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Evidence based review of medicines for sexual dysfunction in females:

A report commissioned by the New Zealand Accident Compensation Corporation (ACC)

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EXECUTIVE SUMMARY

ACC is occasionally called on to fund treatment for female claimants with sexual dysfunction caused by damage due to accident or injury. However, there appears to be little evidence on the usefulness of such products for women generally. The objective of the report was to identify what evidence (if any) there is to support the use of sexual dysfunction medicines in women experiencing sexual dysfunction due to accident or injury. The products investigated (source: May 2003 New Ethicals Catalogue) were:

- Cialis® (tadalafil) tablets
- Levitra® (vardenafil hydrocholoride trihydrate) tablets
- Uprima SL® (apomorphine) tablets, sublingual
- Viagra® (sildenafil) tablets.

Only a small number of good quality studies evaluating the efficacy and safety of female sexual dysfunction medicines were found. From the studies that were available, there was limited or no evidence that the listed medicines (sildenafil, tadalafil, vardenafil, apomorphine SL) or any other pharmacological treatments were effective and safe treatments for female sexual dysfunction. Indeed, approval is no longer being sought for sildenafil as a treatment for female sexual dysfunction. There was currently no substantive evidence available in terms of clinically significant outcomes for any of the proposed pharmacological treatments for women with sexual dysfunction caused by damage due to accident or injury.

Background and research questions

BACKGROUND

ACC is occasionally called on to fund treatment for female claimants with sexual dysfunction caused by damage due to accident or injury. However, there appears to be little evidence on the usefulness of such products for women generally.

RESEARCH QUESTION

What is the evidence (if any) to support the use of sexual dysfunction medicines in women experiencing sexual dysfunction due to accident or injury?

The products investigated (source: May 2003 New Ethicals Catalogue) were:

- Cialis® (tadalafil) tablets
- Levitra® (vardenafil hydrocholoride trihydrate) tablets
- Uprima SL® (apomorphine) tablets, sublingual
- Viagra® (sildenafil) tablets.

INTRODUCTION

Female sexual dysfunction (FSD) is a highly complex problem, affected by psychological, social and biological factors (Mark and Shifren 2003), that is often difficult to identify, classify and treat appropriately (Ragucci and Culhane 2003). What constitutes FSD remains a matter of debate (Bancroft et al., 2003). In contrast to the accepted definition of male erectile dysfunction and widespread interest in research and treatment of male sexual dysfunction, particularly erectile dysfunction, less attention has been focused on women. This is perhaps due in part to the fact that female dysfunction is multicausal and multidimensional as well as less obvious (Ragucci and Culhane 2003). There have been few studies investigating the complexities of FSD which, in turn, have led to fewer treatment options for women than men. The success of Viagra® (sildenafil) in the treatment of male sexual dysfunction has provided an impetus to seek equivalent successful pharmacological interventions for female sexual dysfunction. Controversy has arisen, however, about the role of drug companies in defining FSD and what are seen as attempts to medicalise sexual problems (Moynihan 2003; Bancroft 2002).

DEFINITION

A major barrier to the development of clinical research has been the absence of a well-defined, broadly accepted diagnostic framework and classification for FSD. There are conceptual differences about what constitutes a sexual dysfunction, when is a problem a dysfunction, and how to distinguish between dysfunction and a reaction to circumstance (Bancroft et al. 2003). The emergence of corporate sponsored definitions has led to questions as to whether a new disorder is being identified to meet unmet needs or to build markets for new medications (Moynihan 2003).

Traditional models of women's sexual health are based on a model more characteristic of men than women. In these approaches there are typically four distinct phases, desire, excitement, plateau or orgasm, and orgasmic platform (Steidle 2002). These models emphasise linearity and sequential stages with a focus on genital response to the exclusion of any responsivity of subjective sexual arousal,

excitement, pleasure or satisfaction (Basson et al. 2003). The assumptions that underlie definitions of healthy sexual functioning also define what is considered to be sexual dysfunction.

Challenges have been made to the fundamental assumptions that underlie traditional definitions of FSD (Basson et al. 2003), including that of the female sexual response being the same as in the male. Problems of flawed conception based on male response have led to definitions of FSD that have been unsatisfactory and have been criticised for not reflecting women's actual experience (Basson et al. 2003, p.222). Although there is no directly comparable data, Bancroft et al. (2003) contend that patterns of sexual functioning are different for men, with greater importance attached to genital response and therefore, they argue, it is important to conceptualise sexual problems of women differently than those for men.

