

Title: Efficacy, Safety and Patient Satisfaction of a New Topical Clitoral Vasodilating Cream**Authors:**

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Abstract:

Objective. A new topical clitoral vasodilating cream (CVD Cream) has been developed in an effort to improve the female sexual experience. The objectives of this study were to determine the efficacy, safety and patient satisfaction of the new CVD Cream.

Methods and Materials. This study enrolled 30 sexually active pre-menopausal females. The inclusion criteria was an interest to participate in the study. Patients were given three doses of the CVD Cream to be used on three separate occasions, and required to answer five (5) questions after their use of the CVD Cream.

Results. Of the 30 patients participating in the study, 73.3% reported their sexual experience was improved with use of CVD Cream, 73.3% reported use of CVD Cream resulted in a change in sensation in their external genitalia, 66.7% would buy CVD Cream and 13.3% experienced an unpleasant side effect. In the subset of patients reporting unsatisfactory sexual experience prior to use of CVD Cream, 75.0% reported their sexual experience was improved with use of the new CVD Cream, 100.0% reported CVD Cream made a change in sensation in their external genitalia, 75.0% would buy CVD Cream and 0% experienced any unpleasant side effects.

Conclusion. Results from these 30 patients demonstrated that CVD Cream provided positive results (improved sexual experience and change in sensation in external genitalia) with minimal side effects. A significant majority would buy the new CVD Cream.

Key words:

TITLE: Efficacy, Safety and Patient Satisfaction of a New Topical Clitoral Vasodilating Cream, CVD Cream

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OBJECTIVE:

The aim of this investigation was to add to the understanding of a new topical clitoral vasodilating cream (CVD Cream)* reported to improve female sexual experience¹ through further investigation of its efficacy, safety, and patient satisfaction. The following five (5) questions were asked of 30 sexually active females between ages of 24 and 62: (1) Before using the new CVD Cream, was your typical sexual experience acceptable? (2) After using the new CVD Cream, was your sexual experience improved? (3) After using the new CVD Cream, did you notice a change in sensation in your external genitalia? (4) Would you buy the new CVD Cream? and (5) After using the new CVD Cream, did you notice any unpleasant side effects?

BACKGROUND:

Female Sexual Dysfunction (FSD) is a widespread problem, reported in the literature to be as high as 50% of all women.^{2,3} FSD does not have an adequate treatment solution. Male sexual dysfunction and remedies are widely published and available, with a host of pharmaceutical companies providing treatments. AddyiTM is the only FDA approved drug for FSD (FDA approval August 2015), and for a brief time received worldwide attention as a possible cure for FSD. However, the New York Times reported in April 2016 that an average of less than 223 prescriptions per month in the first 18 months post-FDA approval were being written for Addyi[®].⁴ Much of the poor acceptance of this drug is that it results in a very modest increase in female satisfactory sexual episodes per month, has significant side effects (hypotension, dizziness, sleepiness, and fainting), requires a rigorous physician training program just to allow the doctor to prescribe it due to side effects, cannot be taken with alcohol, must be taken daily, and, is expensive (\$700 per month). Addyi works in the brain, and has no direct effect on female genitalia. It is no wonder Addyi has not received the response for which its manufacturers had hoped.

The numerous topical ointments and creams available to assist in female arousal are generally mentholated and often associated with irritation.^{5,6} The popular topical or spray botanicals, such as Zestra[®], that are touted to be highly effective have associated irritation.⁷

* SensateTM (ClivāsomaxTM) Life Science Enhancement Corporation, Pittsburgh, PA

In a previous paper, the CVD Cream was studied in two Investigational Review Board (IRB) approved trials.¹ The first trial was a double-blinded randomized controlled trial (RCT) which demonstrated efficacy and safety and showed that the application of CVD Cream lead to enhanced female sexual satisfaction. The second IRB approved trial randomly selected a subset of patients from the first trial to evaluate clitoral blood flow using Doppler probes. The second trial demonstrated that, after topical application of CVD Cream, a statistically significant increase in blood flow to the clitoris was achieved with a high patient response rate; clitoral engorgement was confirmed due to enhanced vasodilatation. Lubrication, intercourse, genital sensation, and overall sexual encounter satisfaction were all increased after application of CVD Cream. Following the first paper, the purpose of this paper was to substantiate the efficacy and safety of CVD Cream and determine whether the participants would consider purchasing CVD Cream for future repeated use.

