In SII examination of subscale pre-tx, both partners dissatisfied with frequency of sexual activity (male > females). Males reported < self-acceptance vs. partners pre-tx. • Sexual Satisfaction: Both pts & partner expressed increased satisfaction with frequency of sexual activity post intervention (injection). However, SCI males reported > improvement in sexual pleasure & self-acceptance vs. partners (self acceptance p = 0.05, sexual pleasure p = 0.01) • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function; NIDRR = National Institute on Disability & Rehabilitation Research; MRRTC = Medical Rehabilitation Research & Training Centre

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g.,Pharmacologic/ Device/Behavioral/ Surgical/other)	Outcomes/ Follow-up	Adverse Events/Complications
Sanchez, 2001, Spain (Ref ID 12)	• Enrolled/ evaluated: n=170/ n=NR • % Males: 100% • Race/ethnicity: NR • Age: 37.3 (19-65) y • Level of Injury: cervical 35 (20.6%); thoracic 99 (58.2%); lumbar 30 (17.6%); sacrococcygeal 6 (3.6%) • ASIA Level: n=94 A; n= 14 B; n=27 C; n=29 D • Duration since injury: 7.7+/-66 (0.2-32.7) y • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 16 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: men >18 y with SCI who overcome period of medullary shock, with stable partner & ED • Exclusion: pts with anatomic deformities of penis; pts in whom sexual activity not advised (i.e., pts with severe cardiovascular dysfunction such as unstable angina or severe heart failure not controlled with drugs; hypotension (BP<90/50 mmHg); recent hx (less than 3 mo) of stroke or acute myocardial infarction); pts treated with any drug or therapy for ED that not willing to discontinue during study; pts treated with drugs containing nitrates; hx of retinitis pigmentosa; severe liver or kidney failure; pts already treated with sildenafil • **Quality Assessment:** 8/19 (+) reported	• **Pharmacologic:** • Drug name: sildenafil • Dose: starting dose 50 mg up to 100 mg, 30-45 m before start of sexual activity/ 1 x d • Duration: NR • Schedule: NR • Mode/Admin. Route: NR • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • **Anatomic/Physiologic:** 150 (88.2%) pts reported improved erection; improvement confirmed by 85.3% (99/116) of partners; presence of orgasmic perception pre-tx (p=0.021) & erection grades 3 & 4 (p=0.006) S association with (+) response to sildenafil tx; of total attempts (603) at sexual intercourse made during study, 431 (71.5%) successful; no S Δ's seen in ejaculatory function after tx; level of SCI, ASIA, causes of SCI, ED duration, age, smoking or drinking habits, pre-tx with caverjet, presence of bulbocavernous reflex & ejaculation not factors predicting response to sildenafil • Sexual Satisfaction: sildenafil S improved pts satisfaction with sexual activity & overall satisfaction with sexual life (p<0.001) • **Follow-up:** NR	• **A/E:** • Systemic: In 24.1% (41/170): 10 headache; 15 flushing; 7 G.I. discomfort; 8 nasal congestion; 7 visual disturbances; 9 dry mouth, restlessness, palpitations, hiccup; 1 pt (0.59%) discontinued tx due to unbearable abdominal pain

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function;

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g., Pharmacologic/Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Schmid, 2000, Switzerland (Ref ID 280)	• Enrolled/ evaluated: n=41/ n=NR • % Males: 100% • Race/ethnicity: NR • Age: 36.5 (20-63) y • Level of Injury: cervical C4-C7: 6; thoracic T1-T12: 19; lumbar L1-L5: 8; conus cauda: 4 • ASIA Level: NR • Duration since injury: 5.9 y (0.5-26) y • Dropouts: n=5 • Lost in follow-up: NR • N of sites: 1 • Funding: IRP & SNF	• **Study Design:** NCS • **Duration:** July-December 1998 • **Eligibility Criteria:** • Inclusion: documented hx of chronic SCI (traumatic lesion or spinal disease for > 6 mo) & ED attributable only to SCI • Exclusion: pts prone to autonomic dysreflexia &/or high BP, known or suspected ED of vascular origin, cardiovascular diseases, bleeding disorders, hx of stroke, peripheral neuropathy, brain damage, clinical depression, endocrine diseases, pts taking drugs such as nitrates or anticoagulants, which could interact with sildenafil • **Quality Assessment:** 10/19 (+) reported	• **Pharmacologic (n=41):** • Drug name: oral sildenafil • Dose: 50 mg sildenafil given 3 x, doses then adapted, PRN, according to pts self-reports • Duration: NR • Schedule: NR • Mode/Admin. Route: NR • **Device:** vibrator: El-star Elektronik (n= 41) • Amplitude: NR • Frequency: NR • Mode/Admin. Route: NR • **Other Device:** NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • **Anatomic/Physiologic:** 38 pts (93%) reported improved erections (grade 3-4) post sildenafil permitting sexual intercourse 1 h post intake of drug; using IIEF questionnaire: erectile function improved from a mean score of 9.2+/-4.4 to 25.4+/-4.2 ($p<0.05$); orgasm & ejaculation function slightly but NS increased from a mean of 3.8+/-2.7 to 5.2+/-3.7; NS Δ's in sexual desire post tx from a mean of 6.7+/-2.3 to 7.5+/-1.9 • **Sexual Satisfaction:** using IIEF questionnaire: intercourse satisfaction improved from mean of 4.5+/-2.5 to 10.5+/-2.0 ($p<0.05$); overall sex life satisfaction improved from a mean of 4.2+/-2.0 to 7.8+/-1.6 ($p<0.05$) • **Follow-up:** questionnaires completed pre-tx & post tx3 mo • Length: NR • Duration: NR • Results: NR	• **A/E** • Systemic: 10% (4/41) showed mild to moderate side effects, (e.g., headache (3 pts), dizziness (2 pts), flushing (2 pts), dyspepsia (1 pts) & blurred vision (1 pts)