Older definitions of female sexual dysfunction have come primarily from the mental health field such as in the widely used Diagnostic and Statistical Manual of Mental Disorders – 4th edition (DSM IV) and draw on traditional notions of sexual functioning (Bancroft et al. 2003; Basson et al. 2003; Steidle 2002). The DSM IV delineates categories into disorders of desire, arousal, orgasm and pain. For any particular category to meet the definition, the condition must be persistent and recurrent and cause personal distress (Mark and Shifren 2003).

The category of sexual desire disorder contains the subcategories of hypoactive desire disorder and sexual aversion disorder. Hypoactive sexual desire disorder is defined as the persistent or recurrent deficiency (or absence) of sexual fantasies, thoughts, and/or desire for, or receptivity to sexual activity which causes personal distress. Sexual aversion disorder is the avoidance of genital sexual contact with a sexual partner and is generally found in women who have been through some sort of sexual crisis (Steidle 2002, p.35).

Sexual arousal disorders form the most common type of sexual dysfunction and can include a wide range of disorders, although no subgroups are formally recognised (Fourcroy 2003). Sexual arousal disorders are basically defined as the inability to obtain or maintain adequate lubrication or swelling during the excitement phase (Steidle 2002).

Orgasmic disorder is the persistent or recurrent difficulty, delay in, or absence of attaining orgasm following sufficient sexual stimulation and arousal, causing personal distress. The diagnosis is one that is very difficult to make (Steidle 2002).

Sexual pain disorders include dyspareunia, vaginismus, and other sexual pain disorders that interfere with satisfactory sexual intercourse and orgasm. None of the pharmacological treatments investigated are designed to target sexual pain disorders.

Identified difficulties with this system of classification include the separation of sexual functioning into four distinct phases, which is not seen as representative of actual functioning, and the lack of provision of objective criteria (Meston and Frohlich 2001). An alternative cycle has been offered by Basson (2003) in a biopsychosocial model that contextualises women's sexuality and emphasises the emotional component in female sexual desire (Fourcroy 2003).

An international multidisciplinary group attempted to address the problems identified and create a definition that would be more useful in all types of clinical practice, add context to diagnosis, and have more relevance to ongoing research (Mark and Shifren 2003). The definition built on the DSM IV and WHO International Classification of Diseases-10 (ICD 10) and continued to use the four categories (sexual desire disorders, sexual arousal disorders, orgasmic disorder, sexual pain disorders) of the DSM IV. The personal distress criterion was strengthened so that a woman's personal experience alone should govern diagnosis (Fourcroy 2003). The consensus model has also been called into question, however it continues to be part of the ongoing re-evaluation of women's sexual response cycle and the conceptualisation of FSD (Fourcroy 2003).

AETIOLOGY

A wide range of possible etiologies, both psychogenic and organic, for female sexual dysfunction have been identified. Psychogenic causes can include relationship issues, depression, self-esteem, body image disturbance and a history of sexual abuse. Organic causes include cardiovascular disorders, thyroid disorders, androgen deficiency, neurologic diseases and bladder diseases. Menopause has been a widely debated cause for decline in female sexual function in later life (Mark and Shifren 2003). Although some aspects of sexual function may be attributed to menopausal status, more consistent predictors may be health and relationship indices. A number of medications (e.g., antipsychotics, serotonin selective reuptake inhibitors (SSRIs), cardiovascular and antihypertensive agents) can also cause sexual dysfunction. Bancroft et al. (2003) reported from their survey findings that lack of emotional well-being and negative emotional feelings during sexual intercourse with a woman's partner were more important determinants of sexual difficulties than impairment of the more physiological aspects of female sexual response.

The sexuality of women with spinal cord injury (SCI) received little attention until the 1990s. Much of the information discussed on sexual response following brain dysfunction is based on animal studies with little research available on the impact of traumatic brain injury on female sexual functioning (Sipski and Behnegar 2001). From evidence that is available, however, vaginal lubrication and engorgement appear to occur in response to direct stimulation if the sacral reflex arc is intact and to psychogenic stimulation with LMN lesions (Burns et al. 2001, p.133). It is reported that the ability to achieve orgasm is significantly decreased in women with spinal cord injury when compared with able-bodied controls (Burns et al. 2001).

PREVALENCE

Given the definitional and conceptual debates that surround FSD, it is not surprising that identifying agreed upon prevalence rates is difficult. Methods may be developed that distinguish between dysfunction and reaction to circumstances, but in the meantime Bancroft et al. (2003) urge caution in estimating the prevalence of female sexual dysfunction.

