

Sexual psychophysiology and effects of sildenafil citrate in oestrogenised women with acquired genital arousal disorder and impaired orgasm: a randomised controlled trial

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Objective Some postmenopausal women lose genital sexual responsivity despite preserved subjective sexual arousal from non-genital stimuli. When oestrogen replacement is without benefit, both the underlying pathophysiology and management of this acquired genital female sexual arousal disorder are unclear. We aimed to study the effect of sildenafil on sexual arousal and orgasmic functioning of such women. Secondly, we aimed to explore the concordance between a detailed historical assessment of genital response in real life, with laboratory vaginal photoplethysmographic assessment of genital vasocongestion.

Design Session one consisted of a semi-structured clinical interview to assess real life sexual arousal. Session two employed vaginal pulse amplitude and self-report questionnaire assessment of erotica-induced sexual arousal. Sessions three and four were a randomised, double-blind, placebo-controlled crossover administration of sildenafil on orgasm latency, intensity, perception of genital congestion and subjective arousal to erotica *plus* clitoral vibrostimulation.

Setting University associated Sexual Medicine Clinic and Psychophysiology Laboratory.

Sample Volunteer sample of 34 oestrogenised postmenopausal women with acquired genital female sexual arousal disorder and impaired orgasm.

Methods Sildenafil (50 mg) or placebo administered over two laboratory sessions.

Main outcome measures Orgasm latency and intensity during drug sessions; subjective and psychophysiological sexual arousal during photoplethysmography session.

Results The erotic video significantly increased subjective sexual arousal in all women. Vaginal pulse amplitude responses varied from robust to absent. Although across all women, sildenafil improved neither arousal nor orgasm, subsequent analyses comparing high *versus* low vaginal pulse amplitude responders revealed significantly reduced latency to orgasm, and increased subjective sexual arousal and perception of genital arousal in the latter group of women.

Conclusion The data suggest that oestrogenised postmenopausal women with genital female sexual arousal disorder and orgasmic impairment based only on clinical assessment do not benefit from sildenafil. However, the photoplethysmograph had predictive value—those women showing low vaginal pulse amplitude response benefited from sildenafil compared with women with a higher response. Thus, oestrogenised women diagnosed with acquired genital female sexual arousal disorder may be a heterogeneous group and the photoplethysmograph might be useful in their further characterisation.

INTRODUCTION

New models of women's sexual function accept that sexual arousal might precede awareness of sexual desire and then the two be experienced together^{1–4}. A percentage of women presenting with loss of sexual motivation trace this to losing genital responsivity. Despite retaining their ability to be mentally sexually aroused by erotica and non-genital sexual stimulation, genital stimulation is no longer rewarding³. The latter fails to trigger subjective arousal and desire for more intense stimulation. Typically, orgasm is of reduced intensity, no longer potentially multiple, very much delayed or not experienced at all. The underlying pathophysiology of acquired genital female sexual arousal disorder and diminished orgasmic experience is poorly

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understood except in neurological disease. Its management is also unclear, particularly in the postmenopausal but oestrogen replete woman. The first objective of this study was to explore the effects of a phosphodiesterase inhibitor, sildenafil citrate, on sexual arousal and orgasmic functioning, in a laboratory setting. The literature on efficacy of sildenafil in women with sexual dysfunction has been mixed with reports of (1) no effect in two large diagnostically heterogeneous groups of oestrogenised and non-oestrogenised women with sexual dysfunction that included impairment of arousal⁵, (2) marginally increased subjective sexual arousal and vaginal vasocongestion in women with spinal cord injury⁶ and (3) significantly increased self-reported sexual arousal in premenopausal women with acquired genital female sexual arousal disorder⁷. Caruso *et al.*⁷ hypothesised that postmenopausal women experiencing impaired genital arousal and orgasmic functioning (despite receiving oestrogen replacement therapy) might benefit from the use of sildenafil, and this provides some of the rationale for the current investigation.

A second objective was to assess sexual psychophysiology in women diagnosed clinically (using a detailed semi-structured interview) with acquired genital female sexual arousal disorder and orgasmic impairment, by using a vaginal photoplethysmograph. Although it has been speculated that the vaginal photoplethysmograph may be helpful in assessing women with sexual arousal impairment, there exist only limited published data on its use in women with acquired genital female sexual arousal disorder^{8,9}. The vaginal photoplethysmograph is the most widely used measure of psychophysiological sexual arousal in women¹⁰, although its use is primarily limited to research rather than the clinical setting. The extent to which this instrument provides information on vaginal vasocongestion in women with problematic genital responsivity is unclear. The majority of studies on women with female sexual arousal disorder do not clarify the type of arousal disorder³ and report normal physiological vasocongestive responses to visual erotica despite absence of subjective sexual arousal¹¹. In interesting contrast, genital congestion in women with lifelong anorgasmia was found to significantly differ from control women under conditions of heightened sympathetic nervous system activity¹². However, detailed clinical assessments were not used to recruit these subjects. Our aim was to determine the relationship between these clinical and laboratory-based forms of assessment in a diagnostically homogeneous group of women with acquired genital sexual arousal disorder and orgasm impairment.

METHODS

The Institutional Review Board of the Department of Psychology at the University of British Columbia as well as

that at Vancouver Hospital approved the current study. Based on results of a recent crossover design study in which there was a mean difference of 1.5 between placebo ($n = 18$) and sildenafil 50 mg ($n = 18$), with a pooled standard error of difference of 0.27, in self-reported orgasmic functioning in premenopausal women with female sexual arousal disorder⁷, with α (two-sided) = 0.05 and $1 - \beta = 0.9$, sample size for dependent samples test was calculated at nine per group. Postmenopausal women receiving oestrogen replacement therapy for at least six months were recruited (Fig. 1). Subjects had to meet a diagnosis of acquired genital female sexual arousal disorder, with loss or marked delay and/or diminished intensity of orgasm. Women who lacked any neurological disease but complained of the following were included: 'loss of genital sensation', 'genital numbness with sex', 'feeling nothing genitally', 'genital stimulation being mentally irritating, annoying, or unrewarding, becoming sore if the unrewarding stimulation persists', 'genital stimulation not leading to pleasure or excitement' and 'loss of any former throbbing or tingling'. Women who were unable to be sexually aroused by non-genital sexual stimuli, women with dyspareunia and chronic and/or untreated medical or psychiatric illness were excluded as were women who met criteria for hypoactive sexual desire disorder. Women using nitrates, or reporting previous myocardial infarction, angina, postural hypotension, severe gastroesophageal reflux or retinal disease were also excluded.