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function; IRP = International Institute for Research in Paraplegia; SNF = Swiss National Science Foundation

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g., Pharmacologic/Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Sidi, 1987, US (Ref ID 399)	• Enrolled/ evaluated: n=66/ n=NR • % Males: 100% • Race/ethnicity: NR • Age: 35.8 (18-61) y • Level of Injury: 14 cervical, 32 thoracic & 6 lumbar, 29 UMN, 21 complete 23 LMN, 15 complete • ASIA Level: NR • Duration since injury: NR • Dropouts: n=14 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** 1 y • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 13/19 (+) reported	• **Pharmacologic (n=66):** • Drug name:averine hydrochloride (30 mg/ml), or a combination of papaverine (25 mg/ml) & phentolamine mesylate (0.83mg/ml) • Dose papaverine (25 mg/ml) & phentolamine mesylate (0.83mg/ml) 2 x wk • Duration: NR • Schedule: NR • Mode/Admin. Route • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • **Anatomic/Physiologic:** Average dose required to induce functional erection: Papaverine/phentolamine for 13 UMN 0.42+/-0.246, for 9 LMN 0.37+/-0.299. Papaverine for 10 UMN 0.403+/-0.183, for 10 LMN 0.32+/-0.166. Dose of papaverine/phentolamine in 10 pts (6 UMN, 4 LMN) who did not respond to papaverine alone: 0.395+/-0.37 & 0.4+/-0.297, respectively. No S df in average required doses observed between pts with UMN & LMN lesions or between thoracic, cervical & lumbar in both grps • **Follow-up:** • Length: NR • Duration: NR • Results: Last f/u result in n=52(total): 15 (29%) not practising vasoactive intracavernous therapy for various reasons. Frequency of use for 37 (71%) practicing vasoactive intracavernous pharmocotherapy ranged from < 1 x mo to 1-2 x wk.	• **A/E:** • Systemic: Sustained erections that required irrigation in 4 pts (2 discontinued, & 2 responded to lower doses). Compromised arterial penile blood flow in 2 pts diabetes mellitus n=1, Peyronie's disease =1. Removal of a penile prosthesis n=1

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function; UMN = upper motor neuron; LMN = lower motor neuron

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g., Pharmacologic/Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Sipski, 1995, US (Ref ID 578)	• Enrolled/evaluated: n=21:13 SCI/ 8 AB/ n=NR • % Males: 0% (all female) • Race/ethnicity: NR • Age: SCI 30 (25-44) y; AB 36 (24-49) y • Level of Injury: n=9 C4-7, n=4 T2-5 • ASIA Level: A n=13(tetraplegic) • Duration since injury: (12-232) mo • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NIH	• **Study Design:** Case-control Study • **Duration:** NR (78 m study protocol) • **Eligibility Criteria:** • Inclusion: regular menstrual cycles, no hx of gynecological or neurological surgery, no psychiatric disorders & medically stable. SCI pts of ASIA A tetraplegia of above T • Exclusion: NR • **Quality Assessment:** 6 * (NOS)	• **Pharmacologic:** NR • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Behavioral** (n=21): • Type Erotic A/V & erotic A/V combined with manual stimulation of clitoral region • Duration 6 m baseline, 12 m AV stimulation, 6 m baseline, 12 m of AV + manual stimulation, & 6 m final baseline • Frequency: NR	• **Outcomes:** • Anatomic/Physiologic: • VMP: Baseline 2-5 all S > vs. initial baseline ($p<0.05$) indicating increasing cumulative excitation effect; No S df in baselines for SCI; ABs had S > mean baseline VPA vs. complete SCI subjects ($p=0.03$); S increase in VPA in response to A/V stimulation over baseline ($p=0.03$); addition of manual stimulation to AV resulted in (+) response in VPA in all pts • Subjective arousal: AB pts showed S > levels vs. SCIs ($p=0.04$); arousal levels during A/V stimulation combined with manual stimulation S df between AB & SCI ($p=0.04$) • Interviews/ Other: Divorce: 1 SCI, 3 AB • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; m = minute; ctrl = control(s); grp = group; pbo = placebo; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; NOS = Newcastle Ottawa Scale; A/V = audio visual; ED = erectile dysfunction; IIEF = Index of Erectile Function; VPA = vaginal pulse amplitude; NIH = National Institute of Health