A commonly cited prevalence rate is that from the Lauman et al. (1999) study which indicated 43% of women have sexual dysfunction, a much higher rate than the 31% reported for men (Ragucci and Culhane 2003). The Lauman et al. (1999) findings were based on yes/no answers with no inquiry as to whether there was any distress caused by problems. In spite of Lauman et al.'s conclusion that reported problems were highly associated with negative experiences in sexual relationships and overall well-being, the 43% prevalence rate is widely quoted as evidence for the need for effective medical treatment for women with sexual problems (Bancroft 2002).

A review of five prevalence studies of FSD (Bancroft et al. 2003) found that despite methodological differences, analysis showed broadly similar results when considering prevalence of operationally defined problems. The distribution of these specific problems, however, varied so that estimates of individual problems showed considerable variation. While in Bancroft et al.'s (2003) survey, 44.3% of women qualified for one or more problems, only 24.4% of respondents reported marked distress. Lack of sexual interest was significantly more common in older women but when the association between low interest and marked distress was considered, the age factor largely disappeared (Bancroft et al. 2003). The evidence suggests that aging effects on genital response are more evident in men and aging effects on sexual interest more evident in women and for many women such effects are not a cause of concern.

From the limited research that has been undertaken on sexual functioning for women after spinal cord injury, it has been reported that the frequency of sexual activity appears to decrease after SCI. Sexual satisfaction has also been shown to decrease (Benevento and Sipski 2002).

TREATMENT OPTIONS

The focus of this review is on pharmacological treatment options for FSD. There are a number of psychological and counseling therapies available, but as they fall outside the scope of this review they will not be discussed.

The search for treatment options is complicated by the interaction of the categories of sexual response (desire, arousal and orgasm). Pharmacological treatments developed to date have largely targeted sexual desire and sexual arousal disorders. Most of the agents being trialled have a history in the treatment of male sexual dysfunction, specifically erectile dysfunction. Six major pharmaceutical paths are being pursued for the treatment of female sexual disorders and/or post menopausal symptoms. The major groupings of treatment options identified by Fourcroy (2003) are outlined in Table 1.

Table 1. Potential treatments being developed for female sexual dysfunction

Drug mechanism of action	Probable indication	Product	Developing company (phase of development)
Dopamine receptor agonist	Desire	Intranasal apomorphine	Nastec/Pharmica (phase II)
Nonselective alpha1 and alpha2 androceptor antagonist	Arousal	Oral phentolamine	Zonagen (phase 1)
Nitric oxide system			
▪ Phsophodiesterase IV inhibitor	Arousal	Sildenafil	Pfizer (phase II)
	Arousal	Tadalafil	Liliy/ICOS (phase II)
▪ Other nitric oxide donors	Arousal	Arginine + yohimbine	NitroMED
Alpha-melanocyte stimulating hormone analogue	Desire and arousal	PT-141	Palatin (phase I)
Prostaglandins (smooth muscle relaxant)	Arousal	Alprostadil topical gel	Vivus (phase II)
	Arousal	Alprostadil topical	Nexmed
Androgens			
▪ Testosterone	Desire	Transdermal testosterone	Watson/Proctor & Gamble (phase III)
		Testosterone gel	
▪ Estrogen/androgen combination	Desire	Esterified estrogen/ methyltestosterone	Cellergy Solvay
▪ Anrogenic dietary supplements	No claims for an indication	Multiple androgen substances	Multiple sources
Natural products	No claims for an indication	Zestra (deemed as 'generally recognized as safe' and is available via the internet	Qualilife

Fourcroy (2003, p.1450)

From the listed medicines apomorphine administered intranasally is being developed and apomorphine administered sub-lingually has also been trialled for FSD (Caruso et al. 2004). Intranasal apomorphine is also in development for male sexual dysfunction and apomorphine SL has been marketed for the treatment of male erectile dysfunction.

PDE5 inhibitors, primarily sildenafil, which are used extensively in the treatment of erectile dysfunction are being trialled for FSD. Nitric oxide has been implicated as a vasodilator in clitoral corpus carvernousum and vaginal muscularsis smooth muscle relaxant and this is thought to be the possible mechanism of action with women for these agents (Caruso et al. 2001).