The study was conducted between April 2001 and 2002. Subjects were recruited from newspaper advertisements and postings throughout the community which stated 'Have you recently experienced a change in your sexual functioning?' A total of 78 women responded to advertisements (Fig. 1). A telephone screen by a trained sexual health nurse provided a full description of the study's objectives and procedures and collected preliminary diagnostic information. The first of four assessments took place at the B.C. Center for Sexual Medicine to ensure an accurate diagnosis of acquired genital female sexual arousal disorder (RB). After having obtained written informed consent, a 60-minute assessment by a sexual medicine physician confirmed a clear diagnosis of acquired genital female sexual arousal disorder with loss or marked delay and/or reduction of orgasm intensity. A detailed assessment of sexual arousal was conducted using a semi-structured interview (Detailed Interview Assessment; see Appendix A). This detailed assessment has been common practice in the clinical setting for assessment of women with arousal difficulties and was used to ensure the sample was clinically homogeneous. A medical history, cardiovascular examination and electrocardiogram followed. Participants then completed questionnaires, in private, that assessed various domains of psychological and psychosexual functioning. Demographic assessment included: partner age, sexual status of partner, relationship status, drug and alcohol use, date of menopause and type of hormone replacement therapy. Questionnaires

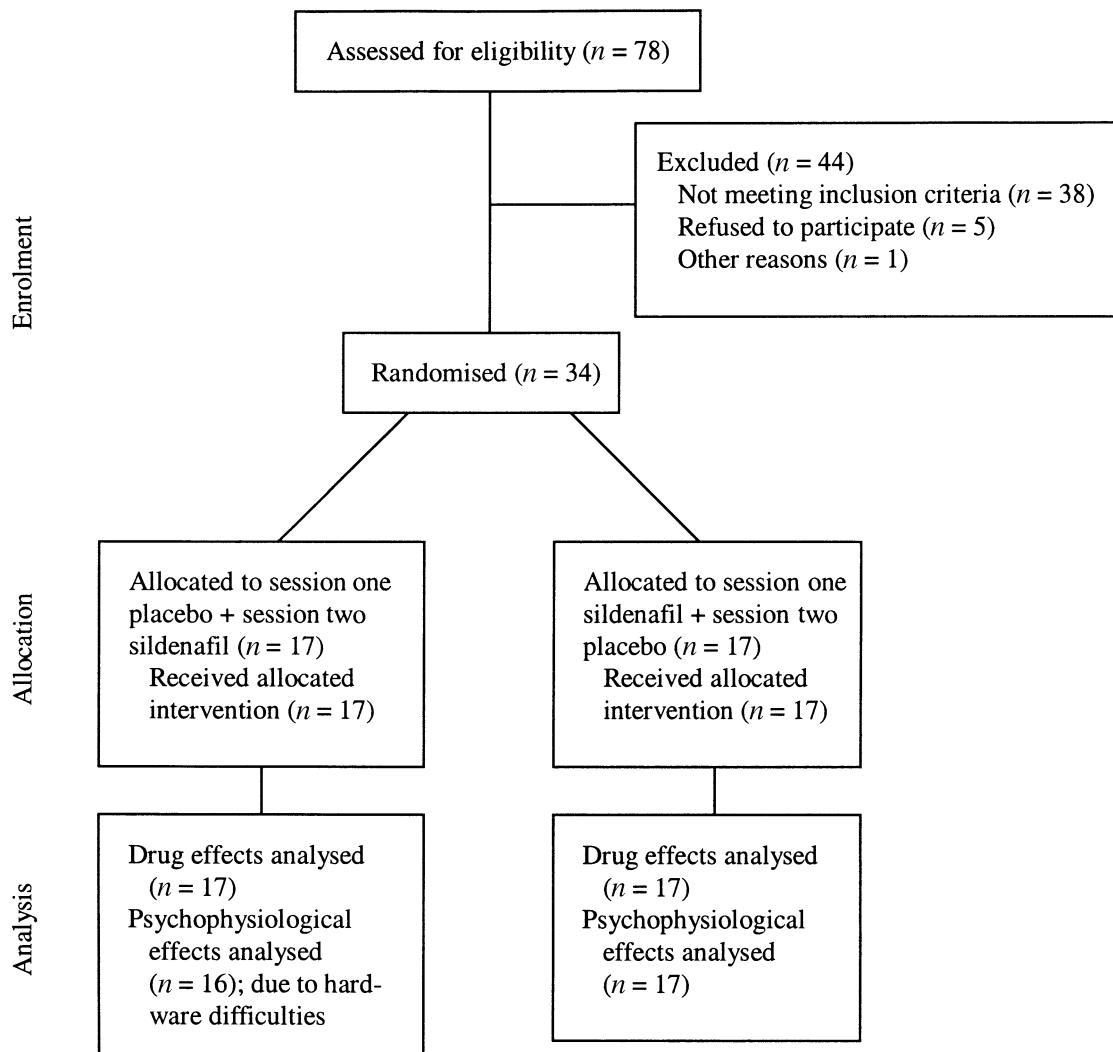


Fig. 1. Flow chart indicating subject enrolment, group allocation and analysis according to CONSORT guidelines.

included: the Derogatis Sexual Functioning Inventory¹³, the Beck Anxiety Inventory¹⁴, the Orgasmic Functioning Screen (unpublished questionnaire) and the Fear of Negative Evaluation¹⁵. All questionnaires involved Likert scales in which the participant indicated her response by circling the best numerical response. Random allocation to group (placebo then sildenafil vs sildenafil then placebo) was performed by a pharmacist affiliated with our study, who also prepared the sildenafil and placebo tablets, individually, in envelopes with the subject's number and session number. The identity of each drug was kept confidential until the study was completed.