MATERIALS AND METHODS:

Materials

Clitoral blood engorgement initiates and enhances the excitement phase of the sexual response cycle increasing sensitivity and fluid across the vaginal wall.⁸ The CVD Cream (Life Science Enhancement Corporation, Pittsburgh, PA) utilizes a unique combination of two vasodilators, a vasodilator modulator and a lipophilic-based transdermal carrier to maximize effect on clitoral blood engorgement and the cascade of female physiological events. The two vasodilators are L-Arginine and Niacin (also known as Nicotinic Acid and is a form of Vitamin B3^{9, 10}). The vasodilator modulator is Niacinamide (which is the amide form of Niacin and another form of Vitamin B3^{9, 10}). The lipophilic transdermal carrier enhances the transdermal migration of the active ingredients. The combination's goal is to provide a positive end organ effect on the clitoris while minimizing burning.

L-Arginine is known to be a potent vasodilator. It is easily metabolized into Nitric Oxide (NO) and is therefore a potent NO donor.¹¹ NO is known to increase vasodilation. Through L-Arginine introduction, NO increases vasodilation and blood flow to the clitoris and female genitalia.^{11, 12} Niacin is a potent activator of the enzyme nitric oxide synthase which catalyzes the formation of (NO) from L-Arginine resulting in rapid, localized vasodilation. Systemic niacin can cause the uncomfortable "niacin flush". When applied locally it can produce burning and uncomfortable tingling.¹³ Niacinamide modulates Niacin in this unique formula to drive the ability to increase NO without the known Niacin side effects. These two compounds act synergistically to influence the relaxation effect on the vasculature of the clitoris and female genitalia increasing blood flow to these anatomical structures.¹⁴

As a zwitter ion, L-Arginine has an electrical charge. The zwitterion electrical charge does not allow L-Arginine to cross human squamous epithelium to any significant degree greatly limiting the effect L-Arginine has on the site where it is topically applied.¹⁵ In order to counteract L-Arginine's inability to cross human squamous epithelium, many of the available consumer products add menthol, which is an irritant to human skin. By irritating the skin, these consumer products can allow some of the L-Arginine to cross human squamous epithelium but not to any significant amount.¹⁵ In order to nullify the charge effect and avoid skin irritation, the CVD Cream uniquely utilizes a lipophilic transdermal delivery vehicle designed to enhance L-Arginine transport across the skin. The effectiveness of CVD Cream's transdermal delivery vehicle is increased because it is based upon lipophilic molecules which penetrate the skin barrier to a much greater extent than hydrophilic molecules.¹⁶ Niacinamide additionally provides a secondary function in the NTVC which is to render the L-Arginine and Niacin less irritating because it has proven anti-inflammatory effect on skin and tissues.¹⁷

Methods

Thirty (30) sexually active pre-menopausal females between the age of 24 and 62 were chosen to participate in this study. They were given a five (5) part patient questionnaire:

Table 1: 5-part Patient Questionnaire

Question
1. Before using the product - on average was your typical sexual experience acceptable?
2. After using the product - was your sexual experience improved?
3. After using the product - did you notice a change in sensation in your external genitalia?
4. Would you buy the product?
5. After using the product - did you notice any unpleasant side effects?

RESULTS:

Thirty (30) patients completed the 5-part patient questionnaire. Table 1 presents the age ranges for this study.