Other male sexual dysfunction treatments that are being trialled for female dysfunction include alprostadil (in topical form) and phentolamine (development of an oral release formulation). Combinations of phentolamine and alprostadil in cream have also been investigated but it appears these studies have been abandoned (Fourcroy 2003).

Considerable attention has been paid to the use of testosterone in treating FSD (administered by injection, orally, transdermal patch or gel). Suggested indications for testosterone replacement therapy include premature ovarian failure, premenopausal iatrogenic causes for testosterone deficiency, deficiency following natural, surgical or post chemotherapy-induced menopause (Berman & Goldstein 2001).

There have been phase III trials with a transdermal testosterone patch and phase I/II trials with a transdermal testosterone metred gel product. Combinations with estrogen have also been investigated (Fourcroy 2003).

OUTCOME MEASURES

The choice of measures is a critical issue both in initial assessment of sexual dysfunction and evaluating treatment effects. Unlike male sexual arousal which is relatively easy to assess and evaluate, the dimensions that characterise female sexual response have been difficult to specify (Islam et al. 2001, p.525). Although there are a variety of possible measures available, relatively few have been developed specifically for use in clinical trials. There are challenges to the design and interpretation of trials that are in part due to characterising the clinical diagnosis, the non-independence of the variables desire, arousal, organism and pain and the contribution of confounding variables and relationship issues (Islam et al. 2001). A FDA guidance paper for the clinical development of FSD treatments recognises four components of sexual response, but has been criticised for treating each as individual components without understanding the complexity and current thinking regarding female sexual functioning, and for its emphasis on orgasm as an endpoint rather than satisfactory sexual intercourse (Fourcroy 2003, p.1449).

Attempts have been made to establish normative data for a range of physiological measures for sexual response (Moynihan, 2003). The design and inclusion of valid, reliable, non-invasive and acceptable endpoints to measure physiological outcomes of clinical trials assessing FSD is complicated (Fourcroy 2003). Much of the recently published research on FSD has focused on physical genital changes that occur as a component of women's sexual response or following exposure to drug products as a surrogate to measure clinically meaningful endpoints such as enhanced sexual functioning and satisfaction (Allen 2002). In addition to the considerable uncertainty as to whether or not physiological measures can meaningfully be used as a substitute for subjective sexual satisfaction, many of the objective measures (e.g., magnetic resonance imaging and photoplethysmorgraph devices) are intrusive, patient 'unfriendly', expensive and not well standardised or normed (Rosen 2002).

A number of quality of life questionnaires have recently been developed. These include Female Sexual Function Index (FSFI), Female Sexual Distress Scale (FSDS), Sexual Function Questionnaire (SFQ), Female Intervention Efficacy Index (FIE) and the Brief Index of Sexual Functioning for Women (BISF-W). Typically questionnaires assess sexual functioning across a number of domains such as sexual desire, arousal, orgasm and satisfaction and measure average responses over a specified period of time, usually four weeks (Rosen 2002). If used, event logs/diaries are completed after each episode of sexual activity and assess sexual functioning and satisfaction. Interview assessments have also been used to gather outcome information.

METHOD

For assessment of efficacy and safety, the review included English-language reports of randomised controlled trials of at least four weeks duration, in adult women of mixed aetiology with symptoms related to FSD, with 50 or more cases at enrolment and that measured clinically relevant outcomes. Studies were included where one identified product was evaluated against placebo. For assessment of adverse effects, observational cohort studies were included where available, as well as randomised controlled trials.

Search strategy

A comprehensive literature search of major relevant bibliographic and review databases was undertaken. Additional searches for clinical trials, guidelines, government publications, and other evidence-based material were also carried out. A range of subject heading and keyword searches were used to search the indexed databases. The search was not restricted by date, but was restricted to English-language. In addition, a methodology filter was used to identify systematic reviews and randomised controlled trials.

The literature search identified 372 potentially relevant journal references. After screening the abstracts of these references, 74 articles were retrieved for analysis.

The following databases were searched using the search strategy outlined in Appendix 2.

Bibliographic databases

- Medline
- Cinahl
- Embase
- Web of Science
- Current Contents
- Psychinfo
- Toxnet
- BIOSIS
- International Pharmaceutical Abstracts
- Cochrane Controlled Trials Register

Review databases

- Cochrane Database of Systematic Reviews
- Database of Abstracts of Reviews of Effects
- Health Technology Assessment Database
- NHS Economic Evaluation Database

RESULTS

While there were many articles that discussed issues in assessment and treatment possibilities of FSD (Basson 2002; Fourcroy 2003; Mark and Shifren 2003; Rosen 2002; Sorbera et al. 2001), there was a dearth of studies actually investigating efficacy and safety of listed medicines or proposed other treatments. Many treatments that are used in practice, primarily for arousal or desire disorders, were not supported by adequate evidence (Modelska and Cummings 2003). What evidence there was produced either mixed results or limited to no evidence for the efficacy of treatments.

