

CASE REPORTS

Persistent Genital Arousal Disorder: A Case Report in a Woman with Lifelong PGAD Where Serendipitous Administration of Varenicline Tartrate Resulted in Symptomatic Improvement

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DOI: 10.1111/j.1743-6109.2008.01210.x

ABSTRACT

Introduction. Persistent genital arousal disorder (PGAD) in women is associated with feelings of persistent, spontaneous, intrusive, unrelenting, and unwanted physical arousal in the absence of conscious thoughts of sexual desire or sexual interest.

Aim. To report the case of a 49-year-old woman with lifelong PGAD who was recently prescribed varenicline for smoking cessation and who subsequently experienced amelioration of PGAD symptoms.

Methods. Patient self-report and literature review. Written consent was obtained from the patient.

Results. Abatement of lifelong PGAD symptoms occurred within approximately two weeks each time varenicline treatment was initiated. PGAD symptoms returned in approximately 2 weeks each time treatment was suspended.

Conclusions. Varenicline is a partial agonist of the $\alpha 2\beta 4$ subtype of nicotinic cholinergic receptor. Its unique pharmacological action stimulates a small amount of brain dopamine release while antagonizing the ability of nicotine to stimulate much larger dopamine release. Genital sexual arousal is controlled in part by the action of hypothalamic and limbic dopamine systems. Based on the mechanism of action of varenicline and the observation of its effectiveness in this case, we hypothesize that: (i) central hyperactive dopamine release is an important component in the pathophysiology of PGAD in this patient; and (ii) use of varenicline resulted in lowering of this hyperstimulated central dopamine release. Objective testing of varenicline's safety and efficacy in the treatment of other women with PGAD is suggested. **Korda JB, Pfaus JG, and Goldstein I. Persistent Genital Arousal Disorder (PGAD): A case report in a woman with lifelong PGAD where serendipitous administration of varenicline tartrate resulted in symptomatic improvement. J Sex Med 2009;6:1479–1486.**

Key Words. Persistent Genital Arousal Disorder; Persistent Sexual Arousal Stimuli; Varenicline; Dopamine; Nicotine; Acetylcholine

Introduction

Persistent genital arousal disorder (PGAD), formerly known as persistent sexual arousal syndrome, is an uncommonly reported sexual health concern [1–20].

PGAD in women may be diagnosed if symptoms include: (i) associations with feelings of persistent, spontaneous, intrusive, unrelenting, and

unwanted physical arousal such as throbbing, pulsating, pounding, engorgement and/or pressure/discomfort in the genital tissues, including the clitoris, labia, vagina perineum, and/or anus; (ii) occurring in the absence of conscious thoughts of sexual desire or sexual interest; (iii) associations with various degrees of bother; (iv) presentation throughout the person's life, consistent with primary, lifelong PGAD or developed at various

ages, consistent with secondary, acquired PGAD; (v) association with spontaneous orgasms or feelings that orgasm is imminent or feelings that orgasmic release is needed to reduce the feelings of persistent arousal; and (vi) where symptoms are not consistently diminished by achieving orgasmic release [2,4,5].

Little is known about the pathophysiology of PGAD. There are no recognized animal models and there have been few reported clinical investigations of women with PGAD [12,15,16]. PGAD may be associated with psychological-related pathophysiologies, including depression and anxiety [4,6,7,9,11].

PGAD may be associated with biologic-related pathophysiologies including vascular, neurologic, pharmacologic, and hormonal etiologies; however, direct cause and effect relationships have not yet been established. Potential arterial vascular causes may be secondary to pelvic arterio-venous malformations with unregulated arterial communications to the genitalia. Potential venous vascular causes may be secondary to pelvic congestion syndrome with ovarian venous incompetence and large varices draining the genitalia [4,12]. Potential central neurologic causes may be secondary to Tourette's Syndrome, epilepsy, post-blunt central nervous system (CNS) trauma, post-neurosurgical intervention of central arteriovenous malformation, or to cervical and lumbosacral surgical interventions [4,7,9,13,14]. Potential peripheral neurologic causes may be secondary to pudendal nerve entrapment or hypersensitivity [4,16]. Potential pharmacologic causes may be secondary to use of certain antidepressants such as the serotonin receptor antagonist, trazodone, or secondary to the sudden withdrawal of selective serotonin reuptake inhibitors (SSRIs) as occurs in sudden SSRI discontinuation syndrome [4,8,11]. Potential hormonal causes may be secondary to initiation and discontinuation of hormone therapy in postmenopausal women, and excess use of herbal estrogens in over-the-counter agents [1,4]. Some cases of PGAD are idiopathic [4,6,7,9,11].