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g.,Pharmacologic/Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Sipski, 1995, US (Ref ID 571)	• Enrolled/ evaluated: n=35 (25 SCI; 10 AB)/NR • % Males: 0% (all female) • Race/ethnicity: NR • Age: SCI 32 (NR) y; AB 34 (NR) y • Level of Injury: n=20 C4-7, n=5 T1-5 • ASIA Level: NR • Duration since injury: 98 (10-242) mo • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NIH	• **Study Design:** Case-control Study • **Duration:** d 2 of 3 d study protocol • **Eligibility Criteria:** • Inclusion: 1. normal menstrual cycles, 2. no gyne- or neurological surgery, 3. free from psychiatric disorders, 4. medically stable • Exclusion: NR • **Quality Assessment:** 5 * (NOS)	• **Pharmacologic:** NR • **Device:** NR • **Other Device** (n=35): • Type: Physiological measurements - PPS • Manufacturer • **Surgical:** NR • **Behavioral** (n=35): • Type: A/V (sexually explicit video), manual & vibratory stimulation (with vaginal lubricant) to reach orgasm • Duration: up to 75 m • Frequency: NR	• **Outcomes:** • Anatomic/Physiologic: • NS df between any pts grps for HR, SBP, & DBP. HR & RR in AB at orgasm>baseline (HR: p=0.002 & RR: p=0.03); for SCIs S increase in HR (p=0.005), RR (p=0.001), &SBP (p=0.05) at orgasm • The ability to achieve orgasm S &(+) related to pts pinprick sensory scores in T11-L2 dermatomes(r=0.49), pinprick sensory scores in S3-S5 dermatomes(r=0.048), light touch sensory scores in T11-L2 dermatomes(r=0.47) & light touch sensory scores in S3-S5 dermatomes(r=0.45); all p<0.01. • Whether pts had orgasm seemed related to SCI but not to degree or type of SCI. • S df between neurologically intact pts (mean time to orgasm=15.11 m) & pts with no lower extremity function (mean time to orgasm =34.63) • Psychological: NR • DSFI: SCIs scored S higher on sexual role subscale (m=52.80) vs. Abs (m38.89) (p=0.005). ABs indicated > sexual satisfaction (m=54.89) vs. SCIs (m=48.24) (p=0.04). • **Follow-up:** NR	• **A/E**: NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; m = minute; ctrl = control(s); grp = group; pbo = placebo; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; NOS = Newcastle Ottawa Scale; ED = erectile dysfunction; IIEF = Index of Erectile Function; DSFI = Derogastis Sexual Function Inventory; PPS = photoelectric pulse sensor; A/V = audio visual; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; RR = respiratory rate; NIH = National Institute of Health

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g.,Pharmacologic/ Device/Behavioral/ Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Sipski, 1996, US (Ref ID 562)	• Enrolled/ evaluated: n=20: n=10 SCI; n=10 control/ n= NR • % Males: 0% (all female) • Race/ethnicity: NR • Age: SCI 30 (NR) y; ctrl 35 (NR) y • Level of Injury: n=6 C4-6, n=3 T2-5 • ASIA Level: n=10 A (tetraplegic) • Duration since injury: 93 (12-242) mo • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NIH	• **Study Design:** Case-control study • **Duration:** 3 d protocol • **Eligibility Criteria:** • Inclusion: All subjects require clearance from gynecologist & verification of absence of gynecologic problems. Monitoring of menstrual cycles for a min of 2 mo pre study participation. All study testing performed between d 16-21 of menstrual cycle • Exclusion: NR • **Quality Assessment:** 7 * (NOS)	• **Pharmacologic:** NR • **Device:** NR • **Other Device** (n=20): • Type Sphincter EMG: Dantec Couterpoint device(no.9018A0041) • Manufacturer Dantec Medical Inc., Grass Instruments, Ferrall Instruments • **Surgical:** NR • **Behavioral** (n=20): • Type: manual stimulation • Duration: 6 m baseline +12 m of Stroop (distraction test), +6min of baseline, + 12 m of Stroop test combined with manual stimulation, +6 m baseline +12 m of baseline followed by 12 m masturbation & 6 final m of baseline • Frequency: NR	• **Outcomes:** • Anatomic/Physiologic: • Comparison of VPA within grps showed S df between baseline conditions for AB subjects. Baseline 3 to 5 S greater vs. initial baseline ($p<0.05$) indicating increasing cumulative excitation effect. NS df in baselines for complete SCI. Normal subjects S greater mean baseline VPA (m=8.95) vs. complete SCI (m=4.71)($p<0.03$) • **Psychological:** • NS Δ in complete SCIs in subjective arousal with performance of distracting task in conjunction with manual genital stimulation, however showed S increases in arousal when distracting task eliminated. • **Follow-up:** NR	• **A/E**: NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; NOS = Newcastle Ottawa Scale; ED = erectile dysfunction; IIEF = Index of Erectile Function; VPA = vaginal pulse amplitude; NIH = National Institute of Health