The three remaining sessions took place at the Sexual Psychophysiology Laboratory and were conducted by a doctoral candidate trained in psychophysiological assessment (LB). The first session was a psychophysiological assessment of sexual arousal in response to audiovisual erotica, designed to characterise genital vasocongestive patterns in women with clinical genital sexual arousal

impairment, as this group has not been extensively studied in the literature. Genital vasocongestion was assessed with a vaginal photoplethysmograph¹⁶, and the vaginal pulse amplitude signal was employed, as it is most specific to erotic stimuli¹⁷. The erotic audiovisual stimulus, a 4-minute video segment of a nude heterosexual couple engaging in foreplay and intercourse, was a female-made, female-focussed film segment previously found to reliably increase genital and subjective sexual arousal in addition to positive affect in sexually healthy postmenopausal women¹⁸. Measures were taken immediately prior to and following the erotic film, and subjects completed a self-report questionnaire assessing mental and physical sexual arousal, perception of autonomic activity and positive and negative affect¹⁹. Subjects were asked to rate the degree to which they experienced these items on a seven-point Likert scale from 1 (*not at all*) to 7 (*intensely*). This questionnaire has been determined to be a sensitive indicator of emotional reactions to erotic stimuli¹⁹.

Sessions three and four involved the randomised, double-blind, placebo-controlled administration of sildenafil citrate (50 mg) 1 hour prior to vibro- and audiovisual erotic stimulation. The primary outcome measures were orgasm latency and intensity. Subjects remained in a temperature-controlled, dimly lit laboratory room for 1 hour following drug ingestion. Testing involved the use of a handheld clitoral vibrator (Natural Contours Medium, Intimacy Institute, Illinois), which provided direct clitoral stimulation at a standard intensity for all women. Women were oriented on the proper use of the vibrator before the study began and diagrammed instructions were available. While using the vibrator, women viewed a 30-minute female-made erotic film depicting non-genital and genital touching, oral-genital contact and vaginal intercourse. Women were instructed to watch the film and apply vibrostimulation until (1) they attained orgasmic release, (2) they wished to discontinue or (3) 30 minutes had elapsed. Latency to orgasm was assessed by having women press a button, which was wired to a digital timer in the experimenter's room, at the time of orgasmic release. Subjective intensity of the orgasm, awareness of genital sensations, subjective rating of overall sexual arousal and affective reactions to the erotic film were also assessed with the use of self-report questionnaires. Women who did not attain orgasm before the 30-minute testing session ended were also asked to rate how 'close' they felt to attaining orgasm.

Sessions three and four were identical except that different films, with similar erotic content, were shown in a counterbalanced order across the two sessions. A research assistant randomly assigned film order to participants so that half the subjects viewed film one during the placebo and film two during the sildenafil session, and the remaining subjects viewed the films in the opposite order. In addition, the administration of sildenafil or the placebo was randomised across subjects. Upon completion of session four, women were fully debriefed in terms of reviewing the study's purpose and answering any questions that may have arisen. A non-advertised honorarium of \$150 was mailed to each participant. An explanatory letter detailing their responses was sent to all participants at their request once the study was completed and the blind broken.

Psychophysiological data analysis involved the assessment of vaginal pulse amplitude throughout exposure to the neutral and erotic film segments of the second session. Data were recorded on a HP Vectra Celeron personal computer using the software program, AcqKnowledge III, Version 3.5 (BIOPAC Systems, Santa Barbara, California) and a Model MP100WSW data acquisition unit (BIOPAC Systems) for analogue/digital conversion.

Between-subjects repeated-measures analysis of variance (ANOVA) with order and treatment as between-subjects factors were used to investigate the effects of sildenafil on orgasm latency, orgasm intensity, subjective ratings of arousal and other subjective/affective responses

to the erotic film. In addition to main effects, the order by treatment interaction was analysed to test for carryover effects. In the second set of analyses in which effects were tested based on vaginal pulse amplitude status, this factor was also included as a between-subjects factor in repeated-measures analyses. In cases of a significant interaction effect in the ANOVA model, simple effects analyses were computed to determine in which group the significant effect was present. Whenever the assumption of sphericity was violated, the Huynh-Feldt Epsilon was used for analyses of repeated measures. SPSS was used for all statistical analyses. A paired-samples *t* test was used to compare the proportion of subjects attaining orgasm on the drug and placebo. The Detailed Interview Assessment was scored by tallying each of the responses in each section, and dividing by the number of items endorsed, resulting in a mean response for that component. Sum totals were not used because there were instances in which an individual did not engage in one of the sexual acts (e.g. oral sex). A multiple regression analysis, using the stepwise method of independent variable entry, was used to determine which variables significantly predicted response to sildenafil. Vaginal pulse amplitude responses during session two were analysed between neutral and erotic film stimuli conditions with a paired-sample *t* test and baseline vaginal pulse amplitude responses were not analysed given the lack of absolute scale in this methodology. Pearson product-moment correlations were used to investigate the degree of association between genital and subjective ratings of arousal during session two, and with results obtained from the Detailed Interview Assessment administered in session one. In all conditions, a *P* level of 0.05 was deemed significant.

RESULTS

One subject dropped from the study after her first session and was subsequently replaced by another subject, giving a total sample size of 34. All women were naturally postmenopausal and receiving oral oestrogen replacement therapy (micronised oestradiol or conjugated oestrogens) with progesterone or medroxy-progesterone. No women were receiving exogenous androgens. The mean age (and standard deviation [SD]) of the women was 56.6 (6.6) years [range: 40–78 years] with a mean (SD) educational attainment of 15.0 (2.9) years [range: 9–21 years]. All women were currently involved in a heterosexual relationship that was on average (SD) 21.7 (11.6) years [range: 1–39 years]. The average (SD) age of the partner was 58.5 (7.7) years [range: 40–76 years]. Anxiety levels (SD), as measured by the Beck Anxiety Inventory, were within one standard deviation of normative levels (mean 3.6 out of a possible 63, SD = 3.6), as were levels of fear of negative evaluation (mean 10.0 out of a possible 30, SD = 7.5). Our sample

exhibited satisfactory knowledge about and attitudes towards sexuality, as measured by the Derogatis Sexual Functioning Inventory Information (mean = 22.2, SD = 2.0) and Attitudes (mean = 25.4, SD = 12.9) subscales.