There are limited data, including no known double-blind, placebo-controlled studies, concerning therapeutic strategies for women who seek management because of distress from PGAD. Psychologic-based treatments engage both couple therapy and cognitive behavioral techniques and management of the depression, or focus on efforts to maximize relaxation, through strategies such as distraction and/or hypnosis [4,21].

Biologic-based treatments include ice or topical anesthetic agents [13]. Discontinuing trazodone, venlafaxine, or excess herbal estrogen products may provide relief [1,10]. Women with PGAD symptoms that stem from known vascular causes might benefit from surgical and/or radiological intervention [12].

Yero and colleagues described a positive outcome in women with PGAD using repeated electroconvulsive therapy [14]. Surgical release of pudendal nerve entrapment has resulted in PGAD symptom improvement. Pharmacologic strategies have included use of tricyclic or SSRI antidepressants (e.g., clomipramine, paroxetine), prolactin-elevating agents (e.g., olanzapine, risperidone), or anti-seizure medications (e.g., carbamazepine) [4,11,13].

To the best of our knowledge, there have been no reports of varenicline tartrate used to alleviate PGAD symptoms in women with distress from PGAD. Herein, we report the case of a woman with primary lifelong PGAD who serendipitously started on varenicline for smoking cessation and, within a few weeks, noted a significant decrease in PGAD symptoms. When she stopped varenicline treatment, PGAD symptoms returned abruptly, and when she restarted varenicline, symptoms again abated.

In this patient with PGAD, varenicline treatment was observed to reduce unwanted arousal symptoms. Varenicline is a partial agonist at the $\alpha 4\beta 2$ nicotinic receptor subtype that decreases the ability of nicotine to stimulate the release of mesolimbic dopamine ([22,23], Figure 1). It was approved by the Food and Drug Administration (FDA) as a smoking cessation treatment.

Central dopamine transmission is critical for the stimulation and maintenance of sexual arousal and desire in all mammals [24–28], and stimulation of dopamine receptors in the hypothalamus and limbic system of the brain controls autonomic outflow. In this patient with PGAD, we therefore hypothesize that: (i) PGAD was the result of a hyperstimulated central dopamine release (Figure 2); and (ii) restoration of more normative sexual arousal was the result of varenicline-associated lowering of this hyperstimulated central dopamine release.

Case Report

Prior to Varenicline

A 46-year-old bisexual, nulliparous Caucasian woman with a history of primary, lifelong PGAD