The studies that were available evaluating FSD treatments were generally limited by their small sample size, lack of standardisation and objective outcome measures, use of populations with undifferentiated sexual disorders, short duration and lack of evaluation of significant clinical outcomes (Everaerd and Laan 2000; Miller and Hunt 2003). There were no long-term studies. Much of the literature related to the treatment of FSD in post-menopausal women. No studies that evaluated clinically significant outcomes were located for women who might be similar to ACC claimants – i.e., women experiencing sexual dysfunction due to accident or injury.

Sildenafil

From the listed medicines, sildenafil use was investigated in the most studies. Three studies with sildenafil use to treat FSD met the criteria for inclusion in evidence tables. However, given Pfizer's recent decision to abandon efforts to file for the approval of sildenafil as a treatment for FSD (Mayor, 2003), it was deemed to be redundant to give detailed information on those studies. Pfizer's decision not to continue with sildenafil as a treatment for FSD came after clinical trials involving around 3,000 women *(www.pfizer.com)* failed to demonstrate conclusive results and would not support seeking regulatory approval to use the drug in the treatment of FSD.

Published studies of sildenafil use in the treatment of mainly arousal disorders reported similar limited or no efficacy findings. A randomised double-blind, placebo controlled study with 577 pre and 204 post menopausal women (Basson et al. 2002) did not find any significant differences between sildenafil and placebo on any patient or partner endpoints used. In studies that reported improvements in sexual functioning from sildenafil use with premenopausal (Caruso et al. 2001) and postmenopausal women

(Berman et al. 2003), participants were reported as highly motivated and given the exclusion criteria in operation, probably not typical of the FSD population.

Adverse events similar to those found in studies with male use of sildenafil have been reported. Adverse events are generally mild to moderate and include headache, flushing, rhinitis, nausea, visual disturbances and dyspepsia (Basson et al. 2002; Berman et al., 2003).

The only study (Sipski and Behnegar 2001) located that specifically looked at sildenafil use in women with spinal cord injury was laboratory based and did not evaluate clinically significant outcomes. The study evaluated the effects of sildenafil on sexual and cardiovascular responses in 19 women with spinal cord injury. While a significant increase in subjective sexual arousal with sildenafil was reported compared with placebo this was in response to laboratory measures, not actual sexual functioning and satisfaction.

Vardenafil and tadalafil

There were no published studies located for the other listed PDE5 inhibitors vardenafil and tadalafil. Tadalafil is undergoing phase II trials (Fourcroy 2003). Given Pfizer's withdrawal from seeking approval for sildenafil, it may be unlikely that the drug companies manufacturing vardenafil and tadalafil will pursue approval for these medicines in the treatment of FSD.

Apomorphine SL

One published study (Caruso et al. 2004) on the listed medicine apomorphine SL was located and included in an Evidence Table (Appendix 1). The study was with 62 premenopausal volunteers who had consulted a sexology service for sexual dysfunction and were diagnosed with sexual arousal disorder or recurring hypoactive desire disorder. Of the 50 women who completed the "as required" phase, 44 had no improved response from apomorphine. The 44 non-responders then took part in double-blind crossover daily intake of either apomorphine 2mg or 3mg or placebo. The daily intake of apomorphine showed some efficacy for improved arousal and desire when compared with placebo. The authors suggested that daily administration may be better than "as required" dosing because of the pharmacokinetics of apomorphine which is rapidly cleared from plasma with an apparent elimination half-life of approximately three hours. Most adverse events reported were rated as mild or moderate and most occurred in people taking 3mg with 7/50 experiencing nausea and 3/50 vomiting during the "as required" phase. During the daily regime of 3mg 7/44 women discontinued apomorphine, two because of fear of problems, two with vomiting and three because of headaches and nausea. Three stopped the 2mg dose because of fear of undesirable side effects. Clearly, further evidence is needed from larger studies with different subgroups before any conclusions can be reached regarding the efficacy and safety of this treatment for FSD.