The orgasmic functioning screen indicated that 20 women previously had experience using a hand-held clitoral vibrator, whereas 14 women had not. Twenty-nine women had experience with manual clitoral masturbation. The average level of distress (and SD) reported by women, ranging from 4 (*satisfied with orgasmic functioning*) to 0 (*greatly distressed about current orgasmic functioning*) was 1.61 (0.99). For women with experience in the use of hand-held vibrators, the average (SD) number of orgasms attained in the previous 10 attempts was 5.70 (4.00). The average (SD) number of orgasms attained through intercourse was 2.64 (3.19).

The main effect of sildenafil on orgasm latency was not statistically significant [$F(1,31) = 0.067, P > 0.05$]. Neither the order of treatment [$F(1,31) = 1.135, P > 0.05$], nor the Treatment \times Order interaction [$F(1,31) = 0.534, P > 0.05$] was significant for this endpoint. The latency to attain orgasm with placebo was 1341 seconds (SD = 520, range = 343–1800 seconds) and with sildenafil citrate was 1363 seconds (SD = 480, range = 343–1800 seconds). Similarly, the main effect of sildenafil on orgasm intensity, in those women who attained orgasm with both placebo and active drug ($n = 16$), was not statistically significant [$F(1,14) = 1.798, P > 0.05$]. Order effects [$F(1,14) = 0.188, P > 0.05$] and the Treatment \times Order interaction [$F(1,14) = 1.798, P > 0.05$] were similarly not statistically significant. Mean orgasm intensity (SD) on placebo was 5.8 (1.8) and on active drug was 6.5 (2.1) out of a possible score of 10.0. The overall level of subjective sexual arousal (SD) out of 10.0 with sildenafil (5.15, SD = 2.5) was slightly higher than with placebo (4.74, SD = 2.4), although this effect did not reach statistical significance [$F(1,32) = 0.791, P > 0.05$]. Neither the order of drug [$F(1,32) = 0.108, P > 0.05$], nor the Order \times Treatment interaction [$F(1,32) = 0.403$], reached statistical significance. There was no significant main effect of sildenafil in how 'close' a woman felt to experiencing orgasm [$F(1,32) = 0.365, P > 0.05$]. Mean 'closeness' (SD) with placebo was 2.85 (1.6) and with sildenafil citrate was 2.68 (1.6) out of a maximum closeness score of 4.0. The order of administration [$F(1,32) = 0.930, P > 0.05$], and the Order \times Treatment interaction [$F(1,32) = 0.041, P > 0.05$] did not reach significance. A paired-samples analysis comparing the proportion of women attaining orgasm with placebo *versus* active drug was not statistically significant [$t(33) = 1.00, P > 0.05$]. Fifty-six percent of women reported attaining orgasm with the active drug, whereas 62% reported orgasm with placebo. Only 3 of 12 women who did not attain climax with placebo were able to attain climax with sildenafil. Of interest, two women reported experiencing an intense nocturnal orgasm following the session in which they had

received sildenafil—such events having self-reportedly ceased more than 10 years previously.

Neither the main effect of sildenafil [$F(1,32) = 0.159, P > 0.05$], nor the main effect of order [$F(1,32) = 0.092, P > 0.05$], reached statistical significance for the endpoint variable perception of genital arousal (mean difference in treatments = -0.50 , 95% CI = -3.22 to 2.22). However, there was a significant Treatment \times Order interaction [$F(1,32) = 5.606, P = 0.024$], such that scores were higher in the first session on this variable, regardless of what treatment they received. For *subjective sexual arousal*, the main effect of sildenafil was not statistically significant [$F(1,32) = 0.158, P > 0.05$ (mean difference = -0.26 , 95% CI = -1.61 to 1.08). Neither the order effect [$F(1,32) = 0.550, P > 0.05$], nor the Treatment \times Order interaction [$F(1,32) = 0.329, P > 0.05$] reached statistical significance. For *autonomic arousal*, neither the main effect of treatment [$F(1,31) = 0.210$], the main effect of order [$F(1,31) = 0.251$], nor the Treatment \times Order interaction [$F(1,31) = 3.66$] reached statistical significance [all $P > 0.05$ (mean treatment difference = 0.576 , 95% CI = -1.79 to 2.94). Positive affect did not statistically differ between treatment groups [$F(1,29) = 0.008, P > 0.05$ (mean difference = 0.194 , 95% CI = -2.68 to 3.07)]. There was also neither an order effect [$F(1,29) = 1.154$], nor a Treatment \times Order interaction [$F(1,29) = 2.384$, both $P > 0.05$]. Negative affect was not significantly affected by sildenafil [$F(1,32) = 1.398, P > 0.05$ (mean difference = -0.912 , 95% CI = -2.48 to 0.65)]. The order effect [$F(1,32) = 2.006$] and the Treatment \times Order interaction [$F(1,32) = 0.769$] were similarly not statistically significant, $P > 0.05$.

Vaginal pulse amplitude change scores were expressed by dividing the vaginal pulse amplitude mean during the erotic segment by the vaginal pulse amplitude mean during the neutral segment $\times 100\%$. Thus, a score of 100% would indicate no change in vaginal pulse amplitude from neutral to erotic stimuli conditions. Computer difficulties resulted in data from one participant not being available for analyses involving vaginal pulse amplitude. The erotic film resulted in a significant increase in vaginal pulse amplitude across women (Table 1). However, there was marked variability from a 71% change score to a 267% change score in response to the erotic stimulus. Self-reported subjective sexual arousal and perception of genital arousal significantly increased after viewing the erotic film. Perception of autonomic activity, and positive affect, also significantly increased, whereas self-reported anxiety decreased after the erotic film. Negative affect was not affected by the erotic film (Table 1).