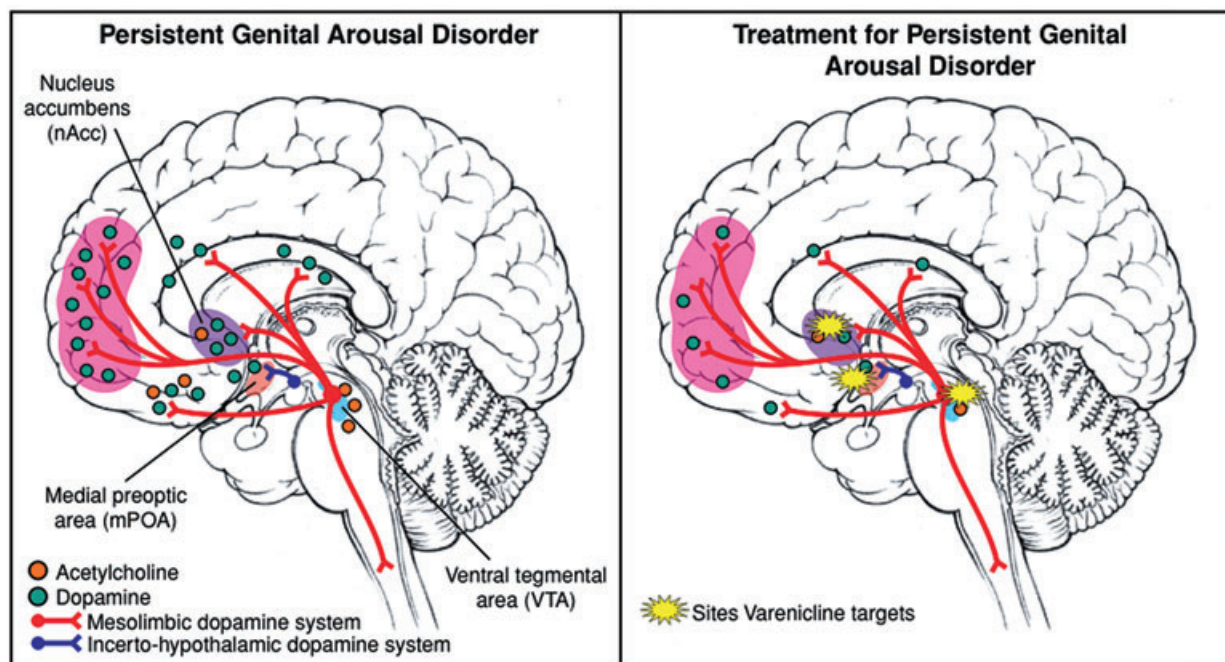


Figure 1 Theoretical mechanism by which varenicline alleviates Persistent Genital Arousal Disorder. (Left) Elevated dopamine transmission in terminal regions of the mesolimbic (red) and incertohypothalamic dopamine systems in Persistent Genital Arousal Disorder. (Right) Reduction in dopamine transmission to normative levels in those regions following varenicline treatment. Varenicline acts on mesolimbic dopaminergic cell bodies in the Ventral Tegmental Area (VTA), on presynaptic dopamine terminals in regions like the nucleus accumbens (nAcc), and on terminal regions of the incertohypothalamic dopamine system in the medial preoptic area (mPOA) to reinstate normal levels of dopamine transmission.

was referred for second opinion to a sexual medicine clinic in December 2005.

She reported that her first autoerotic, orgasmic experience occurred at the age of 6 years and started to engage in frequent masturbation at the age of 12. At that time, she felt distracted and bothered by the growth and large size of her labia majora and was fearful of transforming into a man. At the age of 14, she was very aware of persistent genital arousal feelings. After recognizing that her genital arousal feelings diminished during sporting activities, she became very physically active in part to relieve the bother of those symptoms.

During her first few menstruations, she experienced intense dysmenorrheal pain with occasional fainting. From her 20s to 40s, she often felt “completely out-of-her-mind” from the persistent and unrelenting genital arousal. Raised in a traditional Irish Catholic family with strict principles, she delayed sexual activity for as long as she could. She reported that her first sexual experience was at the age of 19 years old with a fellow student at her all-women’s college and her first intercourse with a man was at 25 years. Both experiences were described as enjoyable. At the age of 26, she

engaged in a 14-year lesbian relationship with a “hyposexual” (as she described) woman. This relationship made her feel uncomfortable for the first time about her sexuality. Compared to her partner, she was “oversexed.” She felt ashamed and frustrated about the disparate sexual interest and activity during the long relationship. She occasionally sought satisfaction for her sexual needs in casual heterosexual affairs and struggled with the thought that she was really a “nymphomaniac.”

In 2000, she was placed on citalopram for management of depression. She also started to smoke cigarettes, one pack per day. After a few months, she stopped the selective serotonin reuptake inhibitor because of diminished libido and difficulty achieving orgasm. When switched to bupropion, her sexual feelings “came back” but orgasm remained difficult to achieve requiring genital stimulation for a protracted period of time.