Testosterone

Most studies investigating treatment with testosterone have been with post menopausal women with sexual dysfunction. One such study with women with total hysterectomy and removal of both ovaries reported a positive effect on sexual functioning for women using transdermal testosterone patches (Mark and Shifren 2003). A strong placebo effect was also seen in the study. While there has been considerable interest in testosterone gel, there have been no controlled studies evaluating its effectiveness (Miller and Hunt 2003). Reported adverse effects of testosterone use in women have included masculinisation, voice changes, facial acne, bloating, fluid retention, agitation and nipple discharge (Miller and Hunt 2003; Modelska and Cummings 2003). The long-term effects of testosterone use in women are unknown.

Topical alprostadil

Topical alprostadil use has undergone several phase I and II trials with transdermal metred gel (Fourcroy 2002). A study (Padma-Nathan et al. 2003) with 92 women presenting with sexual arousal

disorder demonstrated that topical application of alprostadil cream (1,000ug and 1,500ug) prior to vaginal intercourse improved women's arousal. However, the improvement was not statistically significant in comparison to the effects of a placebo cream. Estrogen/progestogen HRT and estrogen/androgen HRT have also been tried in the treatment of FSD in post menopausal women (Modelska and Cummings 2003) but there were no good quality study results available.

Cost-effectiveness of pharmacological treatments for FSD

Goldmeister et al. (2004) suggested that FSD medicines may be a more cost-effective alternative in the treatment of FSD than practitioner-based psychological therapies. Until, there is more compelling evidence for the efficacy and safety of pharmacological treatments than currently exists it is premature to consider cost-effectiveness.

SUMMARY

While there was much discussion in the literature about the possibilities for pharmacological treatment of FSD, there was a lack of good quality studies evaluating the efficacy and safety of proposed treatments. It is unclear at this stage whether any of these treatments will prove both safe and effective for treatment of FSD (Fourcroy 2003). Bancroft (2002) argues that until we can distinguish between adaptive inhibitions of response and those that are maladaptive dysfunctions, it will be difficult to predict when pharmacological treatment will be helpful.

From the studies that were available, there is limited or no evidence that the listed medicines (sildenafil, tadalafil, vardenafil, apomorphine SL) or any other pharmacological treatments were effective and safe treatments for FSD. Indeed approval is no longer being sought for sildenafil as a treatment for female sexual dysfunction. There is currently no substantive evidence available in published studies in terms of clinically significant outcomes for any of the proposed pharmacological treatments for women with sexual dysfunction caused by damage due to accident or injury.

Appendix 1: Evidence Table

Evidence Table 1. Apomorphine

Authors	Study design Objective Study location(s) Duration	Participants Inclusion/ exclusion	Exposure/ Comparison	Outcomes (Include adverse-events), effect size and precision	Conclusions, comments level of evidence, quality rating
Caruso et al., 2004	Study Design Open label prospective study, followed by randomised double-blind, three crossover period, placebo-controlled study. Objective To verify whether apormorphine SL is effective in premenopausal women affected by arousal disorder with hypoactive sexual desire disorder. Study location Italy Duration 12 weeks	Participants 62 women aged 26-45 years (mean age 34.2). Inclusion criteria Women with a stable, satisfying heterosexual relationship affected by acquired or generalised sexual dysfunction and desire disorder towards a heterosexual and constant sexual arousal disorder who were consequently unable to attain orgasm. Recurring deficiency of sexual fantasies and/or thoughts who did not experience any clitoral and vaginal sensation or were slow to respond after sufficient sexual stimulation in whom lubrication did not result, for a minimum of 6 months. Exclusion criteria History of hypertension, thromboembolic disorder, coronary artery disease, diabetes, impaired hepatic function or neoplasia, taking any medication with a known influence on sexual function, smoking and/or alcohol abuse, hormone therapy or oral contraceptives, dysphoric arousal.	Two week screening period and a four week 'as required' dose escalation regimen of 2 or 3 mg apomorphine SL. Those women without a response to 'as required' treatment participated in a randomised, double-blind, three crossover period, placebo-controlled study. Randomly allocated to one of six possible sequences each of which contained three medication series: apomorphine 2mg, apomorphine 3mg or placebo. Each tablet taken daily, placed under tongue during afternoon and allowed to dissolve. Recorded on diary cards frequency of sexual desire success at achieving sexual arousal and orgasm during screening and treatment periods using Personal Experiences Questionnaire. All adverse events reported by women were recorded. At completion of study women were asked to indicate whether they would continue using treatment.	Efficacy Two week 'as required' 2mg apomorphine SL, all 55 used drug; 50 took 3mg for second two weeks and five discontinued for protocol violations. Used dose at least twice a week. Forty-four women reported no change in sexual behaviour. Forty-four as required non-responders started randomised crossover placebo control receiving each drug for two week periods. Daily apomorphine (2 & 3mg) significantly higher than placebo desire ($P<0.05$, $P<0.001$), arousal ($P<0.05$, $P<0.001$), orgasm ($P<0.01$, $P<0.001$), enjoyment ($P<0.05$, $P<0.001$), satisfied by frequency ($P<0.01$, $P<0.001$), frequency of intercourse ($P<0.01$, $P<0.001$). Effects of daily morphine 3mg better than those of 2mg ($P<0.05$). The order in which treatments allocated did not show any carry over effect. Of 37 completors, 20 (69%) reported satisfaction with treatment on sexual desire and arousal. All were willing to continue treatment after end of study. Adverse events Taken as needed phase – most AEs mild or moderate, mainly occurring with 3mg apomorphine. Of 50 women, 7 (14%) had nausea, 3 (6%) vomiting. Daily regimen 3mg apomorphine, of 44 women 7 (16%) stopped taking drug: two had fear of problems, 2 vomiting, 3 headache, nausea and dizziness.	Daily apomorphine may improve sexual life of women affected by sexual difficulties. Apomorphine as needed did not improve sexual functioning. Additional studies need to define daily use of apomorphine in large subgroups of women on the basis of aetiology and severity of dysfunction. Short period of time on treatments. Level of evidence 11 Rating fair to good