A stepwise multiple regression analysis, with 'orgasm attained with sildenafil' as the dependent variable and age, anorgasmic distress, self-reported real life mental sexual arousal (Detailed Interview Assessment—part 1), awareness of genital tingling/throbbing (Detailed Interview Assessment—part 2), awareness of genital wetness

Table 1. Effects of erotic audiovisual stimulus on genital arousal (vaginal pulse amplitude), and self-reports of subjective sexual arousal, perception of genital arousal, autonomic arousal, anxiety and positive and negative affect in postmenopausal women with acquired female sexual arousal disorder with impaired orgasm ($n = 34$). Data represent means (SE).

	Neutral	Erotic	$t_{(33)}$	95% CI
Vaginal pulse amplitude (mV)	6.57 (0.55)	9.41 (0.81)	-5.58 ^b	0.0039 to 0.0018
Subjective sexual arousal	8.06 (0.24)	10.53 (0.26)	-8.89 ^b	-3.09 to -1.91
Perception of genital arousal	7.13 (0.56)	15.41 (1.08)	-7.85 ^b	-10.43 to -6.13
Autonomic arousal	7.90 (0.65)	13.73 (1.05)	-6.78 ^b	-7.59 to -4.07
Anxiety	1.76 (0.20)	1.38 (0.14)	2.42 ^a	0.061 to 0.704
Positive affect	11.09 (0.81)	17.53 (1.34)	-5.73 ^b	-8.73 to -4.15
Negative affect	11.71 (0.44)	11.74 (0.41)	-0.10	-0.62 to 0.56

^a $P < 0.05$.

^b $P < 0.001$.

(Detailed Interview Assessment—part 3), experience of pleasant sexual genital sensations (Detailed Interview Assessment—part 4) and vaginal pulse amplitude percent change score as independent predictors, was conducted. Significant models emerged with both age and vaginal pulse amplitude percent change score as significant predictors [$F(2,30) = 6.532$, $P = 0.004$], and with vaginal pulse amplitude percent change score alone as a significant

predictor [$F(1,31) = 7.214$, $P = 0.012$]. Age was positively related to attaining orgasm ($r = 0.416$, $P = 0.014$) such that older women were more likely to experience orgasm with sildenafil than were younger women. No other independent variables predicted orgasmic ability with sildenafil.

A histogram displaying the percent change in vaginal pulse amplitude from neutral to erotic stimuli (multiplied by 100%) across women confirmed that a proportion of

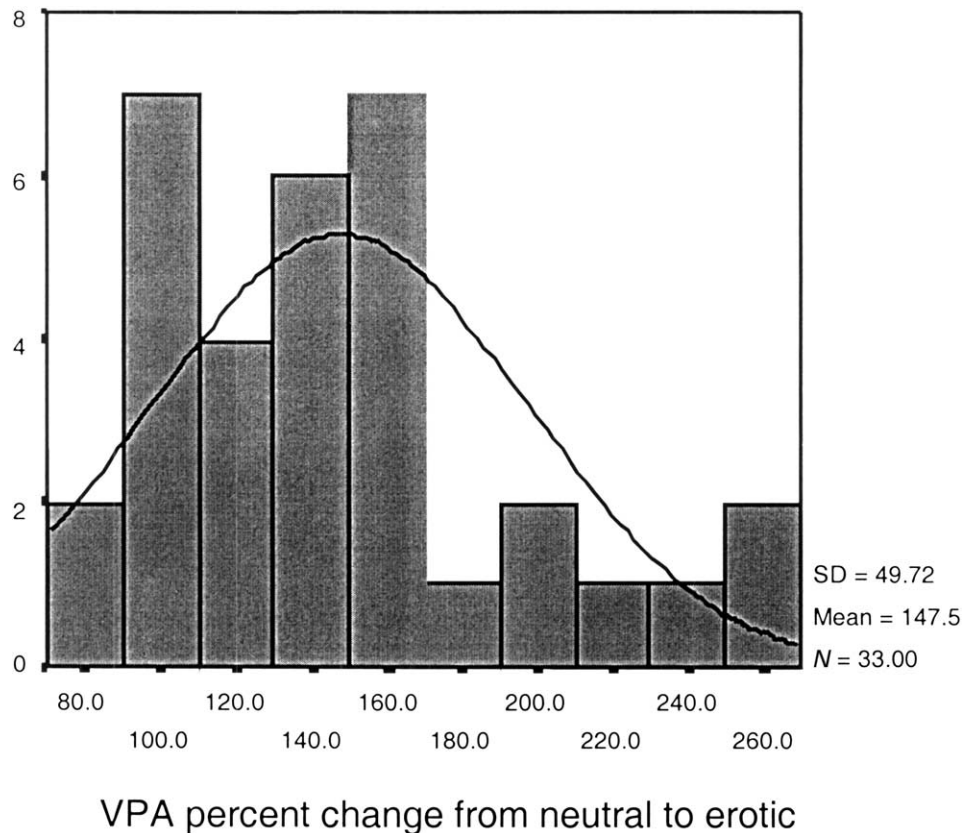


Fig. 2. Histogram of vaginal pulse amplitude percent change score from neutral to erotic stimuli across women with acquired female sexual arousal disorder and impaired orgasm ($n = 33$). Percent change was calculated by dividing the average vaginal pulse amplitude response to erotic stimuli by the average vaginal pulse amplitude response to neutral stimuli, multiplied by 100%.