After the lesbian relationship ended, she started an 8-year relationship with a “very sexual” man, who described her as the “most sexual woman he ever met.” At times he felt intimidated by her need to engage in sexual activity to get relief from the persistent genital arousal symptoms. Although she

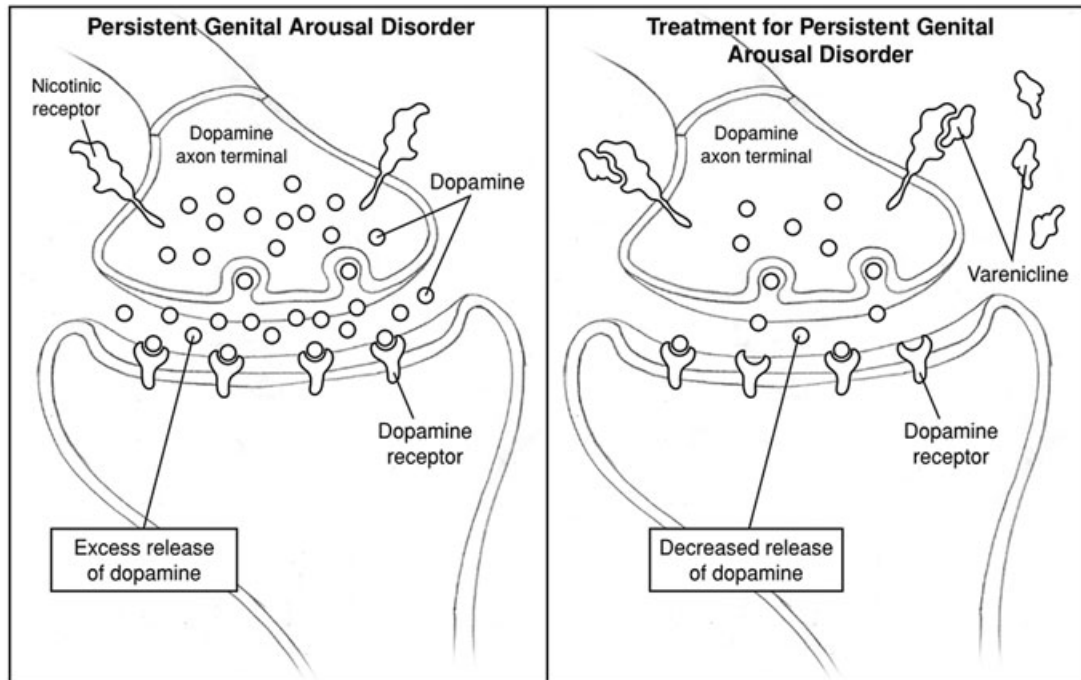


Figure 2 Neuropharmacological mechanism of action of varenicline. (Left) Elevated release of dopamine in Persistent Genital Arousal Disorder. Such release may stimulate genital blood flow in a tonic manner. (Right) Antagonist-like action of varenicline on $\alpha 2\beta 4$ nicotinic cholinergic receptors located on presynaptic terminals (or cell bodies) blocks the excitatory action of acetylcholine on dopamine release. However, its partial agonist action allows dopamine to be released at more normative levels. Thus, varenicline does not prevent dopamine release but rather works against an endogenous imbalance that results in elevated and tonic dopamine transmission.

described herself as very emotionally satisfied, she rarely felt full satisfaction after sex, describing herself as her “own worst enemy.” Sexual activity usually provided only temporary relief from the genital arousal symptoms with unpleasant and unwanted feelings of engorgement returning soon after.

In 2005, she underwent a vaginal hysterectomy for uterine fibroids, which diminished the intensity of her PGAD but her clitoral orgasmic capacity as well. In 2006, she had a laparoscopic removal of endometriotic foci in the pelvic sidewalls, a sigmoidectomy and partial rectum resection for severe extrauterine intestinal endometriosis which had caused dysmenorrhea for years. This surgical intervention did not alter her PGAD.

Also that year, she came across a PGAD survey on the Internet [6,7]. She completed the form and was referred to a sexual medicine clinic for possible medical management.