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g.,Pharmacologic/ Device/Behavioral/ Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Sipski, 2001, US (Ref ID 462)	• Enrolled/ evaluated: Arousal study: 68 SCI, 21 AB; Orgasm study: 66 SCI, 66 ctrl/ n=NR • % Males: 0% (all female) • Race/ethnicity: NR • Age: Arousal study - SCI 33.9 (NR) y; ctrl 34.1 (NR) y. Orgasm study - SCI 32.8 (NR) y; ctrl (NR) y • Level of Injury: Arousal: C2-L4, 55 UMN (S3-5), 13 LMN, 41 incomplete & 27 complete Orgasm: NR, 12 LMN (S2-5), 50 UMN, 40 complete & 22 incomplete • ASIA Level: NR • Duration since injury: 127 (15-494) mo • Dropouts: n=6 • Lost in follow-up: NR • N of sites: 1 • Funding: NIH	• **Study Design:** Case-control study • **Duration:** 2 d protocol: d 1 pre study testing, d 2 - 78 m arousal or a 75 m orgasm protocol performed • **Eligibility Criteria:** • Inclusion: NR • Exclusion: neurological surgery with altered structure of nervous system, genital surgery, irregular or absent menstrual cycles, & active medical or psychiatric problems • **Quality Assessment:** 5 * (NOS)	• **Pharmacologic (n=x):** NR • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Behavioral** (All pts) • Type: A/V erotic stimulation/vaginal/ manual clitoral stimulation (until arousal or orgasm reached) • Duration: 78 m • Frequency: Arousal 5 x 6 m baseline periods alternated with 4 stimulus conditions: 2 x 12 m A/V followed by 2 x 12 m AVM: Orgasm: up to 75 m manual stimulation	• **Outcomes:** • Mean VPA: In ctrl subjects (n=21) S increase in VPA with 28.4 vs. baseline 23.0 ($p<0.001$). SCI: S increase in VPA with 15.7 vs. 13.9($p<0.001$). • Orgasm study results: Historically, 55% of SCI reported orgasmic ability post-SCI, vs. 44% orgasmic in laboratory. (100% of ctrl reported historically & laboratory orgasm). No S dfs in orgasmic ability between SCI according to SS at T11-L2 & S2-S5 dermatomes, completeness of injury & UMN or LMN dysfunction. • Differences in genital responsiveness to A/V based on degree of sensory impairment affecting T11-L2 dermatomes. Regardless of level of injury, marked dfs in response observed based on degree of combined light touch & in prick sensory preservation at T11-L2 dermatomes. No dfs in genital responsiveness occurred when women classified based on sensory preservation in sacral (S2-S5) or thoracic (T6-T9) dermatomes. • Subjective Characteristic of Orgasm: Data reporting location of stimulation to reach orgasm similar for both grps of SCI vs. ctrl • DSFI:SCIs scored S lower (m=46.8) vs. ctrl (m=53.0)($p=0.02$); SCIs scored lower vs. ctrl in body image ($p=0.02$); SCIs S less sexually satisfied vs. ctrl on specific & global measures of sexual satisfaction.	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; mg = milligrams; µg = microgram; tx = treatment; hx = history; ∆ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; NOS = Newcastle Ottawa Scale; ED = erectile dysfunction; DSFI = Derogastis Sexual Function Inventory; IIEF = Index of Erectile Function; A/V = audio visual; VPA = vaginal pulse amplitude; UMN = upper motor neuron; LMN = lower motor neuron; NIH = National Institute of Health

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g.,Pharmacologic/Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Sonksen, 1992, Denmark (Ref ID 356)	• **Enrolled/evaluated:** n=17/ n=NR • % Males: 100% • Race/ethnicity: NR • Age: 41 (19-51) y • Level of Injury: C2-L3, n=13 complete n=4 incomplete • ASIA Level: NR • Duration since injury: 7 (1-27) y • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: (+) erection response to 5-60 mg of papaverine injection sufficient for vaginal penetration • Exclusion: NR • **Quality Assessment:** 7/19 (+) reported	• **Pharmacologic (n=12):** • Drug name: Papaverine • Dose: 5-60 mg • Duration: NR • Schedule: NR • Mode/Admin. Route: NR • **Device:** NR • **Other Device:** • Type: Transcutaneous nitro-glycerin plaster (10mg/24 h) • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • **Anatomic/Physiologic:** 12/17 responded (+) to nitro-glycerine test: 5 complete response (full rigidity), 7 partial response (some rigidity & /or tumescence) & 5 failed to respond. Median plaster application time: 75 m. Duration of erections in 5 with complete response: 20-45 m post removal of plaster • **Follow-up:** NR	• **A/E:** • Systemic: headaches in n=6, 2/6 required tx with mild analgesics (i.e. paracetamol)

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g., Pharmacologic/Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Tang, 1995, Republic of China (Ref ID 314)	• Enrolled/ evaluated: n=15/ n=NR • % Males: 100% • Race/ethnicity: NR • Age: 38.5 (25-50) y • Level of Injury: C5 1; T4-T12 6; L1-L3 8 (n=8 incomplete lesion) • ASIA Level: NR • Duration since injury: mean 6.3 y • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 12/19 (+) reported	• **Pharmacologic (n=15):** • Drug name: prostaglandin E1 • Dose: starting at 0.5 mg with increased dosage to achieve a rigid erection of grade 5 & lasting for at minimum 20 m (a max. dosage of 20 mg would be applied) • Duration: NR • Schedule: max. recommended injection frequency 2 x wk • Mode/Admin. Route intracavernous injection • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • **Anatomic/Physiologic:** • pre-injection Schramek grading: grade 1 - 8 (53%) pts; grade 2 - 1(7.4%) pt; grade 3 - 2 (13.4%) pts; grade 4 - 1 (6.7%) pts; grade 5 - 3 (20%) pts; post-injection Schramek grading: grade 5 - 14 (93.3%) pts; grade 2 - 1 pt (6.7%); erectile condition post-tx found to be S higher vs. pre-tx ($p<0.001$); no S dosage effect of prostaglandin E1 found in df between pre-tx & post-tx • **Follow-up:** NR	• **A/E:** • Local: 2 (13.3%) pts complained of discomfort at injection site

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g., Pharmacologic/Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
van der Aa, 1995, Netherlands (Ref ID 1172)	• Enrolled/ evaluated: n=17/n=NR • % Males: 82%(14) males, 18%(3) females • Race/ethnicity: NR • Age: NR (21-54) y • Level of Injury: C5 16 T1-10, All complete lesion • ASIA Level: NR • Duration since injury: (1-15) y • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: Complete lesion of spinal cord, no previous bladder outlet surgery, incontinence, & at least 12 mo post-injury • Exclusion: NR • **Quality Assessment:** 3/19 (+) reported	• **Pharmacologic:** NR • **Device:** NR • **Other Device** (n=17): Finetech-Brindley bladder control system • Type NR • Manufacturer NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: • Sustained full erection in all (n=14) male pts, in 12 pts by stimulation of S2 anterior roots; in 2pts by stimulating S3 anterior roots • **Additional Outcomes:** Bladder capacity: increase capacity postoperation by >100 ml in 2 pts& >400 ml in 8 pts; Continence: all but 1 continent; Bowel function: 13 pts using implant for defaecation • **Follow-up:** • Length: 1-6 y (longest followup: 4 y) • Duration: NR • Results: Although loss of erection is expected post posterior rhizotomy, in this study all male pts managed to achieve erection, usually by stimulating S2 roots	• **A/E:** • Other: Disadvantage of posterior rhizotomy: loss of reflex erection