Appendix 2: Search strategies

Medline strategy

1 randomized controlled trials/ (33004)
2 randomized controlled trial.pt. (190610)
3 random allocation/ (51057)
4 double blind method/ (78671)
5 single blind method/ (8226)
6 clinical trial.pt. (385495)
7 exp clinical trials/ (155961)
8 (clinic$ adj trial$).tw. (79022)
9 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$ or mask$)).tw. (75265)
10 placebos/ (23100)
11 placebo$.tw. (84777)
12 randomly allocated.tw. (7727)
13 (allocated adj2 random).tw. (607)
14 meta-analysis/ (5442)
15 (metaanaly$ or meta analy$).tw. (11471)
16 meta analysis.pt. (9310)
17 exp review, literature/ (2045)
18 (systematic adj (review$ or overview$)).tw. (5696)
19 or/1-18 (559409)
20 comment.pt. (252952)
21 letter.pt. (508528)
22 editorial.pt. (162961)
23 animal/ (3647785)
24 human/ (8533270)
25 23 not (23 and 24) (2804717)
26 or/20-22,25 (3481219)
27 Sex Disorders/ (3628)
28 "sexual and gender disorders"/ or dyspareunia/ or sexual dysfunctions, psychological/ (2806)
29 Orgasm/ (1185)
30 Vagina/ (17414)
31 "Genitalia, Female"/ (5579)
32 "Sexual Behavior"/ (24325)
33 ((sex$ or orgas$ or arous$) adj3 (disorder$ or difficult$ or dysfunct$ or discomfort$ or pain$)).mp. (9290)
34 or/27-33 (57990)
35 exp Phosphodiesterase Inhibitors/ (54910)
36 cialis.tw. (16)
37 Carbolines/ (2522)
38 levitra.ti. (4)
39 *"Piperazines"/ (11224)
40 exp imidazoles/ or exp piperazines/ (187886)
41 (levitra or vardenafil).tw. (72)
42 Apomorphine/ (7441)
43 (uprima or apomorphine).tw. (7269)
44 (viagra or sildenafil).tw. (1454)
45 or/35-44 (248103)
46 34 and 45 (785)
47 19 and 46 (194)
48 47 not 26 (191)
49 limit 48 to english language (174)