During the subsequent sexual medicine focused evaluation, she described her PGAD symptoms in great detail. The feelings of swelling and pulsation were considered bothersome, uncomfortable, and unwanted, but since she has had PGAD symptoms

all her life, she said “PGAD is an integral part of my life, so therefore it defines me.” The locations were restricted to the vulva, clitoris, and vagina with no other body parts involved. She did not experience overt pain from the PGAD. PGAD symptoms and intensity were described as variable, in part because of the time of day, in part because of her mental state, and in part because of various medications used. PGAD symptoms were usually minimal in the morning and worsened between noon and 3 p.m. They worsened with stress, anxiety, and fatigue, and were alleviated with distraction.

Various pharmacologic agents appeared to diminish PGAD symptom intensity. The first agent was noted following recovery from the two surgeries. Postoperative administration of the opioid mu receptor agonist, morphine, appeared to arrest PGAD symptoms. As soon as the morphine wore off, PGAD symptoms returned. The second agents were noted during treatment for mild hypertension in 2006. Both the angiotensin-converting enzyme inhibitor, enalapril, and the specific angiotensin receptor blocker, valsartan, appeared to diminish her PGAD symptoms. Each

agent was discontinued because of side effects including dry cough and symptoms of hypotension, diminished libido and vaginal dryness, respectively. While on each agent, PGAD symptoms diminished, and after subsequent discontinuation of the drug, unwanted pulsating, throbbing, and other unpleasant genital symptoms recurred.

Other antihypertensive agents such as the calcium channel blocker, nifedipine and then carvedilol—a nonselective beta blocker—resulted in diminished clitoral sensation and displaced the focus of PGAD symptoms more toward vaginal congestion. On these medications, her PGAD symptoms became severe.

After Varenicline

The patient decided to quit smoking soon thereafter and was prescribed varenicline. Within 2 weeks, for the first time in her life, she had no PGAD symptoms. “I have had absolutely no PGAD for the last week or so. Even urinating” she observed, “definitely is different without PGAD; the stream is definitely much stronger. So I guess there is a correlation between voiding and PGAD.” She noted that 2 months into the varenicline, the PGAD has abated considerably. “I feel like I know what it feels like to be a regular person. Pretty cool.” When she stopped the varenicline, the PGAD symptoms returned. She restarted the medication and the symptoms abated. The following month, while on varenicline, PGAD symptoms remained at an extremely low level.

Aside from mild gastric symptoms, she had no noticeable side effects during the varenicline treatment, especially and including no loss of sexual interest.

In early 2008, she was found to have an *in situ* ductal carcinoma of the left breast and underwent a partial lobectomy and radiation therapy. During breast cancer treatment, while on varenicline, the PGAD remained stable. She ultimately decided to stop varenicline again, in part because of financial concerns and in part because of lack of data on long-term use. Within 2 weeks the symptoms of PGAD returned. The total duration of varenicline use was 12 months, during which time, the PGAD symptoms abated.

Discussion

Based on the description of her symptoms, it is believed that this patient meets all criteria for the diagnosis of primary lifelong PGAD. She recognized and experienced persistent genital arousal

feelings which were not related to excessive sexual desire, and as soon as she entered puberty she felt an “urgency to relieve” her PGAD symptoms whenever they were manifested. We did not perform a physical examination on her; therefore, we cannot determine whether she has some physical conditions underlying her PGAD symptoms nor body dysmorphic disorder with a false perception of her genitals.

Addressing the lifelong history of her symptoms, it is understandable that she defines the PGAD as an integral part of her life and does not experience severe distress; however, she does experience distraction, suffering, and is bothered when the symptoms are present.