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g.,Pharmacologic/Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
van der Aa, 1999, Netherlands (Ref ID 1075)	• Enrolled/ evaluated: n=38/NR • % Males: 87%(33) male; 13%(5) female • Race/ethnicity: NR • Age: NR (18-59) y • Level of Injury: 9 C4-6 29 T1-12 (all complete) • ASIA Level: NR • Duration since injury: (1-39) y • Dropouts: n=3 • Lost in follow-up: n=2 • N of sites: 1 • Funding: NR	• **Study Design:** NCS • **Duration:** NR • **Eligibility Criteria:** • Inclusion: Completeness of lesion & intact efferent nerve supply to bladder wall minimum 12 mo post-injury • Exclusion: NR • **Quality Assessment:** 5/19 (+) reported	• **Pharmacologic:** NA • **Device:** NA • **Other Device** (n=38): • Type Brindley bladder controller • Manufacturer: NR • **Surgical:** NA • **Behavioral:** NA	• **Outcomes:** • Anatomoic/Physiologic: • Implant driven sustained full erection achieved in 29/33 males (by stimulating S3 anterior roots in 2 pts, & in 27 pts by stimulation S2 anterior roots. Erection not achieved in 4 pts. BC (n=37): increase in BC observed in all (due to posterior rhizotomy), in 15 more than 200 cc & in 14 pts more than 400 cc. Residual urine volume (n=37): No increase observed postoperation. 27 pts use implant for bowel function. Decrease in urinary tract infection rate postoperation • Psychological: NR • Sexual Satisfaction: NR • Pt logs/diaries: NR • Interviews: NR • **Follow-up:** NR	• **A/E:** • Systemic: death in 3 pts. 1 within 2 wk post intervention & 2 during f/u; pulmonary embolism in 1 pts; implant failure in 3 pts 8, 6 & 3 y post implantation. Cerebro-spinal fluid collection in 3 pts

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function; BC = bladder capacity

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g.,Pharmacologic/ Device/Behavioral/Surgical/ other)	Outcomes/Follow-up	Adverse Events/Complications
Whipple, 1996, US (Ref ID 1713)	• Enrolled/ evaluated: n=16/ n=NR • % Males: 0% (all female) • Race/ethnicity: • Age: SCI 37.2 (NR) y; ctrl 45.4 (NR) y • Level of Injury: at or below T6 • ASIA Level: NR (all complete) • Duration since injury: 12.4 (2-27) y • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** Case-control Study • **Duration:** NR • **Eligibility Criteria:** • Inclusion: SCI grp complete ASIA A SCI>1y, with intact uterus & cervix • Exclusion: psychosis, depression, or hx of cystocele, hysterectomy • **Quality Assessment:** 6 * (NOS)	• **Pharmacologic:** NR • **Device:** NR • **Other Device** (n=16): • Type A pressure transducer embedded in holder behind & aluminum head (Providing self-application to vaginal wall or to cervix) • Manufacturer: NR • **Surgical:** NR • **Behavioral:** • Type vaginal self-stimulation, cervical self-stimulation & hypersensitive area self-stimulation • Duration: 90 m • Frequency: Each experimental condition performed once, preceded & followed by rest period	• **Outcomes:** • Anatomic/Physiologic: multiple orgasms in 1 SCI T11 from vaginal self stimulation, she had increase in SBP, one SCI T8 had six orgasms in lab, two from vaginal self -stimulation, one from cervical self-stimulation, & three from hypersensitive area stimulation • Psychological: NR • Sexual Satisfaction: NR • Pt logs/diaries: NR • Divorce: 2 in SCI & 3 in ctrl grp • **Additional Outcomes:** higher incident of SCI women living with partner vs. women without SCI. BP increased S in response to vaginal & cervical self-stimulation only in complete SCI below T10. No Δ in HR in SCI grp. 3 /16 in SCI, n=1 as high as T7 & n=1 without SCI self reported orgasms during laboratory study. • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; NOS = Newcastle Ottawa Scale; ED = erectile dysfunction; IIEF = Index of Erectile Function; BP = blood pressure; HR = heart rate; SBP = systolic blood pressure

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g.,Pharmacologic/ Device/Behavioral/Surgical/ other)	Outcomes/Follow-up	Adverse Events/Complications
Zaslau, 1999, US (Ref ID 283)	• Enrolled/ evaluated: n=28/ n=37 • % Males: 100% • Race/ethnicity: NR • Age: 43.7 (24-72) y • Level of Injury: 13 cervical 15 thoracic & 9 lumbar • ASIA Level: NR • Duration since injury: 8.6 y (1-20) y • Dropouts: n=5 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design**: NCS • **Duration:** May 1994 to March 1997 • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** 10/19 (+) reported	• **Pharmacologic (n=28):** • Drug name mixture of PGE-1 & papaverin • Dose: post initial test dose of 0.5 cc, doses adjusted in increments of 0.05 cc, up to a maximum of 1.0 cc • Duration: NR • Schedule: 43% of pts inject themselves >1 x wk • Mode/Admin. Route: intracavernous injectable. papaverine 1500 mg/50 ml is combined with PGE-1 1000 miug/2ml; normal saline (48cc) is added to mixture, then subdivided into 10 vials with 10 ml of vasoactive substances/vial. Each vial contains 30 mg/ml papaverine & 10 miμg /ml of PGE-1 • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • **Anatomic/Physiologic:** • Erection: 85% of pts rated pharmacologically produced erections as good or excellent with a mean erection of 43 m; vs. all pts reported never or sometimes being able to ejaculate, 21% of those treated became able to ejaculate > 50% of time, 60% reported being always or almost always successful at intercourse representing a S improvement from 93% reporting successful intercourse occurring never or almost never; 35% pts reported being able to have successful intercourse 25-50% of time • Psychological: NR • Sexual Satisfaction: 77% of pts moderately or extremely satisfied with therapy; 90% of participants would recommend this tx to a friend • Pt logs/diaries: NR • Interviews: NR • **Follow-up:** • Length: quarterly f/u visits • Duration: mean f/u of 15 mo • Results: NR	• **A/E:** • Local: 7% (2/28) reported pain & discomfort at injection site