women showed a very minimal increase in vaginal pulse amplitude, despite an overall significant main effect when the entire sample was analysed (Fig. 2). Additionally, the multiple regression analysis suggested that vaginal pulse amplitude percent change score significantly predicted a positive response to sildenafil. Thus, according to the procedure described by Heiman, 1980, the entire sample was divided into three groups at the 33rd and 66th percentiles²⁰. Individuals with a vaginal pulse amplitude percent increase score less than 114% were included in the lower group ($n = 10$) and those with a percent change score greater than 156% in the higher group ($n = 13$). The middle group ($n = 10$) was not included in the following analyses. A repeated-measures ANOVA, with group (low and high vaginal pulse amplitude responders) and order (placebo–sildenafil and sildenafil–placebo) as between-subjects factors, and drug (sildenafil and placebo) as the within-subjects factor was conducted. The interaction between group and drug was statistically significant for latency to attain orgasm [$F(1,19) = 6.602, P = 0.019$], as shown in Fig. 3. Subsequent simple effects analyses revealed that latency to attain orgasm in low vaginal pulse amplitude responders was reduced with sildenafil, whereas it increased in high vaginal pulse amplitude responders. The main effect of order [$F(1,19) = -0.889, P > 0.05$], and the Order \times Drug interaction [$F(1,19) = 0.437, P > 0.05$] were not statistically significant. Overall subjective sexual arousal level showed a Group \times Drug interaction [$F(1,20) = 4.277, P = 0.050$], with increased sexual arousal following sildenafil in low vaginal pulse amplitude responders and no significant change in high vaginal pulse amplitude responders, as illustrated in Fig. 4. Orgasm intensity, in the 10 individuals who attained orgasm with both placebo and sildenafil, was not significantly affected by vaginal pulse amplitude response status [$F(1,6) = 0.922, P > 0.05$]. Neither the order effect [$F(1,6) = 0.927$], nor the Order \times Drug interaction [$F(1,6) = 0.204$]

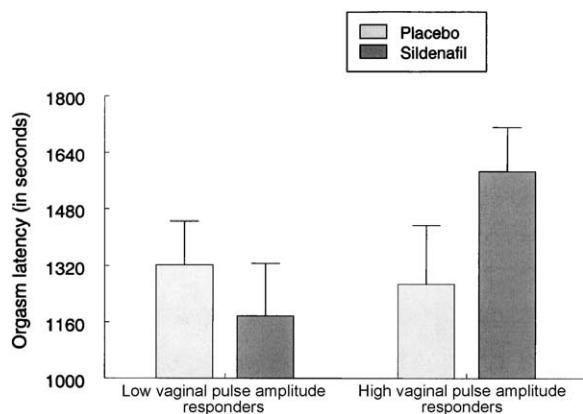


Fig. 3. Effects of sildenafil citrate and vaginal pulse amplitude percent change status on orgasm latency (in seconds) between low and high vaginal pulse amplitude responders ($n = 23$).

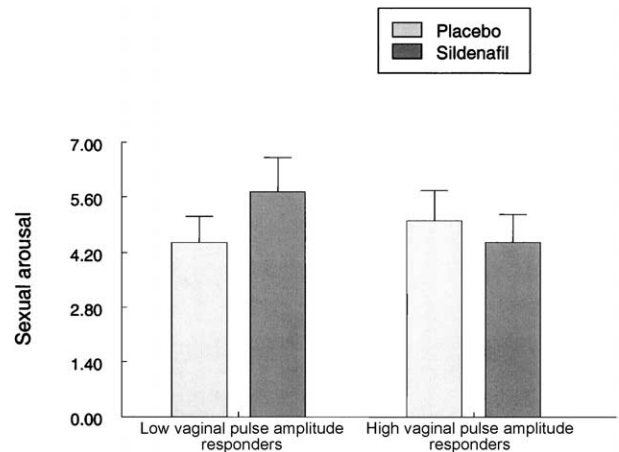


Fig. 4. Effects of sildenafil citrate and vaginal pulse amplitude percent change status on self-reported level of sexual arousal between low and high vaginal pulse amplitude responders ($n = 23$).

was significant for orgasm intensity ($P > 0.05$). Similarly, closeness to attaining orgasm was not significantly affected by vaginal pulse amplitude response status [$F(1,20) = 1.449, P > 0.05$], by the order effect [$F(1,20) = 0.682, P > 0.05$], nor by the Drug \times Order interaction [$F(1,20) = 0.01, P > 0.05$]. Perception of genital arousal during the erotic film was also evaluated based on vaginal pulse amplitude status. A significant interaction emerged, in that perception of genital arousal was significantly increased with sildenafil in those women displaying low vaginal pulse amplitude responding [$F(1,20) = 4.629, P = 0.044$ (Fig. 5)]. There was no significant order effect [$F(1,20) = 0.012$], or Drug \times Order interaction [$F(1,20) = 2.058, P > 0.05$] for this variable.

We compared the vaginal pulse amplitude responders and vaginal pulse amplitude non-responders on all demographic variables and questionnaire data. No significant

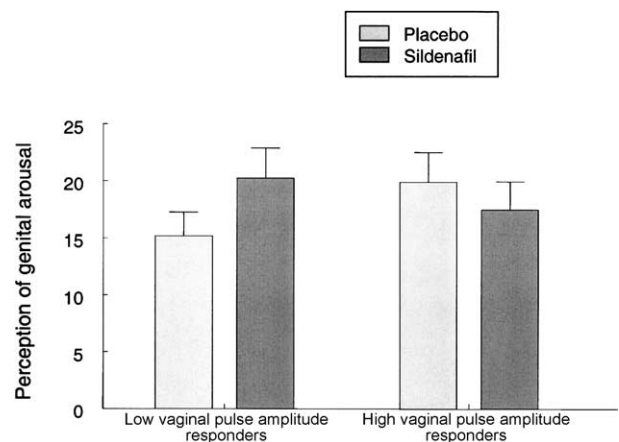


Fig. 5. Effects of sildenafil citrate and vaginal pulse amplitude percent change status on self-reported perceptions of genital arousal between low and high vaginal pulse amplitude responders ($n = 23$).

group differences emerged on any variable. In addition, there were no apparent differences in clinical histories between these two groups during the initial assessment.

Neither self-reported subjective sexual arousal ($r = 0.194$, $P > 0.05$) nor perception of genital arousal ($r = 0.299$, $P > 0.05$) in response to the erotic film correlated with vaginal pulse amplitude. Subsequently, laboratory genital arousal was compared with responses to the detailed assessment of sexual arousal in the real life setting. Laboratory vaginal pulse amplitude did not correlate with mental sexual excitement ($r = 0.115$, $P > 0.05$), with awareness of genital tingling/throbbing ($r = -0.059$, $P > 0.05$), with awareness of genital wetness ($r = -0.056$, $P > 0.05$) or with pleasant sexual genital sensations in response to direct genital stimulation ($r = -0.217$, $P > 0.05$) in the real life sexual setting.