Sexual arousal in women and men is under the control of both the autonomic and CNSs. Blood flow to genital tissues (clitoris, vagina, penis) is controlled mainly by the parasympathetic division of the autonomic nervous system, whereas other indices of sexual arousal (e.g., increased blood pressure, breathing rate, pupil dilation, etc.) are controlled by the sympathetic division of the autonomic nervous system [29]. Brain catecholamines like dopamine and noradrenaline play a causal role in the regulation of autonomic outflow and concomitant sexual desire and behavior [24,27,29–33]. At least two dopamine systems in the brain are known to control sexual arousal and desire. The incertohypothalamic dopamine system arises from the zona incerta and projects to the medial preoptic area (mPOA) of the anterior hypothalamus [34]. Dopamine in the mPOA controls penile erection and ejaculation in male rats through actions on D1 and D2 receptors, respectively [24]. The mesolimbic dopamine system arises from the mid-brain ventral tegmental area and projects diffusely to the limbic system, including the nucleus accumbens (nAcc) ([35], Figure 1). Dopamine in the nAcc and mPOA is increased during sexual arousal in both male and female rats [36–38], and dopamine release in both the nAcc and mPOA is critical for the display of appetitive sexual behaviors and the normal pattern of copulation in rats [27,28]. This phenomenon may be regulated by D1 receptors in both regions [24,39,40].

Of particular relevance to the present report is that dopamine release in these brain regions occurs in response to sexual stimuli and must reach a critical threshold for sexual responses to occur in rats. Such a phenomenon may also occur in humans. We suspect that one potential cause of PGAD may be hyperactive dopamine release. Consistent with this hypothesis, treatment of

women with the dopamine receptor agonist apomorphine increases peak systolic velocity of clitoral engorgement [41], and a burst pattern of firing was observed in the sympathetic uterine nerve of anesthetized female rats treated with apomorphine or another dopamine agonist, piribedil [42,43]. These data suggest that activation of central dopamine receptors activates sexual reflexes in females, as it does in males. Conversely, treatment with the dopamine receptor antagonist, risperidone, decreased genital engorgement in a postmenopausal woman who is troubled by persistent genital arousal during the night [13].

Nicotinic acetylcholine receptors (nAChRs) exist on dopamine cell bodies in the substantia nigra and ventral tegmental area (VTA) [43] and in the terminal regions of both mesolimbic and incerto-hypothalamic dopamine systems [44,45]. Cholinergic interneurons exist in the NAc [46] and appear to modulate dopamine release presynaptically. Varenicline acts primarily as a partial agonist of the $\alpha 2\beta 4$ nAChR [22,23]. Although varenicline alone in that study stimulated a small degree of mesolimbic dopamine release, it reduced extracellular dopamine levels in the nAcc stimulated by nicotine due to partial blockade of the nicotine-binding moiety. This novel action led varenicline into clinical trials as an antismoking medication [22,23].

We propose that varenicline may show clinical efficacy in the treatment of PGAD in this patient partly because PGAD is associated with hyperactive dopamine release and partly also that varenicline specifically reduces extracellular dopamine concentrations (Figure 2). Such hyperactive release could have one or more antecedent conditions, including estradiol binding (to stimulate the dopamine synthesis enzyme tyrosine hydroxylase), androgen actions (to stimulate nitric oxide synthesis thereby contributing to greater dopamine release), or a conditioned hyper-responsivity to sexual or genitally-focused nonsexual cues (e.g., somatosensory stimulation of genital skin rubbing against underwear). Varenicline appears to be tolerated well, possibly because it does not block dopamine release completely in response to external stimulation. To the extent that PGAD is associated with augmented extracellular dopamine transmission, varenicline's action would be expected to restore "normative" dopamine function. Such treatment would be superior to the use of dopamine antagonists or SSRIs, which would have a similar inhibitory action on dopamine release [47] but with a high potential for untoward sexual side-effects (e.g., anorgasmia, decreased

sexual desire). At the time of this writing, however, the FDA is reviewing safety warnings for varenicline because of its association with neuropsychiatric symptoms (changes in behavior, agitation, depressed mood, suicidal ideation, and suicide).

Because varenicline treatment reduced PGAD symptoms in this patient, we hypothesize that lowering hyperstimulated CNS dopamine resulted in the restoration of more normative sexual arousal. Pharmacologic regulation of CNS monoamine neurotransmitters may represent a novel approach to the management of PGAD.

Although more research is needed, the present case may represent a potentially new CNS-focused pharmacologic paradigm for the treatment of PGAD.

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Conflict of Interest: None declared.

Statement of Authorship

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