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; miμg/μg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 5: Evidence from other study designs regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g.,Pharmacologic/ Device/Behavioral/ Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Zasler, 1989, US (Ref ID 386)	• Enrolled/ evaluated: n=20/ n=NR • % Males: 100% • Race/ethnicity: NR • Age: 40 (21-65) y • Level of Injury: C4-L2: 9 cervical 10 thoracic 1 lumbar, n=13 complete n=7 incomplete • ASIA Level: NR • Duration since injury: ≥ 1y post • Dropouts: n=2 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design**: NCS • **Duration:** 1y (included intervention +follow-up) • **Eligibility Criteria:** • Inclusion: At least 1 y post injury, with neurogenic impotence, steady partner • Exclusion: NR • **Quality Assessment:** 13/19 (+) reported	• **Pharmacologic:** NR • **Device:** Synergist erection system) (n=20) • Manufacturer Synergist Ltd.,Fannin, Houston, TX • Frequency: NR • Mode/Admin. Route Couples assessed for first questionnaire after 20 times use of device. Usage of intervention device varied from several times per mo to as frequently as daily during f/u period • **Other Device:** NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: NR • Reflexogenic erectile capability: absent in 4 pts, partial tumescence (insufficient for vaginal penetration), & n=6 complete. Snap-gauge assessment: n=8 without any broken bands, n=4 with one, n=2 with two & n=6 with all three band broken. This assessment correlated well(r=0.92, p<0.001) with subjective reports of erectile capability • Psychological: NR • Sexual Satisfaction: See follow-up • Pt logs/diaries: NR • Interviews: NR • **Follow-up** (n=15 pts & n=14 partners): Sexual Satisfaction questionnaire • Duration: Baseline & at 6 mo • Results: quality of vaginal intercourse rated very good to excellent vs. to previous best since injury(r=0.78, p<0.001), 2 couples rated as fair to good (orogenital preference)	• **A/E:** • Local: iscomfort during intercourse with use of device in n=1. Another partner reported that she could feel seam of device. Several episodes of reflex micturition by males (n=2), resulting in loss of tumescent state but maintenance of voided urine within device

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; ctrl = control(s); grp = group; pbo = placebo; NCS = non-comparative case series; mg = milligrams; µg/miµg = microgram; tx = treatment; hx = history; ∆ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 6: Evidence from conference proceedings regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g.,Pharmacologic/Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Anonymous, 1999 UK (Ref ID 2071)	• Enrolled/ evaluated: n=26/n=26 • % males: 100% • Race/ethnicity: NR • Age: NR (21-49) y • Level of Injury: T6-L5 • ASIA Level: NR • Duration since injury: NR • Drop-outs: n=0 • Lost in Follow-up: NR • N of sites: 1 • Funding: Pfizer	• **Study Design:** Abstract from conference proceeding • **Duration:** 28 d • **Eligibility Criteria:** • Inclusion: Ability to achieve at min. moderate reflexogenic erectile response to PVS • Exclusion: NR • **Quality Assessment:** NA	• **Pharmacologic** (n=26): • Drug name: sildenafil /pbo • Dose: 50 mg • Duration: 28 d for both tx • Schedule: 1 hr pre sexual activity but not > 1x per d • Mode/Admin. Route: NR • **Device**: NR • **Other Device**: NR • **Surgical**: NR • **Behavioral**: NR	• **Outcomes:** • Anatomic/Physiologic: Improved quality of erections post sildenafil tx: After 28 d, 75% of sildenafil-tx & 7% of pbo-tx men reported improved erections. Sildenafil grp had > % of successful attempts at sexual intercourse (30% vs.15%). Total of 67% of sildenafil grp wanted to continue tx vs. 15% of pbo grp. • **Follow-up**: NR	• **A/E:** • Systemic: n=2 with possible sildenafil-related A/E - dyspepsia & respiratory disorder. Neither stopped tx.

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; m = minute; cm = centimeters; sec = seconds; mg = milligrams; µg = microgram; ctrl = control(s); grp = group; pbo = placebo; RCT = randomized clinical trial; tx = treatment; hx = history; Δ = change; S = significant; df(s) = difference(s); NS = nonsignificant; pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; (+) = positive; A/E = Adverse Events; HR = heart rate; BP = blood pressure; t.i.d = three times daily; b.i.d = two times daily; ED = erectile dysfunction; IIEF = Index of Erectile Function; PVS = penile vibratory stimulation