Cinahl strategy

1 Meta Analysis/ (4489)
2 (meta analy$ or metaanaly$).tw. (2349)
3 (systematic$ adj (review$ or overview$)).mp. (5357)
4 "literature review"/ or "systematic review"/ (3240)
5 exp Clinical Trials/ (27262)
6 clinical trial.pt. (11127)
7 (clinic$ adj trial$).tw. (6301)
8 randomi?ed controlled trial$.tw. (5288)
9 ((singl$ or doubl$ or tripl$ or trebl$) adj (blind$ or mask$)).tw. (3635)
10 Placebos/ (2440)
11 placebo$.tw. (5580)
12 (random$ adj allocat$).tw. (787)
13 or/1-12 (36826)
14 sexual dysfunction, female/ or dyspareunia/ (609)
15 sex/ or coitus/ or orgasm/ (689)
16 genitalia, female/ or vagina/ (449)
17 ((sex$ or orgas$ or arous$ or libido) adj3 (disorder$ or difficult$ or dysfunct$ or discomfort$ or pain$)).mp. (1463)
18 or/14-17 (2868)
19 (tadalafil or cialis).mp. [mp=title, cinahl subject headings, abstract, instrumentation] (11)
20 "Enzyme Inhibitors"/ (373)
21 (levitra or vardenafil).mp. (12)
22 Apomorphine/ (18)
23 (uprima or apomorphine).mp. (25)
24 Sildenafil/ (306)
25 (viagra or sildenafil).mp. (347)
26 or/19-25 (728)
27 26 and 18 and 13 (14)

Embase strategy

1 exp meta analysis/ (18627)
2 (metaanaly$ or meta analy$).tw. (10274)
3 (systematic$ adj (review$ or overview$)).mp. (5572)
4 randomized controlled trials/ (86067)
5 clinical trial/ (299499)
6 randomization/ (11241)
7 single blind procedure/ (4799)
8 double blind procedure/ (47734)
9 crossover procedure/ (15075)
10 placebo/ (44976)
11 randomi?ed controlled trial$.tw. (13724)
12 (clinic$ adj trial$).tw. (64387)
13 ((singl$ or doubl$ or tripl$ or trebl$) adj (blind$ or mask$)).tw. (55909)
14 placebo$.tw. (66296)
15 (random$ adj allocat$).tw. (6657)
16 prospective study/ (38643)
17 or/1-16 (425754)
18 case study/ (1690)
19 case report.tw. (66461)
20 abstract report/ or editorial/ or letter/ (411954)
21 or/18-20 (478869)
22 animal/ (7043)
23 exp animal experiment/ (646991)
24 22 or 23 (650888)
25 human/ (3852144)
26 24 not (24 and 25) (604620)

27 sexual dysfunction/ or anorgasmia/ or libido disorder/ or orgasm disorder/ or female sexual dysfunction/ or dyspareunia/ or frigidity/ or vaginism/ (6587)
28 exp female genital system/ (60287)
29 sexual behavior/ or coitus/ or orgasm/ or sexual intercourse/ (21789)
30 ((sex$ or orgas$ or arous$ or libido) adj3 (disorder$ or difficult$ or dysfunct$ or discomfort$ or pain$)).mp. (6711)
31 or/27-30 (90347)
32 Tadalafil/ (229)
33 (cialis or tadalafil).af. (272)
34 Vardenafil/ (293)
35 (levitra or vardenafil).mp. (303)
36 Apomorphine/ (5571)
37 (uprima or apomorphine).mp. (6008)
38 Sildenafil/ (3061)
39 (viagra or sildenafil).af. (3121)
40 or/32-39 (8906)
41 31 and 40 and 17 (340)
42 41 not (21 or 26) (318)
43 limit 42 to english language (297)

PsychInfo strategy

1 exp sexual function disturbances/ or frigidity/ or inhibited sexual desire/ or vaginismus/ (3432)
2 orgasm/ or female orgasm/ (439)
3 sexual arousal/ or inhibited sexual desire/ or sex drive/ or libido/ or sexual satisfaction/ (2129)
4 female genitalia/ or vagina/ (573)
5 ((sex$ or orgas$ or arous$) adj3 (disorder$ or difficult$ or dysfunct$ or discomfort$ or pain$)).tw. (6551)
6 or/1-5 (10122)
7 cialis.mp. (1)
8 tadalafil.mp. (3)
9 cyclic adenosine monophosphate/ (320)
10 (levitra or vardenafil).mp. (1)
11 uprima.mp. (0)
12 apomorphine/ (1550)
13 apomorphine.mp. (2283)
14 viagra.mp. (50)
15 sildenafil.mp. (100)
16 or/7-15 (2716)
17 6 and 16 (111)
18 limit 17 to english language (107)
19 limit 18 to ("0700 editorials" or "0810 case study" or 1200 letter) (7)
20 18 not 19 (100)
21 from 20 keep [SELECTED] (34)

Searches from other sources

In databases and all other sources without controlled vocabulary combinations of the index terms and additional keywords from the above strategies were used in the search. Searching was completed in July 2004.

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