Table 1: Patient Age Range

Patient Age Range	Number Of Patients in the Range	Patient Range %
18 to 19	0	0 %
20 to 29	3	10 %
30 to 39	8	27 %
40 to 49	7	23 %
50 to 59	11	37 %
60 to 63	1	3 %
Total	30	100.0%

The data demonstrated the CVD Cream was effective at generating a positive sexual experience (73.3% positive response rate) and effective at generating a change in sensation in the external genitalia (73.3% positive response rate). The data further demonstrate that a significant majority of patients would purchase the CVD Cream (66.7% response rate) and that the CVD Cream resulted in minimal unpleasant side effects (13.3% response rate) all described as a transient time of mild burning (Table 2).

Table 2: Consolidated Patient Responses – All Patients

Question	Positive Response Patients	Total Patients	% Positive Response
1. Before using the product - on average was your typical sexual experience acceptable?	26	30	86.7%
2. After using the product - was your sexual experience improved?	22	30	73.3%
3. After using the product - did you notice a change in sensation in your external genitalia?	22	30	73.3%
4. Would you buy the product?	20	30	66.7%
5. After using the product - did you notice any unpleasant side effects?	4	30	13.3%

The data was grouped into five 10-year age ranges and analyzed for differences based on these age groupings (Table 3). This analysis demonstrated that all age groupings had acceptable sexual experience before use of the CVD Cream. The data then showed that after use of the CVD Cream the sexual experience was improved in all five age groupings with 57.1 % to 100% of patients reporting improvement and that sensation in the external genitalia was increased in all five age groupings as 57.1 % to 100% of patients reported increase in sexual sensation in the external genitalia. All age groupings reported an interest to purchase the CVD Cream.

Table 3: Consolidated Patient Responses – by Age Group

Patient Age Range:	20 to 29		30 to 39		40 – 49		50 – 59		60 – 69	
Question	# Positive Response	% Positive Response	# Positive Response	% Positive Response	# Positive Response	% Positive Response	# Positive Response	% Positive Response	# Positive Response	% Positive Response
1. Before using the product - on average was your typical sexual experience acceptable?	3	100.0%	6	75.0%	7	100.0%	9	81.8%	1	100.0%
2. After using the product – was your sexual experience improved?	2	66.7%	6	75.0%	4	57.1%	9	81.8%	1	100.0%
3. After using the product – did you notice a change in sensation in your external genitalia?	2	66.7%	6	75.0%	4	57.1%	9	81.8%	1	100.0%
4. Would you buy the product?	1	33.3%	5	62.5%	3	42.9%	10	90.9%	1	100.0%
5. After using the product – did you notice any unpleasant side effects?	0	0.0%	2	25.0%	1	14.3%	1	9.1%	0	0.0%

Table 4 presents the results for the sub-population of patients reporting less than acceptable sexual experience prior to use of the CVD Cream. In this sub-population the data demonstrated a positive result for the CVD Cream. The CVD Cream was effective at generating an improved sexual experience for 75.0% of this sub-population. 75% of this sub-population reported experiencing a change in sensation in the external genitalia. 75% of the sub-population would purchase the CVD Cream and none in this sub-population experienced an unpleasant side effect.

Table 4: Responses Only for Patients with Unacceptable Sexual Experience before use of the New CVD Cream

Question	Positive Response Patients	Total Patients	% Positive Response
1. Before using the product - on average was your typical sexual experience acceptable?	0	4	0.0%
2. After using the product - was your sexual experience improved?	3	4	75.0%
3. After using the product - did you notice a change in sensation in your external genitalia?	4	4	100.0%
4. Would you buy the product?	3	4	75.0%
5. After using the product - did you notice any unpleasant side effects?	0	4	0.0%

The results for the sub-population of patients reporting acceptable sexual experience prior to use of the CVD Cream, reported in table 5, also showed a positive result for the CVD Cream. 73.1% of the patients in this sub-population reported the CVD Cream was effective at generating an improved sexual experience and 69.2% reported experiencing a change in sensation in the external genitalia. 65.4% of this sub-population would purchase the CVD Cream and 15.4% reported experiencing unpleasant side effect, as previously noted all described as a transient time of mild burning.