Paired-samples t tests between real life mental sexual excitement (Detailed Interview Assessment—part 1) and awareness of genital tingling/throbbing (Detailed Interview Assessment—part 2) revealed that the former was significantly higher than the latter [$t(33) = 10.92$, $P < 0.001$ (mean for mental sexual excitement = 4.62 vs mean for awareness of genital tingling/throbbing = 2.36, out of 7)]. Similarly, awareness of genital wetness (Detailed Interview Assessment—part 3) was significantly lower than mental excitement [$t(33) = 12.12$, $P < 0.001$ (mean for awareness of genital wetness = 1.93)]. Finally, experience of pleasant sexual genital sensations to direct genital touch was also significantly lower than mental sexual excitement [$t(33) = 7.79$, $P < 0.001$ (mean = 2.87)].

Twenty-four percent of women reported side effects with placebo, 59% with sildenafil, the most common being flushing, headache and mild dizziness. Three participants noted sildenafil-associated sensations of vasodilation and warmth felt throughout the entire body that interfered with any sexual sensations. One woman reported mild clitoral pain for 48 hours following sildenafil ingestion.

DISCUSSION

Whereas others have investigated the effects of sildenafil on vaginal responding^{6,21}, clitoral stimulation and arousal were assessed in the current study given that phosphodiesterase type 5 has been identified in human clitoral tissue²², and to date, despite the presence of nitric oxide synthase in premenopausal vaginal tissue²³, any role of nitric oxide in vaginal vasocongestion is unclear. The use of the vaginal photoplethysmograph in assessing genital vasocongestion in postmenopausal women diagnosed with acquired genital female sexual arousal disorder and orgasmic impairment based on a detailed clinical assessment, identified one-third of the sample as having a relatively lower vasocongestive response to the erotic stimulus. For a similar number of women, the percent change in vaginal vaso-

congestion from a neutral to a sexual state approached 200%. This confirmed the clinical diagnosis of genital female sexual arousal disorder in approximately half the cases only and questioned the potential relevance of this instrument in diagnostic decision making. In other words, there may or there may not be reduced vasocongestion demonstrable by vaginal photoplethysmograph. Possibly, more subtle loss of vasocongestion or reduced sexual sensations from (normally) congested genitalia may underlie this syndrome. Nevertheless, the present findings do suggest a putative prognostic utility, in that vaginal photoplethysmograph significantly predicted a positive response to sildenafil.

Overall, the data suggest that sildenafil was ineffective at restoring orgasmic capacity or affecting subjective sexual arousal. However, when the vaginal pulse amplitude low responders were compared with women who did show a robust increase in vaginal pulse amplitude with the erotic film (vaginal pulse amplitude high responders), differential responses to sildenafil emerged. Specifically, vaginal pulse amplitude low responders showed significantly reduced latency to orgasm, significantly higher perception of genital arousal and significantly higher levels of overall subjective sexual arousal with sildenafil. Overall, these data suggest that sildenafil may be useful for a subgroup of postmenopausal women with acquired genital female sexual arousal disorder and that use of the vaginal photoplethysmograph might be helpful in their delineation. To the best of our knowledge, this represents the first of such findings.

The current findings cannot be attributed to carryover effects in the crossover design given that in all but one analysis was the effect of order (placebo–sildenafil or sildenafil–placebo) statistically non-significant. The one instance of carryover effect was in the perception of genital arousal when all women were examined as a group. Women in session one reported greater perception of genital arousal than during session two, regardless of drug condition. It is possible that during the first session women were more focussed on genital responding given that they were using a clitoral vibrator, and that many of the women reported never having operated such a device before. By the second session women were familiar with the procedure and perhaps attended more to other erotic cues. This effect on perception of genital arousal was not present when the two subsamples of low and high vaginal pulse amplitude responders were compared.

The prevalence of the acquired genital subtype of female sexual arousal disorder with impairment in orgasmic experience is unknown. The subsequent loss of sexual motivation may obscure the diagnosis. Both the *Diagnostic and Statistical Manual*, 4th edition Text Revised (DSM-IV-TR) of the American Psychiatric Association²⁴ and the American Foundation of Urological Disease definitions²⁵ of female orgasmic disorder address the inability to experience orgasm 'after a period of normal sexual arousal'. Thus, this

cohort of women, although complaining of reduced orgasm experience, does not meet a formal diagnosis of female orgasmic disorder. That this definition of female orgasmic disorder may be unsatisfactory in clinical practice has been previously stated²⁶. The comorbidity of orgasm and arousal disorders has been well documented in the literature^{27–29}. Frequently, enquiry about vulval responsiveness and congestion is omitted, and given both the lack of visible evidence and the minimal direct conscious appreciation of impaired genital engorgement, women may have difficulty in describing their loss³⁰.

The underlying pathophysiology of acquired genital female sexual arousal disorder with impaired orgasm in the postmenopausal woman is quite unclear. Using the vaginal photoplethysmograph as a diagnostic tool, this study suggests that the seemingly homogeneous group of women complaining of impaired genital responding may in fact be heterogeneous. For some, lack of response to massaging genital structures might stem from suboptimal vascular engorgement, potentially remedied by vasoactive medication. For those with adequate genital engorgement, but loss of sexual sensations from massaging, a precise aetiology is unclear. Of interest is the finding that some women after bilateral oophorectomy report sudden onset of loss of genital responsiveness dating from approximately two months postsurgery as they resumed their sexual lives. As women transit through natural peri- and postmenopausal years, they may^{31,32} or may not^{33,34} lose androgen activity. We were not able to accurately document testosterone activity in this study, having access only to the standard (unreliable) assays. Furthermore, there is minimal information regarding the levels of testosterone (total, free or bioavailable) below which sexual symptoms emerge and are remedied by androgen replacement therapy. Thus, any role of androgen in acquired genital female sexual arousal disorder remains speculative.