Evidence Table 6: Evidence from conference proceedings regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (continued)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g., Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Bodner, 1998, US (Ref ID 3021)	• Enrolled/ evaluated: n=15/NR • % male: 100% • Race/ethnicity: NR • Age: NR • Level of Injury: NR • ASIA Level: NR • Duration since injury: all ≥ 1y • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** Abstract from conference proceeding – interventional (time series before/after trial) • **Duration:** NR • **Eligibility Criteria:** • Inclusion: SCI ≥1 y post injury • Exclusion: NR • **Quality Assessment:** NA	• **Pharmacologic** (n=15): • Drug name: alprostadil (MUSE) • Dose: 125-1000 µg • Duration: NR • Schedule: NR • Mode/Admin. Route: intraurethral admin. By physician or pts • **Device:** NR • **Other Device:** Type: Actis ring • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: NR • Psychological: NR • Sexual Satisfaction: only effective dose 1000 µg, 3/15 used MUSE at home; 0/15 satisfied with quality of erection vs. IC tx (rate of 50-60% vs. IC tx); hypotension in 8/17 used MUSE without Actis ring; 7/15 used Actis ring with no transient hypotension • Patient logs/diaries: NR • Interviews: NR • **Follow-up:** NR	• **A/E:** • Local: no evidence of priapism • Systemic: transient hypotension in 8/15

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; m = minute; ctrl = control(s); grp = group; pbo = placebo; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function; IC = intracavernosal

Evidence Table 6: Evidence from conference proceedings regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g., Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Clontz, 1999, US (Ref ID 3023)	• Enrolled/ evaluated: n=12/NR • % males: 100% • Race/ethnicity: NR • Age: 40 (21-54) y • Level of Injury: n=5 cervical; n=5 thoracic; n=2 lumbar; (8/12 incomplete; 4/12 complete) • ASIA Level: NR • Duration since injury: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** Abstract from conference proceeding – interventional (time series before/after trial) • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** NA	• **Pharmacologic (n=12):** • Drug name: sildenafil • Dose: 50 mg • Duration: NR • Schedule: NR • Mode/Admin. Route: 5 samples of sildenafil/ pts • **Device:** NR • **Other Device**: NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: NR • Psychological: NR • Sexual Satisfaction: mean IIEF scores of satisfaction (4 wk f/u; range 1-10) male, 8.9 female, 9.0; erectile function improved in 9/12 (75%); 3/12(25%) experienced side effects • Patient logs/diaries: • Interviews: • **Follow-up:** • Duration: NR • Result: all pts (n=12) continued to use sildenafil	• **A/E:** • Systemic: visual ∆s in 1/12; headache in 3/12

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; m = minute; ctrl = control(s); grp = group; pbo = placebo; mg = milligrams; µg = microgram; tx = treatment; hx = history; ∆ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 6: Evidence from conference proceedings regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g., Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Kier, 1999, US (Ref ID 3033)	• Enrolled/ evaluated: n=29/NR • % males: 100% • Race/ethnicity: NR • Age: 39.3 (21-54) y • Level of Injury: n=11 cervical, n=14 thoracic, n=4 lumbar; 17/29 complete lesion, 12/29 incomplete lesion • ASIA Level: NR • Duration since injury: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** Abstract from conference proceeding – interventional (time series before/after trial) • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** NA	• **Pharmacologic (n=29):** • Drug name: sildenafil • Dose: 50 mg • Duration: NR • Schedule: NR • Mode/Admin. Route: 5 dose of 50 mg /pt • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: NR • Psychological: NR • Sexual Satisfaction: IIEF post 4 wks, improvement in ED - 83%(24/29); mean Δ in IIEF 18.3; range –39 to +55; mean pt & partner satisfaction, 8.29, & 8.46, respectively (range 1-10) • Patient logs/diaries: NR • Interviews: NR • **Follow-up:** • Length: NR • Duration: NR • Results: 25/29 (86%) found sildenafil effective & continue to use tx at home	• **A/E:** • Systemic: headache (17%); dizziness (3%); flushing (3%)

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; m = minute; ctrl = control(s); grp = group; pbo = placebo; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 6: Evidence from conference proceedings regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g., Pharmacologic/Device/ Behavioral/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Laschke, 2002, Germany (Ref ID 3041)	• Enrolled/ evaluated: n=69/n=NR • % Males: 100% • Race/ethnicity: • Age: NR • Level of Injury: NR • ASIA Level: NR • Duration since injury: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** Abstract from conference proceeding – interventional (time series before/after trial) • **Duration:** 12 wk /IIEF questionnaire completed at 4, 8 & 12 wk • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** NA	• **Pharmacologic (n=69):** • Drug name: sildenafil • Dose: NR • Duration: NR • Schedule: NR • Mode/Admin. Route: NR • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: erection & overall sexual satisfaction improvement of approx. 90% in responder grp • **Follow-up:** • Length: 2-3 mo f/u • Results: scores on IIEF NS Δ's in efficacy	• **A/E:** • Systemic: flushing & headache in 25% of pts. 10% had impairment of chromatic vision

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; m = minute; hrs = hours; m = minute; ctrl = control(s); grp = group; pbo = placebo; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 6: Evidence from conference proceedings regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g., Pharmacologic/Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Raviv, 2000, Israel (Ref ID 3006)	• Enrolled/ evaluated: n=60/NR • % males: 100% • Race/ethnicity: NR • Age: 35.2 (19-58) y • Level of Injury: 35 UMN, 13-35 quadriplegic; 25 LMN • ASIA Level: NR • Duration since injury: 26.8 (4-56) y • Dropouts: (n=0) • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** Abstract from conference proceeding – interventional (time series before/after trial) • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** NA	• **Pharmacologic (n=60):** • Drug name: sildenafil • Dose: starting dose of 50 mg increased to 100 mg (25 mg in 13 quadriplegic pts) • Duration: NR • Schedule: NR • Mode/Admin. Route: oral • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: NR • Psychological: NR • Sexual Satisfaction: UMN grp success rate as defined by improvement in ability to have sexual intercourse, & wish to continue tx, 31/35(89%); in UMN grp, 18/25(72%); overall success rate 49/60(82%); IIEF score improvement from mean, 5.48 to 6.55 ($p<0.001$) • Patient logs/diaries: NR • Interviews: NR • **Follow-up:** NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; m = minute; ctrl = control(s); grp = group; pbo = placebo; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function; UMN = upper motor neuron; LMN = lower motor neuron