Table 5: Responses Only for Patients with Acceptable Sexual Experience before use of the New CVD Cream

Question	Positive Response Patients	Total Patients	% Positive Response
1. Before using the product - on average was your typical sexual experience acceptable?	26	26	100.0%
2. After using the product - was your sexual experience improved?	19	26	73.1%
3. After using the product - did you notice a change in sensation in your external genitalia?	18	26	69.2%
4. Would you buy the product?	17	26	65.4%
5. After using the product - did you notice any unpleasant side effects?	4	26	15.4%

The 5-part questionnaire included sections for comment. Overall, 17 of the 30 (57%) patients recorded comments (Table 6). A survey of the comments suggested certain trends. Patients reported that they experienced increased sensitivity in the genitalia. Comments were provided that patients experienced an ability to reach orgasm more quickly and to achieve multiple orgasms. Of those patients in the subset reporting unacceptable sexual experience prior to use of the CVD Cream, 3 of 4 (75%) provided comments (Table 5). For these patients, commonly reported problems prior to use of the CVD Cream were dryness and discomfort which the CVD Cream improved. Within in this sub-population, comments of “Wished I had more!” and “Can we purchase now? I personally don't want to wait for this to hit the market.” demonstrated the CVD Cream had a positive effect for this difficult sub-population.

Table 6: Written Comments

Patient #	Comment(s)	Improved Experience? *	Change In Sensation? ¹	Buy? *	Unacceptable Sexual Experience Prior to CVD Cream? ¹
2	Before using the product, my sexual experience was just OK. Wished I had more!	Y	Y	Y	Y
4	Had more lubrication.	Y	N	Y	N
9	Before using the product, had dryness, leading to irritation / discomfort. Absolutely would buy again. Truly an improved experience. Reminders of 15+ years ago. Hard to describe but not just improvement of dryness and discomfort. This was a more intense and more satisfying experience that lingered for an hour or so post-activity. Can we purchase now? I personally don't want to wait for this to hit the market.	Y	Y	Y	Y
10	Tingling lasted awhile.	N	Y	Maybe	N
11	Before using the product, sexual experience was always good. After product use sexual experience still good. No warming sensation. Would buy for lubrication only. No adverse reaction. I did not experience any warming sensation or change in experience; it was same as without the cream. The only advantage was the lubrication. I remained well lubricated throughout.	N	N	Y	N
12	Slight improvement in sexual experience. Change in sensation was sensitive for a few hours	Y	Y	Y	N
22	Before using the product, my sexual experience was very dry and painful, especially with condoms.	Y	Y	Y	Y
26	Unpleasant side effect of burning. I really didn't notice a difference. It did irritate me a little bit.	N	N	N	N
30	Awesome stuff!	Y	Y	Y	N
40	Each time I applied the product I had burning sensation when applied. I tried using a smaller amount but still had burning. It was more than a warm sensation that's expected. It did help but wasn't as worth it to me to buy knowing the reaction I had.	Y	Y	N	N
41	Before using the product, my sexual experience was not always acceptable.	Y	Y	Y	N
42	Felt like I had a UTI.	N	N	N	N

ANP01	My sexual experience is always great with my husband – but my sex drive has lessened with menopause. I was able to achieve an orgasm very easily & quickly. I became extremely sensitive and could achieve numerous orgasms very easily.	Y	Y	Y	N
ANP02	My partner/husband is wonderful, but my sex drive has diminished with the onset of peri-menopause. The cream increases my sensitivity and makes it unbelievably easy for me to achieve multiple orgasms!	Y	Y	Y	N
CJ	Sexual experience sometimes improved. Genitalia felt warmer.	Y	Y	N	N
DNF	Made the area feel a little warmer than usual but sensation level remained the same. Before using this product my sexual experience was above average so not sure there was much room for improvement!	N	N	N	N
Decline 2	Slight sting but went away. It was like using petroleum jelly. It barely had a sting that I mentioned above but went away shortly.	N	N	N	N

* Y = Yes; N = No

Discussion:

Treatments for female sexual dysfunction (FSD) are lacking. Female sexual response is highly influenced by the emotional, relational, and physical variables present in each sexual event. These complex and inter-related factors continue to challenge researchers in evaluating and developing effective treatments for FSD. Compounding the problem, religious and cultural mores influence attitudes towards sex and complicate sexual response.^{18, 19} Certain medical conditions, such as diabetes and multiple sclerosis, can decrease genital sensitivity²⁰ while medical treatments, for example, selective serotonin reuptake inhibitors (SSRIs) have been associated with decreased orgasmic response and varying degrees of genital anesthesia.²¹

FSD is reported in published papers to be as high as 50% of the female population.^{2, 3} Laumann in a 1767 patient study reported FSD in 43% of the study population.² Although a significant portion of the female population is affected by FSD, at the writing of this paper there is only one FDA approved drug for the treatment of FSD, Flibanserin, (Addyi[™]). Addyi[™] is a pill taken daily and is targeted to modify brain chemistry. Use of Addyi[™] is reported to result in a small increase in satisfactory sexual episodes per month. Addyi[™] has significant side effects, including a contraindication of use with the consumption of alcohol.²² The considerable expense, host of significant side effects, lack of direct effect on the female genitalia, and the mere fact that alcohol was prohibited while on the drug (often consumed during the sexual encounter), set this drug up for failure even before it was made available commercially. Intrinsa, from Proctor & Gamble, was another drug targeted to treat FSD. Intrinsa was a transdermal patch delivering testosterone. In 2004 the FDA rejected approval of Intrinsa and in 2012 Intrinsa was withdrawn from the European market. Intrinsa is another example of the difficulty and expense of addressing concerns of safety and efficacy in developing a therapeutic for FSD.²³

As a result of the cost, challenges and difficulties in demonstrating product efficacy and obtaining a drug approval, product development focused on consumer product options. There are over 100 consumer products that claim to aid female sexual response. One consumer product for example, a botanical product called Zestra[™], completed one study in 256 women⁷ that reported a 14% rate of burning and has been reviewed in the literature with skepticism.²⁴ ²⁵ Many of the other consumer products contain L-Arginine which is a protein amino-acid prevalent in all biological life forms. L-Arginine is a vasodilator but it does not cross human squamous epithelium to any significant degree.¹⁵ Therefore many of these consumer products that contain L-Arginine use menthol to irritate the skin which is said to help L-Arginine penetrate the skin.^{26, 27} By using L-Arginine, these consumer products claim to aid in sexual function. However, none of these consumer L-Arginine products have been studied in prospective, randomized controlled, IRB approved clinical trials as reported elsewhere for the CVD Cream¹. Further, consumer products' use of menthol is known to cause irritation^{26, 27}, a burning sensation^{5, 28} and contact dermatitis.^{5, 28}

The results of this study, which confirmed the results in the first paper reporting on the CVD Cream¹, demonstrated that the CVD Cream applied to the clitoris increased sexual sensitivity, increased lubricity and enhanced the sexual experience. Participants reported the desire to purchase the CVD Cream to reproduce that experience. Patient

response rates of positive results from use of the new CVD Cream were high in both patient sub-populations of (1) unacceptable (75% and greater positive response) and (2) acceptable (65% and greater positive response) sexual experience before use of the new CVD Cream. These results suggest the new CVD cream can be helpful not only for women who are experiencing less than satisfactory sexual encounter results but also benefit to women in the general population.

A fast acting topical that can be discreetly applied (the process of application can in and of itself be arousing, especially in the subset of women that feel uncomfortable in touching their genitalia), enhance female sensitivity, sexual response and satisfaction and have minimal side effects would provide a much-needed option for woman wanting to enhance their sexual experience for a host of reasons. The CVD Cream in previous studies¹ and in this study has been demonstrated to provide a measurable and enhanced clitoral blood flow, while minimizing the typical side effect of burning associated with currently available topical consumer products. It further has been demonstrated to increase sexual sensitivity and enhanced sexual response and satisfaction. The CVD Cream increased blood flow was reported to increase lubricity, and a clitoral erection has been described as pleasurable. The CVD Cream provides women the chance to experience a heightened sexual experience in a reproducible fashion.

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