The use of the Detailed Interview Assessment of real life experience of arousal confirmed that for these 34 women, awareness of genital fullness, genital lubrication and experience of pleasant sexual sensations from genital stimulation were all significantly impaired, whereas the experience of mental sexual excitement from non-genital erotic stimulation continued. This clinical instrument is therefore useful in identifying the *genital* subtype of female sexual arousal disorder. Watching the erotic video resulted in significant arousal for these 34 women, and a significant increase in positive affect. This is in contrast to women commonly presenting with 'female sexual arousal disorder', characterised no further, who typically exhibit a robust vasocongestive response to erotica comparable to healthy control women, but deny any subjective sexual arousal during the experience¹¹. Also, unlike the previous studies of women with unspecified female sexual arousal disorder³⁵, the present sample of women with genital female sexual arousal disorder experienced a significant

reduction in anxiety and facilitation in positive affect. That their estimation of genital engorgement did not significantly correlate with actual genital vasocongestion confirms previous research.

Twenty of the 34 women had tried vibratory self-stimulation prior to the current study. Orgasm can be triggered by fantasy, physical stimulation of breast, vulval 'erectile structures' including the shaft and head of the clitoris, the spongiosal tissue around the urethra in the anterior vaginal wall, the vaginal vault and may occur in sleep. Moreover, the stimulus eliciting arousal is variable, and can include the finger, tongue, penis or vibrator. Some women report qualitative differences in the experienced arousal and orgasmic sensations elicited from these different stimuli. Vibratory self-stimulation of the clitoris in a controlled environment was chosen in the current study to reduce possible confounding variables and to allow for comparison with other investigators. With erotic audiovisual stimulation, which the women rated as 'highly arousing', and up to 30 minutes of constant vibrostimulation, 56% of the women with sildenafil and 62% of the women with placebo did reach orgasm. Nevertheless, in their unchanged sexual situations at home, they reported a marked loss of arousal and impaired orgasm. All women reported during the initial assessment that they had experienced a recent decrease in their orgasmic function, in that orgasms were very much delayed, experienced with reduced intensity or not reached at all. The artificiality of the experimental setting is recognised and clearly any findings in the laboratory can only serve as a guide for clinical practice. Clearly, many other contextual factors must be pertinent including the type of sexual stimulation and context, the act of intercourse itself and the partner's sexual function.

The current findings of normal levels of at-home mental sexual excitement (component 1), but impaired awareness of genital throbbing (component 2), reduced awareness of genital wetness (component 3), and a blunted pleasurable sensation from direct genital stimulation (component 4) (Detailed Interview Assessment; Appendix A) support the use of a detailed semi-structured assessment of genital and non-genital aspects of arousal in women presenting with sexual arousal concerns. A subjective loss of specifically genital responsiveness can be identified. This subgroup can be identified with photoplethysmographic monitoring showing robust subjective arousal from the audiovisual erotica and variable vaginal pulse amplitude responses. Those women with lower vaginal pulse amplitude response appeared to benefit from sildenafil, which in controlled laboratory setting increased perceptions of genital arousal during vibro- and audiovisual erotic stimulation, decreased the latency to orgasm and increased subjective sexual arousal. The generalisability of any laboratory-based investigation of sexuality³⁶, but especially studies involving psychophysiological assessment³⁷, is tenuous and may suffer from a volunteer bias effect. Future studies may aim to

replicate these findings using more naturalistic, 'at-home' methodologies.

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Appendix A. Detailed interview assessment of real life sexual arousal.

Sexual arousal means different things to different women—there is mental excitement, pleasant ‘sexual’ changes in your body including breathing, temperature, muscle tension. Some women are quite aware of genital tingling, throbbing or wetness. Some will become aware of genital changes only when stimulated directly around the labia and clitoris by fingers, partner’s body, orally, with a vibrator, etc., or with a partner’s penis stimulating from the inside of the vagina (often far less sensitive).

1. On a scale from 1–7 where: 1 = low, 4 = average, 7 = extremely intense, how mentally excited would you be for each of the following types of stimulation:

	Low		Average			Intense	
a) verbal/visual/written sexual stimuli	1	2	3	4	5	6	7
b) physical, hugging, holding, non-deep kissing	1	2	3	4	5	6	7
c) breast stimulation	1	2	3	4	5	6	7
d) deep-mouth kissing	1	2	3	4	5	6	7
e) manual–genital stimulation	1	2	3	4	5	6	7
f) oral–genital stimulation	1	2	3	4	5	6	7
g) penile–vulval contact	1	2	3	4	5	6	7
h) vaginal intercourse	1	2	3	4	5	6	7
i) self-stimulation	1	2	3	4	5	6	7

2. On a scale from 1–7 where: 1 = low, 4 = average, 7 = extremely intense, how much awareness of genital tingling, throbbing, or wetness would you experience for each of the following types of stimulation:

	Low		Average			Intense	
a) verbal/visual/written sexual stimuli	1	2	3	4	5	6	7
b) physical, hugging, holding, nondeep kissing	1	2	3	4	5	6	7
c) breast stimulation	1	2	3	4	5	6	7
d) deep-mouth kissing	1	2	3	4	5	6	7
e) manual–genital stimulation	1	2	3	4	5	6	7
f) oral–genital stimulation	1	2	3	4	5	6	7
g) penile–vulval contact	1	2	3	4	5	6	7
h) vaginal intercourse	1	2	3	4	5	6	7
i) self-stimulation	1	2	3	4	5	6	7

3. On a scale from 1–7 where: 1 = low, 4 = average, 7 = extremely intense, how much pleasant sexual genital sensations and increasing urge to receive more stimulation would you experience from each of the following types of stimulation:

	Low		Average			Intense	
a) manual–genital stimulation	1	2	3	4	5	6	7
b) oral–genital stimulation	1	2	3	4	5	6	7
c) penile–vulval contact	1	2	3	4	5	6	7
d) vaginal intercourse	1	2	3	4	5	6	7
e) self-stimulation	1	2	3	4	5	6	7