Evidence Table 6: Evidence from conference proceedings regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g.,Pharmacologic/Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Shenot, 1999, US (Ref ID 3024)	• Enrolled/ evaluated: n=29/NR • % males: 100% • Race/ethnicity: NR • Age: 26.3 (NR) y • Level of Injury: C5-L1 • ASIA Level: NR • Duration since injury: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** Abstract from conference proceeding –interventional (time series before/after trial) • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** NA	• **Pharmacologic (n=29):** • Drug name: sildenafil • Dose: starting dose 50 mg; titrated to 100 mg if submaximal result obtained with 50 mg • Duration: NR • Schedule: NR • Mode/Admin. Route: oral • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes**: • Anatomic/Physiologic: NR • Psychological: NR • Sexual Satisfaction: all pts used 100 mg sildenafi; (efficacy at 6-8 wks using a physician-administered questionnaire) (+) drug effect on duration & rigidity of erections in 12/29(41%); erections satisfactory for intercourse in 4/29(14%) • Patient logs/diaries: NR • Interviews: NR • **Follow-up**: NR	• **A/E:** • Systemic: headache (7%); flushing (7%)

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; m = minute; ctrl = control(s); grp = group; pbo = placebo; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 6: Evidence from conference proceedings regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/ Eligibility Criteria	Intervention (e.g.,Pharmacologic/ Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/Complications
Takeda, 2000, Japan (Ref ID 3005)	• Enrolled/ evaluated: n=36/NR • % males: 100% • Race/ethnicity: NR • Age: 33.9 (18-59) y • Level of Injury: n=10 cervical; n=5 T1-6; n=12 T7-12; n=9 lumbar lesions • ASIA Level: NR • Duration since injury: NR • Dropouts: (n=0) • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** Abstract from conference proceeding – interventional (time series before/after trial) • **Duration:** 3 mo • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** NA	• **Pharmacologic (n=36):** • Drug name: sildenafil • Dose: NR • Duration: 3 mo • Schedule: NR • Mode/Admin. Route: oral • Device: NR • **Other Device:** NR • **Surgical:** NR • **Behavioral:** NR	• **Outcomes:** • Anatomic/Physiologic: IIEF5 score range 1-16 with mean of 5.8; drug assessed effective 22(56%); ineffective 5(13%); & unknown in 12 pts (efficacy evaluation only in pts with successful sexual intercourse followed 1 mo post dispensing the drug) • Psychological: NR • Sexual Satisfaction: NR • Patient logs/diaries: NR • Interviews: NR • **Follow-up:** NR	• **A/E:** • Systemic: autonomic dysreflexia in n=6 included headache, facial flush, chest strangled feeling

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; m = minute; ctrl = control(s); grp = group; pbo = placebo; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

Evidence Table 6: Evidence from conference proceedings regarding sildenafil & other remediation for the treatment of sexual dysfunction in individuals after SCI (cont'd)

Author, Year, Location	Study Characteristics	Study Design & Duration/Quality Assessment/Eligibility Criteria	Intervention (e.g.,Pharmacologic/Device/ Behavioural/Surgical/other)	Outcomes/Follow-up	Adverse Events/ Complications
Waldbaum, 1998, US (Ref ID 3004)	• Enrolled/ evaluated: n=15/NR • % males: 100% • Race/ethnicity: NR • Age: NR • Level of Injury: NR • ASIA Level: NR • Duration since injury: NR • Dropouts: n=0 • Lost in follow-up: NR • N of sites: 1 • Funding: NR	• **Study Design:** Abstract from conference proceeding – interventional (time series before/after trial) • **Duration:** NR • **Eligibility Criteria:** • Inclusion: NR • Exclusion: NR • **Quality Assessment:** NA	• **Pharmacologic (n=15):** • Drug name: MUSE/ prostaglandin E1 • Dose: NR • Duration: NR • Schedule: NR • Mode/Admin. Route: intraurethral admin of MUSE; intracavernous injection of prostaglandine E1(alprostadil) • **Device:** NR • **Other Device:** NR • **Surgical:** NR • **Behavioural:** NR	• **Outcomes:** • Anatomic/Physiologic: 4/15 achieved erection (grade?) with MUSE tx; 7/8/ remainder 11 pts achieved erection with prostaglandine E1 tx. • Psychological: NR • Sexual Satisfaction: NR • Patient logs/diaries: NR • Interviews: NR • Follow-up: NR	• **A/E:** NR

SCI = spinal cord injury; AB = able-bodied; NR = not reported; NA = not applicable; y = year; d = day; mo = month; wk = week; hrs = hours; m = minute; ctrl = control(s); grp = group; pbo = placebo; mg = milligrams; µg = microgram; tx = treatment; hx = history; Δ = change; S = significant; NS = nonsignificant; df(s) = difference(s); pts = participants; n = n of participants; enrolled = n qualified; evaluated = n analyzed; t.i.d = three times daily; b.i.d = two times daily; (+) = positive; A/E = adverse event; ED = erectile dysfunction; IIEF = Index of Erectile Function

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Appendix F. Additional Acknowledgments

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